DISCUSSION

Response to critique by Indira Chakravarthi

INDRANEEL MITTRA, GAURAVI MISHRA, RAJENDRA BADWE, RAJESH DIKSHIT

Abstract

Indira Chakravarthi's critique relates to our paper published in the British Medical Journal in 2021 titled "Effect of screening by clinical breast examination on breast cancer incidence and mortality after 20 years: prospective, cluster randomised controlled trial in Mumbai". The study addressed the unanswered questions as to whether clinical breast examination (CBE) conducted by female health workers would lead to a reduction in mortality from breast cancer. Chakravarthi raises multiple issues relating to our study and we provide in this paper point-by-point responses to these issues. The results of our study show that two-yearly CBE screening can reduce death rate from breast cancer by 30% in women above the age of 50 and to a lesser extent to those below this age. CBE screening if implemented in low- and middle-income countries can save thousands of lives globally each year.

Keywords: *Breast cancer screening, mammography, clinical breast examination, over-diagnosis, false positive diagnosis*

We thank Indira Chakravarthi for her critical commentary on our study [1].

Our study on using clinical breast examination to screen for breast cancer was published in 2021 in the *British Medical Journal (BMJ),* titled "Effect of screening by clinical breast examination on breast cancer incidence and mortality after 20 years: prospective, cluster randomised controlled trial in Mumbai" [2]. The *BMJ* is one of the most respected medical journals in the world and our manuscript was subjected to four rounds of rigorous peer review by four different experts (one of whom was an ethicist) before it was accepted for publication. The paper has so far been read by 43,016 individuals globally and has received 172 citations. It has also received acclaim from major international cancer organisations [3]. The *BMJ* paper is accompanied by an article, "The Story of the Mumbai Study", which highlights the enormous effort required to screen 150,000 women in Mumbai and follow them up for 20 years.

It is important to acknowledge that this is a pioneering study, as it is the first of its kind to provide evidence that clinical breast examination (CBE) can reduce mortality by 30% in women over the age of 50. The study also suggests a potential benefit of CBE, albeit to a lesser extent, in women under 50, although this finding did not reach statistical significance. These results can potentially save thousands of lives globally and are being incorporated in India's national cancer screening programme, the National Programme for Prevention and Control of Non-Communicable Diseases (NP-NCD). Before providing a detailed response to Chakravarthi's commentary, it is crucial to point out that India's national programme does not include population-based screening mammography even today.

We have identified several issues raised by Chakravarthi that necessitate our response.

1) Withholding an established intervention in the control arm

The author questions why we did not offer mammography to the control arm participants of our study when it is the established screening approach in Western countries and is commonly available in Mumbai. We would like to submit the following:

a. Mammography is costly, technically complex, and requires stringent quality control for optimal performance. It is not currently considered an appropriate population-based screening intervention in low- and middle-income countries (LMICs) including India by almost all authorities and experts globally [4]. The current mammography facilities in Mumbai exist in busy hospitals and a few public sector centres and are overwhelmingly dedicated to diagnostic rather than screening purposes. Our purpose was to evaluate a screening intervention that would be effective and implementable in diverse settings in India.

b. In addition, the efficacy of mammography in reducing breast cancer mortality among women under the age of 50 has not been proven [5]. This is particularly salient given that 71.5% of the participants in our study were below that age. Consequently, it would not have been prudent to design a study with the knowledge that the majority of women would not have derived any benefit from the intervention.

c. Even among women older than 50 years, there is some debate about the mortality benefit of screening mammography, especially the balance between benefits and potential harms [5,6]. Even if it is conceded that mammography reduces breast cancer mortality, a comprehensive analysis has revealed that the screening of 2,000 women over a 10-year period would be required to save a single life [5]. This underscores the impracticality, inefficiency, and high financial cost of mammography. However, it is established that mammography is associated with substantial harm, which may outweigh any potential

