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REVIEW ARTICLE

Breast cancer screening: review of benefits and harms, and recommendations for developing and low-income countries

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Abstract Breast cancer is the most common cancer in women worldwide. The disease remains a public health concern as recent evidence indicates that the breast cancer burden has increased mainly in developing and low-income countries (DLICs). Despite the demonstrated benefits, the debate about the real benefits and harms of breast cancer screening is ongoing. Many experts believe that the benefits of screening, in terms of reduced breast cancer mortality, outweigh the harms, whereas others think the opposite. In this review, we assess the clinical utility of available screening modalities, present evidence, overdiagnosis, cost-effectiveness, and other pertinent issues. We also examine relevant data from DLICs to underscore the barriers and challenges that impede implementation of screening strategies in those populations. We also provide recommendations concerning rational preventive strategies for breast cancer control for women in DLICs.

Keywords Breast cancer · Screening · Early detection · Developing countries · Low-income countries · Guidelines

Introduction

Breast cancer is the most common cancer in women worldwide. It was recently reported that the global breast cancer incidence has increased from 641,000 cases in 1980 to 1,643,000 cases in 2010, a global annual rate of increase of 3.1 %, with a higher annual change in developing regions [1], where in 2010 among individuals aged 15–49 years, there were 367,000 new patients. There is a prediction that future decades will witness further increase in the number of women diagnosed with breast cancer in developing and low-income countries (DLICs). Breast cancer killed 425,000 women in 2010, of which 68,000 were aged 15–49 years in DLICs [1]. Thus, 45 % of breast cancer diagnosed each year, and more than 55 % of breast cancer–related deaths occur in those countries [2].

The most widely cited reason for the global increase in breast cancer is the "Westernization" of the developing world, for example, increase life expectancy, nutritional changes, decreased physical activities, delayed pregnancy, lower parity rates, and reduced breast-feeding practice [3]. Because there is an inadequate breast cancer awareness in DLICs, most breast cancer are detected in rather advanced stages where treatment would be less effective [4].

Breast cancer in the Kingdom of Saudi Arabia (KSA)

The population-based Saudi Cancer Registry (SCR) was established in 1994. The latest version in 2007 showed that breast cancer constituted 26 % of all female cancer sites at an age-standardized rate of 21.6 per 100,000 women [5]. From 1994 to 2004, the 5-year survival rate was only 64.4 %. Forouzanfar et al. [1] estimated that in 2010, the cumulative probability of incidence and mortality from age 15 to 79 years in the KSA is 2.9 and 0.8 %, respectively, significantly lower rates when compared with those in developed countries.

Despite the present low breast cancer incidence in the KSA, like in many other DLICs, it is expected that over the

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coming few decades, the country will embrace a substantial increase in disease burden [6]. There are several socio-cultural and economic changes, which would make such prediction a reality: growth and aging of the country population, decline in fertility rates [7], older age at first full-term pregnancy, alarming increase in obesity [8], high prevalence of physical inactivity [9], and the adoption of Westernized dietary habits [10].

Data from different regions in the KSA showed that the majority of breast cancer patients are in the age group of 40 to 50 years and are predominantly premenopausal. More than 50 % were stage II and III, whereas ductal carcinoma in situ (DCIS) represented <5 % of cases [6, 11–13].

In the KSA, although there are several pilot mammographic screening projects, the country has no formal nationwide or regional screening projects. A recently published pilot study enrolled 1215 women [14], of whom 16 patients with breast cancer were diagnosed; however, of the entire population, 39 % of the participants were symptomatic. Low utilization of mammography screening was mainly attributed to lack of education and awareness among Saudi women [15].

Breast screening modalities

There are multiple modalities, which are currently in use for breast screening. In DLICs, it is not clear which is the best screening strategy to be employed.

Breast self-examination (BSE)

BSE has been questioned in view of 2 negative randomized trials—one from Russia [16] and the other from China [17]. A meta-analyses of randomized and non-randomized studies have shown that BSE has no effect on mortality from breast cancer [18]. On the basis of these results, a working group of the International Agency for Research on Cancer concluded that evidence that BSE can reduce mortality from breast cancer is insufficient [19]. Nevertheless, BSE is promoted as a tool for increasing public awareness, although there is currently no evidence to support such an endeavor.

Clinical breast examination (CBE)

Although CBE detects some cancers that are missed on mammography, there is no randomized controlled trials have been conducted of CBE in women not receiving other forms of screening. A meta-analysis of clinical trials showed that the sensitivity and specificity of CBC are 54 and 94 %, respectively [20]. The Health Insurance Plan (HIP) trial examined BCE and mammography, and each examination was done in total independence from the other. Results reported for each screening modality showed that 55 % of screen-detected cancers were found by BCE and 77 % was found by mammography [21]. Given the primitive nature of the mammography technology used in the HIP study, mammography and CBE contributed independently to breast cancer detection, with 33 % of cases detected by mammography alone, 45 % with CBE alone, and 22 % with both modalities [22].

Of three randomized trials designed to compare CBE with no screening in countries without screening mammography programs, one had inconclusive results [23] and two are ongoing [24, 25]. The Canadian National Breast Screening Study (NBSS) II is strongly suggestive of such an effect [26]. This trial of women aged 50–59 years who randomized to receiving CBE or CBE plus mammography showed no difference in mortality between the two groups. Therefore, it seems appropriate to consider CBE as an acceptable screening modality in DLICs. It may also be more appropriate for such population is to consider a two-stage approach. The latter was recently tested in a large Egyptian population [27]; 5,900 women aged 25–65 years received surgeon's clinical examination, and abnormal clinical findings were found in 3.2 % (191 patients). The 191 women then underwent a second stage of examination that included repeat clinical examination plus ultrasonography and/or mammography. The investigators identified 18 breast cancers at an estimated cost of approximately US$415 per cancer case detected.

