Review Article

Screening for breast cancer: Cost-effective solutions for low- & middle-income countries

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Low- and middle-income countries (LMICs) have limited financial resources and proportionately smaller portions allocated for health budget. With competing health priorities, treatment of the diagnosed cases and establishment of treatment facilities are the main concerns in LMICs. Infectious diseases, reducing infant, child and maternal mortality may seem crucial as compared to early cancer detection. LMICs that are committed to providing comprehensive cancer care, will need to judiciously choose the screening tool depending on specifics of how the tool is expected to perform in the population and the cost-effectiveness with respect to the number of lives expected to be saved. Increasing awareness about breast health in general and common cancers and non-communicable diseases (NCDs), in particular, may lead to symptomatic women approaching the healthcare facilities at an earlier stage. When the limited available resources are mobilized towards cancer screening, increasing awareness would lead to greater acceptability of the programme. The reach of the programme to achieve good population coverage, the establishment of the diagnostic referral linkages and the availability and accessibility of treatment facilities, will all decide the outcome of the screening programme.

Key words Awareness - breast cancer - cost-effective - LMICs - screening

An estimated 441,728 of the total 20,73,529 new breast cancer cases were from low- and middle- income countries (LMICs) in 2020. The age standardized incidence (ASI) of breast cancer in LMICs is 31.4. This is less than half of the ASI (78.3) recorded in high-income countries (HICs). However, the age-standardized mortality of 14 in LMICs is more than that recorded in HICs (12.9)[1]. The HICs have been able to reduce the mortality due to breast cancer because of mammography screening at the population level, leading to early-stage diagnosis, combined with the availability of good treatment facilities. The high cost of mammography (as compared to income), sparse mammography facilities and scarcity of trained and qualified workforce have led to minimal screening in most LMICs. The three major reasons for greater mortality despite lower incidence in LMICs are less awareness regarding the necessity and importance of screening in asymptomatic individuals combined with the absence of screening facilities, poor and non-uniform distribution of treatment facilities after diagnosis and LMICs comprising larger proportion of

population <50 yr compared to the developed countries, wherein for this group, there is no effective breast cancer screening modality. Age-specific breast cancer incidence rate is not high in <50 yr group in LMICs[2]. The overall younger age distribution of the population in most LMICs is responsible for the average younger age at presentation of breast cancers.

There is always a dearth of financial resources in LMICs. Resource allocation for cancer control will be with reference to other important causes of death in the population. The cost-benefit ratio of incorporating breast cancer screening in the healthcare systems of a country needs to be carefully weighed. If we look at the Indian scenario as an example of LMICs, we see that breast cancer is the most common cancer among women[3]. Breast cancer awareness and screening have been incorporated in the integrated National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke[3].

Choice of screening test

In recent years, there has been a focus on the weighing benefits versus harms of mammography and attention to controversies surrounding screening mammography in terms of overdiagnosis and subsequent overtreatment[4]. While comparing the different breast cancer screening strategies, tumour size and axillary nodal status form the two most significant surrogate measures that predict the prognosis. If the detected tumours are small and lymph nodes are negative, there is a chance to save lives with less radical treatment[5]. About one-fifth of the breast cancers detected by mammography are ductal carcinoma *in situ* (DCIS)[6]. Mass screening with mammography leads to an increase in DCIS diagnosis, and this is a much-discussed aspect of screening. However, mammography has been widely used for breast cancer screening in HICs and has shown effectiveness in reducing breast cancer mortality mainly in women older than 50 yr[7]. A viewpoint on breast cancer screening from the International Agency for Research on Cancer (IARC) Working Group which was compiled by the experts from 16 countries[8], raises questions on the relevance of breast cancer screening randomized controlled trials (RCTs) that were conducted over 20 yr back as there have been major developments in the mammography device and management of breast cancers over years. The Group further included the current evidence especially from large cohort studies for the age group of 50-69 yr and stated that among

invited women as opposed to participated women for screening mammography, there was 23 per cent reduction in the former group and 40 per cent in the latter[8].

Mammography screening is a complex undertaking involving substantial resources and infrastructure and similar results are unlikely to be replicated in LMICs due to several factors. LMICs usually have younger population age structure, resulting in younger age at diagnosis of breast cancer, wherein mammography is not very effective. The over-diagnosis and over-treatment associated with mammography is likely to overburden the healthcare system in LMICs already facing resource crunch. There may be other competing causes of death which may need prioritization. In LMICs, instead of having a programme focusing on one issue like breast cancer, clubbing programmes like screening of common cancers or overall women's health may be more sustainable[9]. Some of the cost-effective solutions for LMICs are creating awareness about causes, early detection measures and preventive strategies of common cancers and early identification and diagnosis of patients with symptoms. Despite these, in general, there is fascination about health care measures such as screening mammography adopted by the HICs. This leads to a pressure on the public healthcare administrators of LMICs to adopt similar interventions with implicit assumptions that the benefits would be replicated.

