Ann Surg Oncol (2024) 31:1430–1432
https://doi.org/10.1245/s10434-023-14785-6

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – GLOBAL HEALTH SERVICES RESEARCH

Prioritizing Mammography Screening in Developing Countries: Are We Putting the Cart Before the Horse?

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Many low- and middle-income countries (LMICs), including India, Kazakhstan, Lebanon, South Africa, Uzbekistan, and Indonesia, are prioritizing the implementation of population-based mammography screening with the hope of reducing the burden of breast cancer mortality.[1–6] However, those who advocate population-based screening in these countries often fail to recognize that the benefit of breast cancer screening is inextricably linked to the availability of effective breast cancer treatments. That is, to fully discern the benefits of breast cancer screening, effective treatment infrastructures must first be in place. Hence, we believe that prioritizing cancer screening in LMICs is misguided and is akin to putting the cart before the horse. In low-resource settings, priority should be given to the implementation of effective treatment infrastructures, and screening should only be considered after effective treatments are widely available. Moreover, we believe that screening clinical breast examination (CBE), which has been validated as an effective low-cost screening method in India, should be considered as the breast cancer screening method of choice in low-resource settings.[7]

The importance of an effective treatment infrastructure prior to initiation of cancer screening was highlighted in the Philippines screening CBE trial, initiated in 1995.[8] In that trial, the potential benefit of screening CBE could not be discerned because women enrolled in the trial did not have access to effective breast cancer treatments. When this became evident, the decision was then made to discontinue the trial.

First Received: 13 November 2023
Accepted: 28 November 2023
Published online: 19 December 2023

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The intertwined relationship between cancer screening and treatment (i.e., treatment interaction) is best illustrated if we consider three categories of breast cancers: those curable only if screen-detected, those curable with clinical detection, and those that cannot be cured with either screening or clinical detection.[9] Cancers that are curable only if screen-detected may represent a small subset of cancers, but availability of treatments is paramount for screening to have a beneficial effect. Moreover, as treatments improve over time, many patients whose cancers were curable only if screen-detected will eventually be effectively treated even after clinical detection. This is evident in the historical overview of the nine mammography trials. The greatest benefit of mammography screening was seen with the Health Insurance Plan (HIP) trial of New York, initiated in 1963, which showed that screening reduced breast cancer mortality by about 30%.[10] During the era of the HIP trial, the treatment of breast cancer was largely predicated on surgery alone, and the trial seemed to suggest that earlier surgical treatment had a beneficial effect on mortality. The eight subsequent mammography trials demonstrated a diminishing benefit of mammography screening over time, with the three most recent trials (i.e., the Canadian National Breast Screening Studies (CNBSS) I and II, and the UK Age Trial) showing no discernible mortality benefit.[11] The decreasing mortality benefit of screening over time, despite advancements in screening technology, is likely attributable to improvements in breast cancer treatments over the past few decades.[9] The introduction of effective adjuvant systemic and radiotherapy has reduced breast cancer mortality and negated the beneficial effect of screening. Thus, in the developing world, once modern treatments become widely available, screening may have very little effect in further lowering the burden of breast cancer mortality. However, it will nonetheless continue to play an important role in downstaging tumors and thereby improving the quality of life for women.

Although there is considerable interest in widespread implementation of population-based mammography screening, it is not cost effective in LMICs and is associated with two particularly harmful effects for developing countries—overdiagnosis and false positives. Overdiagnosis refers to the detection of cancers that pose no threat to life and would never have been detected in the absence of screening, and there are several ways that this can occur.[12] Some screen-detected cancers may progress so slowly that they might never have become clinically evident during the patient's lifetime. Alternatively, some screen-detected cancers may have never become clinically evident because the patient would have died of other causes before the cancer became clinically evident; this is particularly true for older patients because of competing causes of mortality, and even some younger patients with numerous comorbidities. Finally, investigators have even speculated that some screen-detected cancers may have regressed over time.[13] A recent review for the United States Preventive Service Task Force (USPSTF) concluded that 11–22% of all breast cancer cases in the United States (US) are overdiagnosed because of mammography screening.[14] A highly cited analysis using population-based data suggests that the rate of breast cancer overdiagnosis attributable to mammography screening might be even higher, perhaps as high as 30%, and that up to 70,000 women in the US are potentially overdiagnosed with breast cancer annually.[15] Overdiagnosis results in overtreatment, and in LMICs, this will needlessly direct scarce resources away from important healthcare priorities and overburden their fragile healthcare infrastructures.

False-positives are lesions detected on mammograms that are categorized as suspicious (i.e., Breast Imaging-Reporting and Data Systems [BIRADS] 3, 4, or 5) which, after additional diagnostic work-up, ultimately prove to be benign. Approximately 10.7% of all screening mammograms in the US lead to a false-positive result.[16] The false-positive rates are somewhat lower in Europe, and the difference between the rates observed in the US and Europe may be explained by the medicolegal environment in the US, often resulting in radiologists unwilling to commit to a benign diagnosis. In developing countries with limited financial resources, the additional expenditures needed to work-up false-positive results would needlessly create a significant burden. Both overdiagnosis and false positives attributable to mammography screening are significant concerns in LMICs, as they would needlessly increase healthcare expenditures.

As an alternative, screening CBE, which has been validated in low-resource settings in India as an effective breast cancer screening method, mitigates the risks of overdiagnosis and false-positives. The first screening CBE trial, initiated in 1998, was conducted in Mumbai, India, with 151,538 women randomized to undergo CBE screening versus usual care.[17] The trial showed that biennial CBE screening performed by primary health care workers resulted in significant downstaging of tumors at diagnosis and a non-significant 15% reduction in breast cancer mortality ($p = 0.07$). A similar randomized trial in Trivandrum, India, initiated in 2006, randomized 115,652 women to CBE screening versus usual care.[18] The study failed to demonstrate any statistically significant difference in mortality between the two groups but showed a shift towards an early stage of diagnosis in the CBE group. Furthermore, CBE screening was associated with substantially lower rates of overdiagnosis when compared with mammography screening. In the Mumbai trial, CBE screening showed an expected initial increase in breast cancer cases (an excess of 47 breast cancer cases in the screening arm when compared with the control arm). However, this difference gradually reduced from year 12 and disappeared completely by study year 18 (crude incidence rates of 62.76 and 64.43 per 100,000 women-years in the screening and control arms, respectively), thus demonstrating an absence of overdiagnosis attributable to CBE screening. Furthermore, a 2020 overview evaluating the efficacy of CBE as a stand-alone modality for diagnosing breast cancer also noted that CBE has lower false-positive rates when compared with mammography (1–5% for CBE vs. 7–12% for mammography).[19,20] Thus, the two trials conducted in India have validated CBE as an effective method for breast cancer screening in a low-resource setting after adequate treatments were available.

The implementation of breast cancer screening in developing countries has been a contentious topic for many years. Healthcare policy makers should acknowledge the treatment interaction associated with breast cancer screening and ensure that prior to implementation of any screening intervention in LMICs, effective treatments are widely available. While mammography screening is utilized in developed countries, it is not a cost-effective screening method for implementation in LMICs. Once effective breast cancer treatments are available throughout the population, we believe that CBE screening, which has been validated as an effective screening method in low-resource settings, should be considered as the optimal screening method in developing counties. Screening CBE results in a substantial downstaging of breast cancers at the time of presentation and will undoubtedly serve to improve the quality of life for countless women in the developing world.

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