Screening film mammography

Ravert et al. [28] recently published a literature review of articles, which specifically addressed various screening modalities for the detection of breast cancer. The authors reported that the specificity for mammography ranged from 65.2 to 99.5 % in studies that stated specificity as an outcome, whereas the sensitivity ranged from 13 to 77.6 %.

High radiological breast density reduces mammographic sensitivity [29]; it is usually lower than 70 % in women under 50, whereas the positive predictive value of mammography increases with age because of increasing incidence and improved test performance [30]. Mammography density is usually greater among premenopausal women, which partly explains the lower sensitivity of mammography screening in young women. Radiologist's experience, technical quality, and the screening interval also influence mammographic sensitivity.

Many women with abnormal mammographic test results will not have cancer (false positive). Elmore et al. [31] estimated that 56 % of women screened annually, beginning at the age of 40 years, will be falsely identified as having cancer. It is to be understood that false-positive rates vary widely,

from a low 2 % in the Netherlands, 4 % in the UK, and up to 11 % in some areas in the USA [32]. The age of the screened population and the nature of subsequent diagnostic interventions can partially explain the variability of reported false-positive rates. Castells et al. [33] reported on cancer detection in subsequent screening participations in women with initially false-positive results. The study showed that those undergoing a fine-needle aspiration cytology or a biopsy had a higher cancer detection risk than those involving additional imaging procedures alone (odds ratio [OR] = 2.69).

False-negative mammography is also an important clinical problem. Weinstein et al. [34] prospectively compared cancer detection of digital mammography, breast ultrasound, and contrast-enhanced magnetic resonance imaging (MRI) in 609 high-risk women previously screened negative by film screen mammogram. The overall cancer yield on a per-patient basis was 3.0 %. The cancer yield by modality was 1.0 % for film screen mammogram, 1.2 % for digital mammography, 0.53 % for breast ultrasound, and 2.1 % for MRI. The authors concluded that the addition of MRI to mammography in the high-risk group has the greatest potential to detect additional mammographically occult cancers. However, this conclusion may be applicable only to high-risk women; moreover, among 48 biopsies performed, cancer was detected in 12 (9 invasive tumor, and 3 DCIS), that is, MRI was associated with 3 in 4 false-positive tests.

Digital mammography

In the Digital Mammographic Imaging Screening Trial [35], almost 50,000 asymptomatic women 40 years of age or older underwent digital and film mammography, and the two techniques showed similar sensitivity (70 and 66 %, respectively) and specificity (92 % for both). However, in women under the age of 50 years, digital mammography was significantly more sensitive than film mammography (78 vs. 51 %). However, this low sensitivity rate for film mammography is below the population-based average of 68 % [36]. Moreover, the 10 studies that compared digital to film mammography showed conflicting results, and it is still unknown whether digital mammography would not lead to more false-positive results and overdiagnosis [37], and therefore, digital mammography could not be recommended for mass screening; besides, digital screening mammography is an expensive diagnostic tool.

A simulation model showed that all-digital mammography cost $331,000 per quality-adjusted life-year (QALY) gained relative to all-film mammography [38].

Breast ultrasonography

Breast ultrasonography is commonly used as an additional procedure to complement mammography. Ravert et al. [28] reported that the specificity for ultrasound ranged from 77.5 to 96.8 %, whereas the sensitivity ranged from 13 to 100 %. Ultrasound particularly has a high diagnostic utility among women with dense breast [39, 40]. The modality has been reported to result in up to a 30 % absolute increase in the detection of invasive cancer in women with dense breasts, for whom the sensitivity of mammography is reduced and the risk of cancer is increased [40–42]. Yet, the rate of false-positive results ranges from 2.4 to 12.9 %, when compared with 0.7–6.0 % for mammography. Therefore, the available data indicate that breast screening using ultrasonography only would result in an unacceptably high false-positive rate and cannot be recommended as a stand-alone modality. Moreover, the diversity of the reported sensitivity and specificity rates attests to the primary disadvantage of sonography of being highly operator dependent.

Breast MRI

In the review published by Ravert et al. [28], the specificity for breast MRI ranged from 59.4 to 95 %. Although the use of MRI more than doubles the diagnostic sensitivity when used to screen women at high risk for breast cancer, it is not recommended for screening the general population because of the higher rate of false-positive results and higher cost [43]. Besides, MRI frequently discovers lesions of uncertain clinical significance.

In April 2007, the American Cancer Society (ACS) released guidelines for the use of MRI as an adjunct to mammography in breast cancer screening [44]. The guideline panel recommended annual breast MRI for the following specific, high-risk groups: (1) breast cancer gene (BRCA) mutation carriers; (2) first-degree relatives of known BRCA mutation carriers but untested; and (3) women with an approximate lifetime risk from 20 to 25 %. Despite those evidence-based recommendations, MRI screening either alone or adjunct to other imaging tools could not be recommended for DLICs because of its high cost, lack of adequate number of MRI units, scarcely of radiologists with sufficient MRI experience, and lack of useful clinical utility when used for the general population.