Breast self-examination (BSE) appears to be the least expensive method. It is likely to reduce mortality only if competently performed and if backed up with appropriate diagnostic follow up[10]. However, field experience shows that even after detailed health education women often forget the method and are highly irregular. Many women in areas with low socio-economic status in Mumbai perceive touching the breast while bathing to be BSE. Two large RCTs on BSE, one from Shanghai[11] and other from St. Pettersberg have not demonstrated any decrease in breast cancer mortality[12]. Major health authorities like the U.S. Preventive Services Task Force, the Canadian Task Force on Preventive Health Care and the World Health Organization have all indicated the absence of evidence about BSE downstaging or reducing mortality due to breast cancers[13-15]. It is felt that BSE may increase awareness and lead to diagnosing smaller tumours and also downstage breast cancers at diagnosis, especially in countries where breast cancers are currently detected at the higher stage. Presently, there is no evidence

regarding this. Even if BSE is undertaken by women in LMICs, it should not convey the false message that this could help them detect breast cancers earlier and would save lives. There is also a possibility of BSE creating anxiety among women. This may in turn lead to unnecessary referrals for diagnostic evaluations. In countries with less medical regulations, BSE may lead to women being easily induced to overconsume medical services[16].

Clinical breast examination (CBE) is a simple and less expensive screening tool and appears promising. The 25 yr follow up results of the Canadian National Breast Screening Study concluded that in the current scenario with adjuvant therapy being available for the management of breast cancers, there is no further reduction in breast cancer mortality in women in the age group of 40-59 yr with the addition of yearly mammograms over and above physical examination or usual care[17]. The findings of three RCTs on CBE screening versus no screening showed smaller tumour detection and downstaging with CBE compared to no screening[18-20]. Among these, the largest and the only completed trial on CBE, wherein CBE was conducted by trained primary healthcare workers in Mumbai, India, demonstrated significant downstaging of breast cancers in all age groups[18,21] and 30 per cent reduction in mortality among women ≥50 yr at the end of 20 yr without any overdiagnosis[22]. The other ongoing RCT from Thiruvananthapuram, India, also showed significant downstaging from CBE[19]. Five observational studies from the 1970s reported five to 10 per cent increase in the breast cancer detection rate by CBE in combination with mammography as compared to mammography alone[23]. Gyawali *et al*[24] have advised against the implementation of mammography screening in low-income countries since it does not improve overall mortality and also leads to unnecessary utilization of scarce financial resources. Instead, LMICs may go for CBE screening which is less expensive and provides similar benefits.

Some of the other imaging techniques that were originally developed for diagnosis have also been investigated for screening breast cancers. These include tomosynthesis, magnetic resonance imaging (MRI) (with or without the administration of contrast material) independently and as adjunct, ultrasonography independently or as adjunct, positron-emission tomography and positron-emission mammography. Overall, none of these are suitable for population-based screening in LMICs. The use of MRI as an adjunct to mammography, in women with high familial risk and BRCA1 or BRCA2 mutation significantly increases the sensitivity but at the cost of decrease in the specificity[25]. The US Preventive Services Task Force (USPSTF) states that the current evidence is insufficient to assess the benefits and harms of breast cancer screening using digital breast tomosynthesis (DBT) as primary screening and also of adjunctive screening using breast ultrasonography, MRI, DBT or other methods in women identified to have dense breasts on an otherwise negative screening mammogram[26].

Cost-effectiveness

Cost-effectiveness analyses can help local health authorities of countries in taking decisions regarding investing their scarce resources. A cost-effectiveness analysis is comparison of the cost of a programme with the health effects it provides. The result is presented as a cost-effectiveness ratio (C/E ratio). To evaluate population-based screening programmes, there is a need to have well-functioning registries in place. All the costs involved in the programme need to be well documented and classified under various programme heads. Various programmes may include different costs to estimate the same; however, it needs to be well defined. For example, the programme may include the cost of invitation, screening and diagnostic work-up among screen positives until a final benign/malignant diagnosis, but not that of treatment to calculate the cost per screen. The cost of personnel can be calculated by multiplying the number of procedures by time per procedure and wages of the involved personnel per time unit. Calculation of the number of life-years saved involves evaluating lives saved at a particular time post-diagnosis, *e.g.* five, 10 yr, *etc*. If we assume that 10 per cent women will primarily be positive on screening mammograms and consider the cost involved in diagnostic evaluations such as biopsies for these women, then the actual cost of programme implementation doubles, compared with the cost of only mammograms[27].