benefits [7-10].The two primary drawbacks of mammography are overdiagnosis [7-8] and false-positive diagnoses [9-10]. The term "overdiagnosis" refers to the detection of cancers that would never have progressed to a life- threatening stage during a person's lifetime. The extent of overdiagnosis has been variable across different studies; however, on average, approximately 30% of women who undergo screening would be considered overdiagnosed [8]. The phenomenon of overdiagnosis signifies the identification of conditions that are not medically significant, resulting in the subsequent administration of unnecessary treatments. In the context of breast cancer, these treatments may encompass mutilating surgical procedures which may involve unnecessary mastectomy, and the administration of aggressive chemotherapy and radiotherapy, which can have deleterious consequences for patients. In this context, it is imperative to emphasise that CBE did not result in overdiagnosis in our study.

A second detrimental outcome of mammographic screening is the occurrence of false-positive diagnoses. These diagnoses result in the repetition of mammography and biopsies to confirm the nature of mammographic findings. In the United States, approximately 11% of women receive a false positive result from a single screening [9]. Similarly, approximately 50% of women who undergo annual mammograms over a 10-year period had a false positive finding at some point [10]. A false positive diagnosis is associated with considerable psychological harm, including severe anxiety and depression, which may persist for several months until the lesion is finally declared non-cancerous [11].

d. The Government of India has prudently abstained from incorporating mammography screening as a component of its population-based programmes. States that have adopted breast cancer screening as a public health policy employ clinical breast examination, a decision informed by the findings of our study published in the BMJ.

e. We believe that, based on the above evidence, the design of our study to withhold screening mammography from the women in the study may in fact have been beneficial to them. We disapprove of the author's assertion that our study was a calculated exploitation of economically disadvantaged women as a means to an end.

f. In our study, women in the intervention arm received a health education programme comprising the following components: explanations of risk factors, signs and symptoms, methods of prevention, early detection, screening facilities available, benefits of screening, harms of being diagnosed at a later stage, and basic modalities of treatment. Women in the control arm received the same health education programme. Additionally, women in the intervention arm were also screened with CBE at two-year intervals. Women diagnosed with breast cancer in either arm were administered the same treatment. The treating physicians were unaware of the arm to which each case belonged. The prevailing reality is that less than 2% of women in India undergo cancer screening. The general population is analogous to the control group of our study. The majority of women in India have not received a standardised awareness programme, and as a result, the disease often manifests itself at advanced stages.

g. Chakravarthi mentions avoidable morbidity and mortality. She makes an erroneous assertion that women in the control group were denied breast cancer screening. We would like to point out that no participant woman in either arm was deprived of pertinent information regarding breast cancer screening. The women in the control arm were permitted to undergo screening using any modality outside of the trial. Participant Information Sheets in Hindi and Marathi detailing mammography and Pap smear screening were distributed and the participants were advised that they could request a facility list from the project's medical-social worker if they so desired. The preliminary findings of the study were disseminated to the local population via information sheets in the local language by medical social workers (MSW). MSWs conducted regular door-to-door visits in both arms to ascertain the status of the participants and were a strong communication channel in the community. It is worth pointing out that 68 women from the intervention arm and 57 women from the control arm underwent mammography, although they were not referred by the study team.

2) Research equipoise and framing of the research question

Chakravarthi questions whether genuine equipoise existed for launching our study. Her argument rests on the Canadian National Breast Screening Study (CNBSS), which showed that in women aged 50–59 years, adding mammography to CBE did not improve mortality [12]. Yet the CNBSS did not compare CBE with no organised screening — the real-world situation for Indian women. Thus, a critical gap remained: could CBE by itself reduce mortality when introduced in a population with no existing screening programmes?

Breast cancer is now India's leading malignancy in women, with approximately 70% of cases still presenting at Stage III/IV. Mammography, although standard in high-income countries, is neither affordable nor logistically feasible in most Indian districts; even today, thousands of *talukas* have no functioning units. Transplanting such a technology without indigenous evidence would squander resources and widen

inequality. Conversely, our pilot work showed that trained female health workers could deliver high-quality CBEs at the community level.