Examining the benefits of breast screening

Randomized trials

There are two requirements for screening to reduce the rate of death from cancer. First, screening must advance the time of diagnosis of cancers that are destined to cause death. Second, early treatment of these cancers must confer survival advantage. Before examining the potential benefits

from breast cancer screening, it is critical to distinguish the differences between "early detection" and "screening." Early detection is the diagnosis of breast cancer in symptomatic women at a time when the disease is potentially curable. On the other hand, screening for a disease means using tests on asymptomatic women who are unaware of the conditions and who have not specifically sought medical intervention [45]. Mammography, which detects breast cancer at earlier stages, is a major step in reducing mortality as it was estimated to prevent approximately 20–40 % of all deaths from breast cancer among women undergoing screening mammography [46–48].

The five Swedish trials used mammography only. Four trials used various types of individual randomization procedures, and the Two-County Trial randomized women by geographical cluster [49]. In the later study, 77,080 women aged 40–74 years randomized to mammographic screening and 55,985 women randomized to no invitation. Mammographic screening achieved a significant 29 % reduction in breast cancer mortality (relative risk [RR] = 0.71, 95 % confidence interval [CI] = 0.60–0.83). That benefit remained at 18 years of follow-up. Age-specific analyses show a smaller and later mortality advantage in women aged 40–49 years.

The two Canadian trials NBSS II and I compared mammography screening to CBE (women 40–49) or CBE (women 50–59). The two trials found no decrease in breast cancer mortality associated with mammography screening [50]. There were criticisms of the two Canadian trials concerning suboptimal mammography quality and method of participants' selection; however, independent investigators showed that those concerns were unsupported. For instance, the size of breast cancers in the Canadian trials was on average smaller than in the Two-County Trial [51]. Such difference would not have occurred if the quality of mammography in the Canadian trials had been suboptimal.

Prompted by the inconsistent results, a Cochrane group conducted a systematic review of all breast screening randomized trials [52, 53]. From 1962 to 2006, there were altogether 10 randomized trials, while the eleventh trial (Edinburgh, UK) was considered as unhelpful because of socioeconomic imbalances in cluster randomization groups [53]. The authors considered that the randomization methods adopted by all trials but three (NBSS I, NBSS II, and Malmö I) were flawed. The Cochrane report concluded that based on all trials, the RR reduction is 20 %, but as the effect is lower in the highest quality trials, a more reasonable estimate is a 15 % RR reduction. Based on the risk level of women in those trials, the absolute risk reduction was 0.05 %. The report also concluded that screening leads to overdiagnosis and overtreatment, with an estimated 30 % proportional increase or an absolute excess risk of 0.5 % [53].

Despite the conclusions of that meta-analysis, the heated debate about breast screening continued. The Independent UK Panel on Breast Cancer Screening was convened to reach conclusions about the benefits and harms of breast screening on the basis of a review of published studies and other available evidence [54]. The approach assumed that women who are first invited to screening at the age of 50 years and continued to be invited for 20 years would gain no benefit in the first 5 years, but that the mortality reduction would continue for 10 years after screening has ended. This assumption yielded the estimate that for every 235 women invited to screening, one breast cancer death would be prevented, representing 43 breast cancer deaths prevented per 10,000 women invited to screening.

The results derived from the meta-analysis and the UK Panel suggest that the benefit from screening is probably overestimated, while the harm is perhaps underestimated.

Systematic review of observational evidence of breast cancer screening

Recently, Harris et al. [55] reported a systemic review of observational evidence to provide recommendations concerning the implementation of breast cancer screening. Of seventeen eligible studies for women ages 50–69 years, five studies found no small effect of screening (0–12 % RR reduction in breast cancer mortality), 4 found a large effect (greater than 33 % reduction), and 8 found a moderate effect (13–33 % reduction). There were concerns about quality in all studies. The authors concluded that current observational evidence shows that breast cancer screening reduces breast cancer mortality; however, the magnitude of the effect is probably smaller than that predicted from randomized controlled trials [55]. Despite the observational nature of such data, the derived conclusions may truly reflect the effect of screening programs.

Service mammographic screening

In literature, there are several published reports of the results of service screening programs. The authors from British Columbia, Canada, analyzed the impact of annual service mammographic screening on breast cancer mortality among women who volunteered to be screened by the screening mammography program of British Columbia [56]. The mortality ratio was 0.60 (95 % CI 0.55, 0.65) for all ages combined ($P < 0.0001$). The mortality ratio in women aged 40–49 years at first screening was 0.61 (95 % CI 0.52, 0.71), similar to that in women over 50 (mortality ratio = 0.63). The authors drew two major conclusions: (1) service screening was effective in reducing breast cancer mortality among women 40–79 years old; and (2) relative mortality reduction among women 40–49 years old was

similar to that among women 50–79 years old. The mortality reduction of 40 % in the Canadian study for all women 40–79 years old was comparable with reports from other service screening studies [57, 58]. These data show that modern, high quality, high attendance, organized breast screening can achieve breast cancer mortality reduction equal to or greater than that observed in randomized trials.

On the other hand, a service screening program in Norway was started in 1996 and reported a different conclusion [59]. In this study, the death rate was reduced by 7.2 deaths per 100,000 person-years in the screening group when compared with the historical screening group and by 4.8 deaths per 100,000 person-years in the non-screening group when compared with the historical non-screening group for a relative reduction in mortality of 10 % in the screening group. The study concluded that the difference in the reduction in mortality between the current and historical groups attributed to screening alone was 2.4 deaths per 100,000 person-years or a third of the total reduction (7.2 deaths). Self-selection bias could explain the contradictory outcome from this Norwegian study, because there is no pre-study randomization into study and control groups. However, in the British Columbia study, the investigators corrected for this bias and reported a slight increase in the mortality ratio to only 0.76.