Whenever a screening programme is undertaken by any method, the cost of initial treatment and follow up for cancers is high, since more cancers are expected to be detected by screening and the cost associated with these extra cases would outweigh the cost saved due to downstaging. On the other hand, in the absence of screening, some women with asymptomatic breast cancers may die before experiencing symptoms and

being diagnosed. In order for a screening programme to be cost-effective, the main considerations are the age of women being screened, the age to initiate screening, age to stop screening and the frequency of screening. This has to be decided depending on the burden of the disease, distribution in various age categories and the resources available. Mandelblatt *et al*[28] estimated potential benefits and harms of mammography screening under different screening schedules based on modelling studies and reported that biennial screening mammography while retaining nearly 67-99 per cent advantage of yearly screening, almost halved the number of false-positives.

Participation in the programme has been a strong predictor of the impact of a programme, and death from breast cancer has been more common among non-participants than participants[5]. The European guidelines for quality assurance in mammography screening[29] claim that a 60 per cent attendance rate is acceptable whereas 75 per cent is desirable. In a mammography screening programme in Oslo, Norway, there was considerable variation in the attendance rate between the counties. While the attendance in rural areas was close to 90 per cent, the attendance rate in Oslo was around 70 per cent[30]. This was probably due to the poor access to private mammography services in different areas. The screening programmes in Stockholm and Copenhagen achieved attendance rates similar to those of Oslo[31,32]. In a CBE-based population-level trial in Mumbai, the compliance to the first round of screening was 76 per cent and when three rounds of screening were considered the mean compliance was 71 per cent[33]. Various studies in Mumbai[33-36], Thiruvananthapuram[37], India, in Kenya[38,39], in Mexico[40] and other LMICs have explored the barriers and facilitators for participation in breast cancer screening, referrals and treatment. The compliance rates reported in these studies were in the trial set up, with separate staff appointed for reminders, counselling and follow ups. However, in recent times, there have been debates about the reproducibility of results achieved in trial setups to population-based programmes. A systematic review conducted by Islam *et al*[41] identified lack of knowledge about cancers of the breast and cervix and about the importance of screening as the main barriers for the uptake of breast cancer screening in LMICs. The main facilitators for uptake of screening were related to the opportunities for acquiring knowledge, like educational background, residence in the urban locality, job outside home *etc*[41].

Programmes utilizing mammography as a screening tool turn out to be very resource intensive. To have any kind of assessable impact on reduction in the cause-specific mortality, the compliance of participants at all levels, *i.e.* screening, diagnostics, treatment and follow up need to be good. Japanese government recommended physical examination alone for breast cancer screening[42]. A study conducted in Japan that looked at the cost-effectiveness modelling to compare five breast cancer screening strategies concluded that this was neither the cheapest nor the best in terms of both effectiveness and cost-effectiveness[42]. The projected ratio of cost-effectiveness was USD ($) 2150 per life-year gained (8% of GNI per capita) with two-yearly mammography screenings in the Netherlands[43].

Breast cancer screening in low- and middle-income countries (LMICs)

Zelle and Baltussen[44] conducted a review of the available economic evidence to support the development of global strategies against breast cancer for LMICs and stated that the economic evidence on costs and cost-effectiveness was limited for control of breast cancers in these regions. Cost-effectiveness is influenced by various aspects such as incidence of the disease, its stage distribution and savings on the cost of prevented palliative care. In LMICs the incidence of breast cancer is substantially less as compared to developed countries. Hence, considerably more asymptomatic women would need to be examined to find a true case of breast cancer. The WHO criteria for a health intervention to be categorized as cost-effective is saving yield of one disability-adjusted life year for less than three times a country's gross domestic product (GDP)[45,46]. As the GDP differs in countries globally, mammography may be indicated as cost-effective in countries with higher GDP but not in countries with lower GDP.

The incidence of breast cancer is low in India[1]. Furthermore, mammography screening would be effective only in 30 per cent of the population <50 yr. Hence, the overall yield of screening in terms of breast cancers detected per woman screened would be low. Cost-effectiveness of the programme is to a large extent decided by the total spending on health by a particular country *vis-a-vis* the cost of the proposed intervention. The per capita spending on health in India is $ 81[47]. This is almost the same as the cost of a single mammography screening in the USA. Mammography screening is not estimated to be a cost-effective solution for India[44]. Egypt spent $ 310 per-capita on

health in 2007[47]. While the Medicare reimbursement for the cost of a single mammography screening in the USA or a film mammogram is $ 82 and for a digital mammogram is $ 130. Okonkwo *et al*[43] estimated a C/E ratio of $ 1341 that was nearly 50 per cent of the (GNI) per capita per life-year gained for biennial CBE in India. Black *et al*[48] commented that breast cancer screening with mammography was likely to have a higher harm-to-benefit ratio in sub-Saharan Africa (SSA). CBE and BSE are less resource-intensive and more widely used in the SSA. However, clinical downstaging might be more appropriate and effective approach to breast cancer mortality reduction in SSA, where resources to implement and maintain population-based screening programmes are limited[43].