Taken together, these facts indicated authentic uncertainty — and therefore equipoise — about whether introducing stand-alone CBE would save lives. Randomising clusters to CBE plus health education versus health education only was the only scientifically and ethically rigorous way to resolve that uncertainty. Notably, the 25-year follow-up of CNBSS later confirmed no mortality benefit for mammography, retrospectively validating our decision to omit that modality from both arms [6].

Screening interventions — whether mammography or faecal-occult blood testing — cannot be adopted wholesale on data from dissimilar settings, including marked differences in incidence patterns, infrastructure, acceptability, and human resources. By establishing the efficacy of CBE under Indian conditions, our study now permits the NP-NCD programme to evaluate its effectiveness nationwide.

3) Choice of Cluster-Randomised Controlled Trial Design

Chakravarthi raises a question about individual randomisation, and whether this design is ethically sound. Population-based screening interventions are frequently assessed through cluster-randomised controlled trials (CRCTs) because the unit of delivery, behaviour change, and potential contamination is the community rather than the individual. Indeed, three of the landmark mammography trials that shaped policy in Europe and North America had adopted cluster designs: The Health Insurance Plan (HIP) Trial, New York — randomised 62 neighbourhood medical practices to invitation for annual mammography ± CBE versus usual care [13]. The Swedish Two-County Trial — assigned entire counties [14] to population invitations, reducing mortality by 31%. The Edinburgh Randomised Trial of Breast Screening — allocated general-practice clusters to mammography invitation or routine care [15]. These studies illustrate that CRCTs are not only scientifically acceptable but often necessary when the goal is to test a service-delivery strategy rather than a pharmacologic agent.

Mumbai's slum households are densely packed. Randomising women living in adjacent houses to different arms would invite cross-contamination, ie, a woman allocated to the screening arm might encourage the next-door woman in the control arm to seek CBE screening, and vice a versa, — a situation which might confound the result of the study. Additionally, our intervention (group education, doorstep CBE by nurses, navigation to tertiary centres) is delivered at neighbourhood scale, reinforcing the appropriateness of a cluster unit.

We identified 20 clusters (~7500 eligible women each) and allocated them 1:1 to (i) CBE + education or (ii) education only, by draw of lots. To account for within-cluster correlation, we prospectively estimated an intra-cluster correlation coefficient (ICC) = 0.015 from baseline data, incorporated it in the sample-size calculation, and used mixed-effects Cox models in analysis. The corresponding design effect ($DE = 1 + [m - 1] \times ICC$) inflated our target enrolment and is reported in the *BMJ* paper (Statistical Analysis, Methods).

Thus, cluster-randomisation was likely the only possible design to answer a very important unanswered clinical question.

4) Community engagement and gatekeeper approval

The commentary asks who acted as gatekeepers, how were they selected, and what exactly was their role? The Ottawa Statement on CRCTs [16] recommends that when entire communities are randomised, investigators engage with bona-fide community representatives — or gatekeepers — who can speak to the collective interests of the participants.

After boundary-mapping each of the 20 clusters, we conducted a rapid stakeholder scan using three criteria: (i) legitimacy (formally elected or widely acknowledged in the community), (ii) reach (routine interaction with a substantial proportion of households), and (iii) commitment to women's health. Potential gatekeepers were shortlisted from four categories: family physicians, presidents of women's self-help groups, school principals/teachers, and faith-based leaders. No financial honorarium was provided; instead, gatekeepers were publicly recognised at an annual ceremony at the Tata Memorial Hospital (TMH).

Gatekeepers: (a) hosted neighbourhood meetings where investigators presented the protocol; (b) provided community spaces for screening camps; (c) dispelled rumours (eg, blood samples being sold) through ward-level posters; and (d) monitored that field staff treated participants respectfully. Gatekeepers did not give consent on behalf of the participants. Instead, individual participants, after understanding the study consented, following the process as mentioned below.

5) Individual informed consent integrity

The informed-consent forms were prepared in line with the standard operating procedures (SOPs) of the Institutional Ethics Committee (IEC). They were translated into Marathi because most participants spoke that language. Each woman either signed the form or, if she could not read or write, placed her left-thumb impression on it. A second woman from the same community witnessed the procedure and signed as a witness. When a verbal translation into another language was required, both the medical social worker and the translator signed the form. The social worker stayed with the participant until all questions had been answered.