Breast screening schedule

The cost-effectiveness of the frequency of breast screening has always been a question of a substantial debate. A provocative change from the 2002 US Preventive Services Task Force (USPSTF) guidelines to the 2009 guidelines was a switch from recommending screening every 1–2 years to screening every 2 years [60–62]. The Breast Cancer Working Group of the Cancer Intervention and Surveillance Modeling Network (CISNET) used 6 different models to evaluate U.S. breast cancer screening strategies under a variety of policies [63]. The study reached several conclusions (1) screening biennially maintained an average of 81 % (67–99 %) of the benefit of annual screening with almost half the number of false-positive results; (2) screening biennially from ages 50–69 years achieved a median 16.5 % (15–23 %) reduction in breast cancer deaths versus no screening; and (3) initiating biennial screening at the age of 40 years (vs. 50 years) reduced mortality by an additional 3 % (range 1–6 %), but consumed more resources, and yielded more false-positive results.

Moreover, other studies have also shown that there was little difference in the likelihood of detecting advanced breast cancer with annual versus biennial screening programs [64, 65]. In an analyses based on data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute [66], a 2-year screening interval was not associated with an increased risk of late-stage disease in women 50 years of age or older, when compared with a 1-year screening interval. When compared with screening every 2 years, annual screening prevented about 2 additional deaths from breast cancer per 1,000 women screened.

The lack of significant survival advantage of annual screening was attributed to the fact that slow-growing tumors are much more common than fast-growing tumors, and the ratio of slow- to fast-growing tumors increases with age, so that small survival benefit is lost between screening annually versus biennially [67].

Thus, if there is enough justification and resources for screening mammography in a given DLIC, it may not be necessary to adopt an annual screening strategy and longer interval between screening encounters may be equally effective and less costly.

At what age screening should start? And at what age it should end?

The efficacy of screening women 40–49 years old has always been a major issue in the mammography dispute. The basis of the argument was that breast cancer incidence is much lower in younger women and that too few of those younger women were included in the randomized trials. A statistically significant reduction in breast cancer mortality in this group did not appear until many years later than that for older women. Mammographic screening every 2 years of women in their 40 s will detect 2 out of 3 cancers and will reduce risk of death from breast cancer by 15 %. Nevertheless, there is about a 40 % chance a woman will be called back for further imaging tests and a 3 % chance that she will undergo biopsy, with a benign finding.

Of the earlier studies, only one, the HIP trial, has established the usefulness of breast cancer screening in women aged 40–49 years. Yet, on a longer follow-up, the study concluded that the difference in those young women occurred in the subgroup with breast cancer diagnosed after these women had passed their 50th birthday [22]. On the other hand, support for screening all women 40–49 years old is found in the results of a Swedish service screening study that found, even after adjustment for self-selection bias, there was a 29 % mortality reduction for screening women 40–49 years old [68]. However, the design of this study was recently criticized [69, 70]. There were several methodological concerns about when to adjust between those invited to screening and the controls during the pre-screening period, the method used in matching, and the adjustment for lead-time bias.

The proponents for screening younger women argued that a statistically significant reduction in breast cancer mortality in this group might not appear until many years later than that for older women. In DLICs, if a screening mammography is to be adopted, it may have to include younger women for two reasons. First, the population pyramids in DLICs show larger proportions of younger women compared with that seen in developed countries. Second, the peak age at breast cancer incidence tends to occur one or even two decades earlier than that in the developed world.

For older women, it is important to balance any benefits of screening against probable harms. Mandelblatt et al. [63] have shown that screening strategies beyond the age of 69 years remained effective, however, with low incremental gains over strategies that stop screening at earlier ages and with greater harms. This conclusion is consistent with previously reported results of screening from observational studies and modeled data [71–73]. The cost of screening older women is also a concern. The USPSTF reported a systemic review concerning the cost-effectiveness of screening mammography beyond the age of 65 years [74]. Results from 10 included studies showed that extending biennial screening to the age of 75 or 80 years would cost $34,000 to $88,000 per life year gained, compared with stopping screening at the age of 65 years.

It seems that screening older women may not be cost effective, and it is not recommended in many Western countries. On the other hand, in DLICs, where there are fewer older women at risk and that risk is proportionally higher than that in younger women, breast screening of elderly women may be more cost effective. Nevertheless, because of the shorter life expectancy in DLICs, detection of breast cancer in old women may not translate into a true survival advantage. At present, there is no evidence to support this hypothesis, and further research may prove or refute this assumption.

Breast screening of high-risk patients

BRACA mutation carriers

It is important to identify the group of women who are at high risk and who require earlier, more sensitive, and more frequent screening than do women at lower risk [75]. Although BRCA mutation carriers are at the highest risk of developing breast cancer, women with increased familial risk of breast cancer without BRCA mutation may harbor breast cancer susceptibility genes that yet to be characterized. MRI screening for high-risk women is highly sensitive and can detect cancers that are missed on mammography [76–79]. However, none of the randomized, controlled trials of mammography screening stratified women by risk, and, to date, no randomized, controlled trial has proven that earlier detection among high-risk women using MRI actually will result in lives saved.