On evaluation of benefits of mammography screening for LMICs in terms of cost-benefit ratio Corbex *et al*[16] stated that it was unlikely to result in any benefit. This may be due to several factors including 2 to 10 times lower breast cancer incidence, the younger peak of incidence, difficulty in obtaining optimum participation rates and high cost associated with mammographic screening programmes[16]. Okonkwo *et al*[43] performed cost-effectiveness analysis for breast cancer in India based on microsimulation screening analysis model. The model included evaluation of CBE and mammography screening among various age groups and at different time intervals based on projected costs, its benefits in terms of mortality reduction and its effectiveness *vis-a-vis* cost. Accordingly, in India, two-yearly CBE screening was projected to be a cost-effective breast cancer screening method, meeting the WHO criterion. If changed to yearly screening the benefit in terms of cost-effectiveness would not be retained. The authors predicted that annual CBE was nearly as efficacious as biennial mammography screening for reducing breast cancer mortality among ages 40 to 60, while incurring only half the net costs. The estimated cost-effectiveness of CBE screening for breast cancer in India compares favourably with that of mammography in developed countries[44].

Increasing breast cancer awareness

Population-based, organized breast cancer screening services are almost non-existent in LMICs. Women in LMICs present at advanced stages, not only because of lack of facilities but also due to low awareness. Increasing breast cancer awareness through mass education using mass media and education in smaller groups would help in early clinical diagnosis and treatment and would add value to the breast cancer control options in LMICs.

The implementation of Breast Health Global Initiative (BHGI) guidelines[49] was looked into by specialists from various disciplines. The perspective of early detection of breast cancer was related to different parameters such as expenses for public awareness, various tools of screening and assessment goals. The third Global Summit in BHGI in 2007, recognized public education and awareness as the main steps towards the implementation of guidelines for screening, diagnosis and management of breast health in LMICs[49,50].

Raising breast awareness is a laudable goal which should be aggressively pursued by advocacy groups and healthcare systems in LMICs. The limited available resources in some of the LMICs might be better used to raise awareness and encourage more women with palpable breast lumps to seek and receive treatment promptly. Some advocacy groups consider that everything done abroad is the best and needs to be replicated. Hence, a demand is created for mammography-based breast-cancer screening in LMICs facing a severe resource crunch. These decisions should be made with the clear understanding that resources for any programme will be met by compromising resources in other programmes, whereas these decisions need to be primarily established on economics[51].

Summary

The introduction of breast cancer screening in LMICs should be based on the perspective of other health priorities in settings with limited resources. Diagnosis and treatment of symptomatic and screen-positive women are of utmost importance if any benefits of breast cancer screening are to be accrued. In LMICs, treatment facilities may be inadequate and implementation of screening programmes will need to go hand in hand with improvement in diagnostics and management facilities. Not only is the availability and accessibility of services important but also the acceptability of services by overcoming socio-cultural barriers is vital. This can be achieved by incorporating culturally and linguistically appropriate education programmes and informing women about the advantages of screening. Identifying the barriers to early detection at individual, family, community and health services levels is important. LMICs will acquire greater worth for investments by using primary prevention methods such as focussing on tobacco

cessation, encouraging the use of healthier food options and promoting healthier lifestyle changes and then by adding common cancer screening to it. For example, the three-most common cancers in India, breast cancer, uterine cervix cancer and oral cavity cancers may be clubbed together so as not to miss an opportunity once the eligible person is contacted. The awareness programmes for cancer and non-communicable diseases prevention and screening with evidence-based cost-effective strategies would be important. The emerging evidence indicates breast cancer awareness along with biennial CBE by health personnel, medical or paramedical to be the most cost-effective breast cancer control strategy for LMICs.

Selection of an appropriate screening test for population-level screening involves evaluating the test characteristics of the screening tool, assessing its cost-effectiveness, its availability in the region, evaluating its acceptability and also the feasibility of implementing the same in the chosen population. However, choosing an appropriate screening test is only one aspect of the screening programme. The organization of the screening programme in totality, achieving good population coverage, the diagnostic referral linkage, compliance of the screen positives to referrals, the availability of treatment facilities, compliance to treatment for the diagnosed cases, follow up care, quality assurance, documentation of data and ongoing monitoring and evaluation all decide the outcome of the screening programme.

Conflicts of Interest: None.

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