The first version of the consent referred to 70,000 participants and annual screening. Later versions reflected

the larger sample size and the move to biennial screening. Participant information sheets in Marathi and Hindi (with an English source version) were then distributed in both trial arms; these explained mammography and listed the nearest imaging centres.

6) Data Safety Monitoring and Transparency

The commentary raises concern about Data Safety Monitoring and Transparency (DSMB) reports not being publicly available. Both the internal study team and an independent external Data Safety Monitoring Committee reviewed the trial each year. Because their reports contain confidential participant information, they cannot be placed in the public domain

7) Protocol amendments and sample-size inflation

The study protocol remained essentially unchanged throughout the trial. All minor amendments were fully documented, submitted through the NIH/NCI grant review process, and approved by the IEC of the TMH. The only substantive modification involved enlarging the sample size to account for the design effect introduced by cluster randomisation. When the trial began in 1998, design effect adjustments were rarely applied, even internationally. As the study progressed and we incorporated this correction, it became clear that a larger cohort was required. The follow-up period was extended accordingly to ensure adequate event accrual. The initial target was 70,000 women aged 35–64 years. This figure was increased twice as field experience revealed the practical realities of population screening in disadvantaged communities, ultimately reaching 150,000 participants. The original protocol, drafted in 1996, relied on limited mortality data. It is noteworthy that, breast screening sample sizes must be based on mortality rates, and more accurate local data only became available later.

8) Fair participant selection and vulnerability

The commentary raises a concern about why socially disadvantaged slum women were chosen when breast-cancer risk spans all socioeconomic groups, and how power imbalances were mitigated. However, ethical recruitment requires that populations bearing the highest disease burden receive the prospect of benefit. Mumbai's urban-poor women face a higher risk of advanced-stage disease, limited health literacy, and higher probability of catastrophic health expenditure. By locating the intervention where the need was greatest, the trial advanced distributive justice.

Overall, our study was intended to find an appropriate solution for the vast majority of women in India and other LMICs.

9) Internal and external ethics critiques

The Office for Human Research Protections did ask whether participants had been informed about screening options available outside the study. The study team explained that medical social workers had verbally informed the participants about nearby mammography and Pap smear centres during informed consent, but no written list was given. This information was given verbally rather than in writing to avoid the implication that Tata Memorial endorsed facilities over which it had no control. The IEC concurred that, in the absence of any national breast or cervical screening programme, enrolment in the study caused no harm to the participants.

To formalise this information, we later distributed Participant Information Sheets in Hindi and Marathi that described mammography and Pap smear screening and advised participants that they could request a facility list from the project's medical social worker. With this clarification in place, the IEC allowed the study to proceed.

10) Potential harms — both of omission and commission

As explained earlier, women detected with breast cancer from either arm were offered the same treatment. Also, there was no over diagnosis in the trial.

11) Post-hoc analyses and statistical integrity

The commentary questions why the ≥50 years subgroup was highlighted when it was not pre-specified. Primary intention-to-treat analysis across all ages showed a 15% mortality reduction (Hazard Ratio:0.85; 95% Confidence Interval: 0.71 to 1.01; P=0.07). We made it clear — both in the abstract and in the main text of our *BMJ* paper — that the age-stratified analyses were conducted post hoc. This additional analysis became necessary as emerging evidence indicated that the mortality benefit of mammography, and potentially of CBE, is largely confined to women aged ≥ 50 years. Age-specific subgroup analyses have been common practice in breast screening trials, except for the two Canadian National Breast Screening Studies. Virtually all other major trials have reported their age breakdowns retrospectively rather than as pre-specified comparisons.

Conclusions

The Mumbai CRCT adhered to national and international ethical norms, provided immediate benefits (breast-health literacy, expedited care) to all participants, and delivered practice-changing evidence for low-resource settings. We trust we have addressed all the points raised by Chakravarthi.

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