In a simulated Markov model of cohort of women aged 30–65 years, who tested positive for BRCA1 or BRCA2 mutations, Grann et al. [79] compared outcomes of mammography with and without MRI, prophylactic oophorectomy with and without mastectomy, mastectomy alone, and chemoprevention. The analysis suggested that among BRCA1/2 mutation carriers, prophylactic surgery would dominate or be more cost effective compared with chemoprevention and screening. Nevertheless, annual screening with MRI and mammography was the most effective strategy as it was associated with the longest quality-adjusted survival, but it was also very costly.

Women with increased breast density

Breast density may mask non-palpable cancers presenting on mammography as a mass or architectural distortion but is less likely to mask calcification. Authors examined the association between the measured percentage of density in the baseline mammogram and the risk of breast cancer in 1,112 matched case–control pairs [80]. Compared with women with density in less than 10 % of the mammogram, women with density in 75 % or more had an increased risk of breast cancer (OR = 4.7), whether detected by screening (OR = 3.5), or less than 12 months after a negative screening examination (OR = 17.8). The results suggest that annual screening examinations in women with extensive mammographic density are not likely to increase the rate of cancer detection. On the other hand, digital mammography [35], ultrasonography [39], and MRI [81] may increase the detection of cancer in women who have extensive mammographic density.

DCIS

The diagnosis of DCIS was rare before the introduction of screening mammography and now accounts for approximately 25 % of all cases of breast cancer, with more than 90 % of DCIS cases detected only by imaging [82]. The proponents of breast cancer screening use that data to reinforce the benefits from screening.

The pertinent question, however, is not whether DCIS progresses to invasive cancer but whether it might progress to an invasive cancer that causes symptoms within the lifetime of the woman concerned. Progression will depend mainly on the age of the woman, her life expectancy, and possibly other factors, such as hormonal exposure and

obesity. Thus, in the diagnosis of DCIS with a screening program, one must draw the balance between the potential benefits for some women and the risks for others of the treatment of a disease that would never have affected them in their lifetime.

Breast screening and effects on breast cancer stage distribution

Mammographic screening aims to detect cancer at an earlier stage; therefore, if reduction in breast cancer deaths is induced by mammography screening, then decreases in advanced breast cancer incidence should also be evident. Nonetheless, published data showed conflicting results.

A systematic review of the trends of advanced breast cancer incidence in areas where mammographic screening was in operation for at least 7 years and where participation to screening was high was recently published [83]. Relevant published data from 14 areas in 10 Western countries were included. Age-adjusted annual percent changes in the incidence of advanced disease were stable or increasing in 10 areas (20.5–1.7 %), and in 4, there were transient downward trends followed by increases back to pre-screening rates. The study concluded that trends in advanced breast cancer incidence do not support a major role for screening in the decrease in mortality.

Autier et al. [84] estimated the incidence of advanced breast cancer in West Midlands from 1989 to 2004, UK, where breast screening of women of 50–64 years started in 1988. The incidence rates of lymph node-positive breast cancer increased from 1989 to 1992, decreased from 1993 to 1995, and from 1996 to 2000, they returned to pre-screening levels. Moreover, the incidence of cancer greater than 5 cm remained stable from 1989 to 2004. Based on those results, the authors suggested that the breast screening did not play a significant role in reductions in mortality caused by breast cancer.

In another study, Chen et al. [85] investigated survival benefits of breast cancer screening beyond stage shift using data from three large breast cancer screening trials (HIP and two Canadian NBSS I/II). The authors reported that breast cancers detected by screening mammography had a shift in stage distribution to earlier stages. Patients with interval cancers had a 53 % greater hazard of death from breast cancer compared with patients with screen-detected cancers, and patients with cancer in the control groups had a 36 % greater hazard of death than patients with screen-detected cancer. Therefore, there was a survival benefit beyond stage shift for patients with screen-detected breast cancers compared with patients with breast cancers detected otherwise.

Recently, Bleyer and Welch [86] used SEER data to examine trends from 1976 through 2008 in the incidence of early-stage breast cancer (ductal carcinoma in situ and localized disease) and late-stage breast cancer (regional and distant disease) among women 40 years of age or older. While introduction of screening mammography in the US resulted in doubling of the annual number of cases of early-stage breast from 112 to 234 cases per 100,000 women, the rate at which women present with late-stage cancer has decreased by only 8 %. The authors also estimated that only 8 of the 122 additional early-stage cancers diagnosed are expected to progress to higher stages.

Analysis of these data suggests that while there is a true shift toward earlier stages, however, this shift may be only transit; besides, it is associated with less change in the rate of detection of more advanced disease. On the other hand, in DLICs where advanced breast cancer stages predominate, it is plausible that screening may lead to clinically useful stage shift.

Contribution of screening and adjuvant treatment to reduction in breast cancer mortality

There is a continuing debate about the relative and absolute contributions of screening mammography and current adjuvant treatment to the reduction in breast cancer mortality. To address this perplexing debate, a consortium of investigators developed seven independent statistical models of breast cancer incidence and mortality in the United States from 1975 to 2000 [87].

The percentage of the total reduction in the rate of death from breast cancer attributed to screening varied in the seven models from 28 to 65 % (median, 46 %), with adjuvant treatment contributing the rest. All seven groups concluded that both screening and treatment have contributed to the observed decline in the rate of death from breast cancer.

In DLICs, opportunities for early detection and treatment are often unavailable, unaffordable, or inaccessible because of multiple resource-constrained settings and many other barriers. Therefore, the contribution of adjuvant therapy to improved breast cancer outcome may be significantly different from that reported in the West.

Potential harms of breast screening and the advisories' views

For each screening test done, the chance of finding and effectively treating an early cancer is quite low. Likewise, the chance of causing harm, such as a false-positive screen

followed by an invasive test resulting in complications, is unlikely but probable.

Some women have pain with mammography, which is sometimes enough to discourage them from further participation. About 4 % of women attending for screening are recalled for repeat mammography and possible biopsy [88]. Of those women, nearly 1 in 5 will have cancer; of the remainder, nearly 70 % will need only further imaging, and 30 % a biopsy. Additionally, the adverse psychological results of a breast cancer diagnosis and subsequent treatment have been well documented [89].

Breast cancer incidence generally increases with screening coverage, first because some cancers are detected earlier (lead time), and second, because a proportion of screen-detected cancers are slow growing or indolent small tumors that would probably have never become clinically apparent (length-time) [90]. If lead time was the true underlying reason, the total number of breast cancers diagnosed in a population over a 10- or 20-year period after screening start should remain constant. In this respect, the screening-induced increased incidence should be temporary and, after several years, incidence should come back to levels close to pre-screening levels. Hence, the main reason of increased incidence is not lead time, but length time, suggesting that additional cancers found after screening start are rather slow-growing tumors with low malignant potential.

The USPSTF calculated the number needed to screen to prevent one death from breast cancer after approximately 14 years of observation [61]. The numbers were 1,224 for women 40–74, 1,792 for women 40–49, and 838 for women 50 years old at the start of screening. Using results from the age trial [91], the number of women 39–41 at screening start needed to be screened and followed during 13 years was 1,785.

Adversaries of screening argued that that mammography may not be an appropriate screening test in DLICs because the procedure is expensive, requires skilled manpower, needs stringent quality control, and on the whole is a complex process [92]. In addition, because the median age at diagnosis of breast cancer is approximately 10 years younger in DLICs than that in the developed world, and because mammography is less effective in women below the age of fifty years, this test may not significantly affect mortality in those populations.

Radiation risk

Another concern about breast screening is related to radiation-induced risk [93]. For women over 50 years of age, the benefits of mammography greatly outweigh the risk of radiation-induced breast cancer. In addition, annual mammography for women aged 30–39 years who carry breast cancer susceptibility gene or who have a strong family breast cancer history has a favorable benefit-to-risk ratio. Mammography is estimated to detect 16–18 breast cancer cases for every one induced by radiation. Conversely, mammography for women under 30 years of age has an unfavorable benefit-to-risk ratio due to the challenges of detecting cancer in younger women, the aggressiveness of cancers at this age, the potential for radiation predisposition at younger ages, and the greater cumulative radiation exposure [93].

In another study, Barrington de Gonzales et al. [94] estimated the risk of radiation-induced breast cancer for mammographic screening of young women with BRCA gene mutations. Based on an assumption of a 15–25 % reduction in mortality from mammography, the authors concluded that such a reduction is not considerably greater than the risk of radiation-induced breast cancer mortality when screening before the age of 34 years. Moreover, there would be no net benefit from annual mammographic screening of BRCA mutation carriers at ages 25–29 years.

These data suggest that any risk of radiation-induced breast cancer for mammography is relatively small and may be higher among younger population and those who harbor mutation risk genes.

Overdiagnosis

Mammography screening detects many non-life-threatening cancers (length time bias). This phenomenon will increase the overall prognosis of breast cancers and make believe that lives have been saved, when in reality, mortality did not change [95]. This adverse consequence of screening is called overdiagnosis [19]. The problem is to judge whether a particular woman has had an overdiagnosed cancer.

The magnitude of screen-induced overdiagnosis is a subject of great disagreement. In a meta-analysis of randomized trials, the Independent UK Panel on Breast Cancer Screening estimated that the excess incidence was 11 % (95 % CI 9–12) when expressed as a proportion of cancers diagnosed in the invited group in the long term, and 19 % (95 % CI 15–23) when expressed as a proportion of the cancers diagnosed during the active screening period [54]. The Panel also estimated that for every 10,000 UK women aged 50 years invited to screening for the next 20 years, 43 deaths from breast cancer would be prevented and 129 cases of breast cancer, invasive and non-invasive, would be overdiagnosed. On the contrary, in the Swedish randomized trials, overdiagnosis accounted for only 1 % of screen-detected cancers [96].

The CISNET study that analyzed six prediction models showed that biennial strategies decrease the rate of overdiagnosis, but by much less than one half. The absolute estimate of overdiagnosis varied between models depending on

whether DCIS was or was not included and on the assumptions related to progression of DCIS to an invasive disease [63].

Exploring SEER data from 1976 through 2008 estimated that breast cancer was overdiagnosed in 1.3 million U.S. women over three decades, and in 2008 only, this accounted for 31 % of all breast cancers diagnosed [86]. The authors suggested that screening is having, at best, only a small effect on the rate of breast cancer mortality.

The contrasting reported overdiagnosis rates in screening programs is probably attributed to multiple factors including age at which screening starts, underlying breast cancer risk in the studied population, and the method used to estimate overdiagnosis. For example, using different estimation models, the Independent UK Panel reported different overdiagnosis rates, for example, 14.1 % using one method to as high as 29.4 % when another method was tested in the same population [54].

Estimation of overdiagnosis from observational studies is another challenge. Analysis of the nationwide mammography screening program in Norway showed that 15–25 % of cases of breast cancer are overdiagnosed, translating to 6–10 women overdiagnosed for every 2,500 women invited [97].

Cost-effectiveness of breast screening

Only few studies have assessed cost-effectiveness of the breast cancer screening activities in DLICs [98, 99]. Authors used a microsimulation model to estimate the costs of screening, its effects on mortality, and its cost-effectiveness in India [99]. The authors reported that a single CBE at the age of 50 years had an estimated cost-effective ratio of international $793 per life year gained and a mortality reduction of 2 %. The cost-effective ratio increased to international $1135 per life year gained for every 5-year CBE and to international $1341 for biennial CBE, with reductions in breast cancer mortality of 8.2 and 16.3 %, respectively. The investigators concluded that annual CBE performed from ages 40–60 was almost as effective as biennial mammography screening for reducing breast cancer mortality at only half the net costs.

Using a Markov model, Wong et al. estimated the cost-effectiveness of mass biennial mammography in Hong Kong Chinese women [100]. The analysis showed that biennial screening resulted in a gain in life expectancy ranging from 4.3 to 9.4 days compared with no screening at an incremental cost of US$1,166 to US$2,425 per woman.

In Western world, several cost-effective analyses were published. In New Zealand, using a microsimulation mode explored the cost-effectiveness of mammography screening relative to no screening and examined the change in costs and benefits of various scenarios [101]. The model showed that although mammography screening does not "save money" overall, the cost per year of life saved for a range of policies compared favorably with other health services. Screening women 50–64 years of age at 3-yearly intervals was the most cost-effective screening strategy with a net cost of New Zealand $105,714 and $26,541 per life saved and per cancer detected, respectively.

In DLICs, in view of a relatively low incidence of breast cancer, many women will have to be screened to detect one breast cancer, and hence, a screening program may not be cost effective and would be more costly per each cancer-detected case compared with that in the developed world. Moreover, mass screening programs cannot be implemented in those countries where there are other equally deserving and competing healthcare needs within the limited available resources.

Barriers to breast screening in DLICs

Concerning breast cancer, DLICs share two main features. First, the incidence of breast cancer is considerably lower than that in the developed world. Second, awareness about breast cancer is significantly low [102]. The low incidence of breast cancer means that we need to screen many more women to detect a cancer. Screening therefore may appear to be a relatively waste of already limited resources.

A high level of compliance is essential for the success of any preventive intervention. In DLICs, the absence of a high level of awareness, the necessary compliance may not be accomplished. In addition to compliance to the screening procedure, adherence is also crucial for the subsequent steps of screening programs.

The Breast Health Global Initiative (BHGI) identified education and cultural values as important aspects for breast cancer screening practices in DLICs [103]. In Bangladesh, women with higher educational levels were more likely to know about BSE, about mammograms, and to practice BSE compared with those with lower educational levels [104]. Surprisingly, in a sample of 376 educated females in the KSA, the authors reported that more than half of the women showed a limited knowledge about the risk factors of breast cancer [15]. The authors also identified the negative influence of low knowledge on the practice of BSE. Regular performance of screening behavior such as BSE varied from less than 10–80 %, depending on education, occupational, and socioeconomic status [105, 106]. The important role of education was also illustrated from Iran where 100 women with a family history of breast cancer were equally randomized between interventional educational sessions versus no intervention [107]. After educational sessions, breast self-examination

and clinical examination practice rates were elevated in the intervention group.

Several studies addressed additional obstacles for implementation of screening program in DLICs [108–110]. The most common barriers include lack of knowledge, sociodemographic factors, psychosocial factors, social and cultural factors, conservative attitudes on women's bodily experience, stigma, misconceptions, lack of support by family for women diagnosed with breast cancer, and lack of available testing and treatment facilities.

Therefore, a successful screening program in DLICs necessitates the identification of local potential barriers and the development of effective strategies to address them.

Communicating benefits and harms

Communicating benefits and harms involved with cancer screening presents significant challenge [111].

It has been pointed that the information offered to women invited breast screening programs lacks balance, omits information on harms, and substantially exaggerates the benefit [112].

During a clinical encounter, communicating the best current evidence is only the first step. The clinician must describe what the intervention is and why a woman may participate. To avoid information overload, communication strategies must be targeted and simplified. Because of lack of adequate epidemiological data about breast cancer burden in many DLICs, communicating the estimates of absolute risk, relative risk, and number needed to screen would constitute a formidable challenge.

Alternative cost-effective interventional strategies for DLICs

In DLICs, raising breast cancer awareness may be the single most cost-effective strategy to combat the disease. Efforts should emphasize educating women about breast cancer symptoms and the value of BSE. Alleviating fear about breast cancer treatment and reducing stigma of the disease are equally important. Despite the universal acceptance of the benefit of breast cancer awareness as an effective preventive strategy, there are only a few published reports that fully described successful interventions [113].

Fighting obesity in DLICs is an achievable breast cancer preventive strategy because obesity is a well-established risk factor for many common cancers including breast cancer [114]. In addition to the impact of obesity on disease incidence and progression, concern has been raised regarding compromising dosing of therapy in obese patients [115] and interfering with the ability to deliver endocrine and radiation therapy [116].

Physical inactivity is another attainable modifiable lifestyle risk factor. Physical inactivity may not be only a significant contributing factor for breast cancer incidence [117], but it may also contribute to poorer outcome for those who have the disease. In a recently published meta-analysis, we have estimated that adopting appropriate post-diagnosis level of physical activity may reduce breast cancer deaths by 34 % and all causes mortality by 41 % [118].

Breast screening recommendations for DLICs

Simply declaring screening as a solution without an adequate diagnostic and therapeutic infrastructure to support, it is destined to fail in DLICs. With all the information at hand, the Global Summit Early Detection Panel and the BHGI [119] formulated practical recommendations. They stratified national health resources according to a 4-tiered system (basic, limited, enhanced, and maximal) based on available resources relevant to program implementation (Table 1).

Guided by the initiative proposal, and the available evidence concerning the benefits and harms of breast screening, we propose the following recommendations to guide breast cancer control in DLICs:

1. Accurate incidence, mortality, and survival data are necessary to be determined for prioritization, resource distribution, and appraisal of controlling plans. Therefore, we recommend that DLICs should consider establishing regional population-based cancer registries. Without accurate epidemiological data, we would not be able to determine the actual burden of cancer in any given society. To overcome barriers that may face the implementation of population-based registries, hospital-based statistics may be an acceptable alternative because of the relative ease with which data are collected and in the range and completeness of this information. Cancer registration should not be considered as a luxury endeavor even in countries with limited resources. Cancer is already a significant health problem in DLICs, and one that is likely to increase in future, and secondly because the presence of an adequate information system is a fundamental part of any cancer control strategy.
2. Promoting breast cancer awareness is the essential first step and the most cost-effective controlling strategy. There is no single approach that suits all communities, however, determining the most effective strategies depends on the prevailing barriers, for example,

Table 1 Early detection resources allocation and evaluation goals as proposed by the Global Summit Early Detection Panel and the Breast Health Global Initiative [119]

Level of resources	Public education and awareness	Detection method	Evaluation goal
Basic	Development of culturally sensitive, linguistically appropriate local programs for target population to teach value of early detection, breast cancer risk factors, and breast health awareness (education and self-examination)	Clinical history and CBE	Breast health awareness regarding value of early detection in improving breast cancer outcome
Limited	Culturally and linguistically appropriate targeted outreach/education encouraging CBE for age groups at risk administered at district/provincial level using healthcare providers in the field	Diagnostic breast US +/− diagnostic mammography in women with positive CBE Mammographic screening of target group*	Downsizing of symptomatic disease
Enhanced	Regional awareness programs regarding breast health linked to general health and women' s health programs	Mammographic screening every 2 years in women ages 50–69[a] Consider mammographic screening every 12–18 months in women ages 40–49[a]	Downsizing and/or downstaging of asymptomatic disease in women in highest yield target groups
Maximal	National awareness campaigns regarding breast health using media	Consider annual mammographic screening in women aged 40 years and older Other imaging technologies as appropriate for high-risk groups	Downsizing and/or downstaging of asymptomatic disease in women in all risk groups

CBE clinical breast examination, *US* ultrasonography

[a] Target group selection for mammographic screening should consider breast cancer demographics and resource constrains within the population

education, sociocultural, economical, accessibility to healthcare facilities. [120]. Raising awareness may be achieved using various interventions such as building strong partnerships with religious and community leaders in rural areas [113], training social workers and school teachers, establishing breast cancer culture and advocacy, launching targeted media campaigns.

3. Breast cancer awareness efforts should be able to achieve a clear understating of benefits and harms to all potential participants regardless of their age, educational level, socioeconomic status, cultural beliefs, or religious values.
4. In DLICs, developing adequate treatment facilities is more likely to affect breast cancer mortality than any screening program alone. Easy accessibility to cancer care units or bringing treatment close to patients is essential for the success of any breast cancer control program. Without adequate effective treatment options, screening would be a pure waste of resources.
5. Health authorities and policy makers in DLICs should realize that comprehensive screening programs are expensive endeavor because of the low incidence of breast cancer incidence and the need to screen many women to detect and/or save one patient. Decision to launch breast screening program should be considered against other competing health needs.
6. Despite the lack of evidence about its effectiveness, BSE ought to be encouraged as a tool for increasing public awareness about breast cancer in DLICs.
7. Primary care physicians, obstetricians, and nurses should serve as important partners to promote and practice CBE. In settings where there is significant limitation of resources, community healthcare workers could be trained to perform breast examinations.
8. Where there are limited resources, screening strategy that combine CBE and breast ultrasonography may be an acceptable approach. Ultrasonography alone is associated with high false-positive rates and subsequent costly and unnecessary interventions; therefore, it is not recommended as a sole screening tool.
9. The cost-effective two-stage screening approach that was used for Egyptians women may be considered for countries where reasonable diagnostic resources are available for individuals identified following initial CBE screening [27].
10. When resources permit and disease burden justifies screening mammography in DLICs, it may not be necessary to adopt an annual screening strategy.

Longer intervals between screening encounters may be equally effective and less costly.

11. In DLICs, if a screening mammography is considered as a warranted strategy, screening may have to include younger women as they represent a large proportion in the DLICs population; besides, breast cancer incidence reaches its peak one or two decades earlier than that observed in the developed world.
12. To achieve the most cost-effective screening strategy in DLICs, we recommend targeting high-risk population based on age, personal risk, family history, breast density, or genetic mutations. Identification of those risk groups can be only determined if accurate and complete population- or hospital-based statistics exist.
13. Neither digital mammography nor MRI is considered for DLICs because of the associated cost and the limited clinical utility.
14. Authority should explore other preventive approaches such as combating obesity, physical inactivity, and low compliance to breast-feeding practice.

To improve breast cancer outcomes in DLICs, we should use pragmatic interventions and gradual plans that are realistic and cost effective. Early breast cancer detection and appropriate cancer treatment play crucial roles in this. Population-based screening for breast cancer in DLICs, independent of such plans and infrastructures, is likely to be ineffective.

Conflict of interest None.

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