Breast-cancer early detection in low-income and middle-income countries: do what you can versus one size fits all

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In general, rates of breast cancer are lower in low-income and middle-income countries (LMCs) than they are in more industrialised countries of North America and Europe. This lower incidence means that screening programmes aimed at early detection in asymptomatic women would have a lower yield—ie, substantially more women would need to be examined to find a true case of breast cancer. Because the average age of breast cancer is generally younger in LMCs, it has been suggested that breast-cancer screening programmes begin at an earlier age in these settings. However, the younger average age of breast cancer is mainly driven by the age distribution of the population, and fewer older women with breast cancer, rather than by higher age-specific incidence rates in younger women. Resources in LMCs might be better used to raise awareness and encourage more women with palpable breast lumps to seek and receive treatment in a timely manner.

Introduction

Breast cancer is the world's most common female cancer, with about 1·4 million cases annually accounting for nearly a quarter of all cancers in women.[1] More than half of the more than 400 000 breast-cancer deaths worldwide occur in low-income and middle-income countries (LMCs).[1] Breast-cancer incidence varies widely; age-standardised incidence is around four times higher in high-income countries in North America and Europe than in countries in the lowest income grouping of the World Bank.[2] Indeed, there is a reasonably good correlation between a country's gross domestic product (GDP) and its age-standardised breast-cancer incidence (figure 1A). The mortality-to-incidence ratio (number of deaths to number of cases per year) is reflective of survival for most but not all cancers;[3] in five high-income countries, where breast-cancer survival times are relatively long, 5-year breast-cancer survival is underestimated by 15–20% using mortality-to-incidence ratios. In LMCs, where average breast-cancer survival is shorter, discordance between survival and the mortality-to-incidence ratio is expected to be less. Despite its imperfection, mortality-to-incidence ratios for breast cancer correlate with GDP, with poorer countries having markedly higher ratios (figure 1B). The most relevant metric for measuring progress might be mortality over time, which is less complicated by issues such as lead-time bias and length bias that can contribute to apparent changes in survival.[4] In the USA, breast-cancer mortality has decreased substantially in a somewhat short period (24% between 1990 and 2000). An estimate from the US National Cancer Institute-supported Cancer Intervention and Surveillance and Modeling Network (CISNET), based on seven independent statistical models, suggests that 28–65% (median 46%) of the observed decrease can be attributed to screening, with the remainder ascribed to adjuvant treatment.[5] In a recent study, the contribution of mammography to the decrease in mortality in Norway was estimated to be only about 10%, with the remainder of the roughly 28% decrease ascribed to a time effect, presumed to be the result of increased breast-cancer awareness, improved therapy, and use of more sensitive diagnostic tools that were occurring concurrently with implementation of mammographic screening.[6,7]

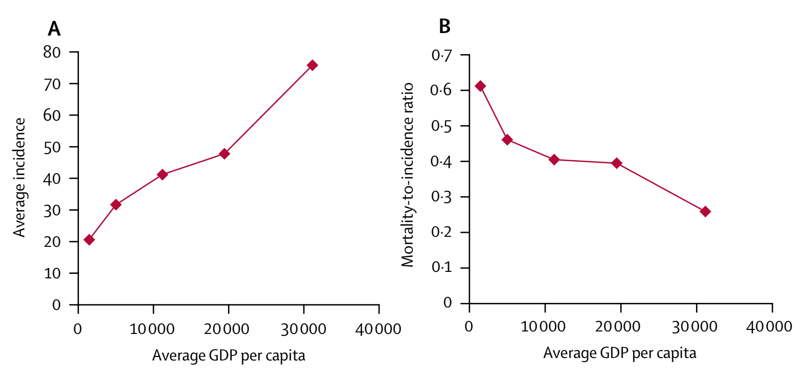

Figure 1: **Relationship between GDP and breast-cancer incidence and outcomes**
Relationship between average GDP and average age-standardised breast-cancer incidence (per 100 000; A). Relationship between average GDP and mortality-to-incidence ratio (B). Datapoints represent the following World Bank income groupings: low income, lower middle income, upper middle income, high income non-OECD, and high income OECD. GDP=gross domestic product. OECD=Organization for Economic Cooperation and Development. Plots were created from data published in reference 2.

Despite the contribution of mammography to the decrease in breast-cancer mortality in high-income countries, it is far from a perfect means of early detection. Not every breast carcinoma is detected by mammography and not every death is averted, even among individuals who faithfully participate in a mammographic screening programme. We often forget that if such a programme reduces mortality by 30%, seven of 10 participants who would have died without the programme still die with it. Nonetheless, screen-detected tumours tend to be smaller, well-differentiated, and less likely to have regional lymph-node involvement,[8,9] factors that make treatment more effective and survival more likely.[4] Smaller, lower-stage tumours also affect treatment options (eg, allowing for breast-conserving surgery).

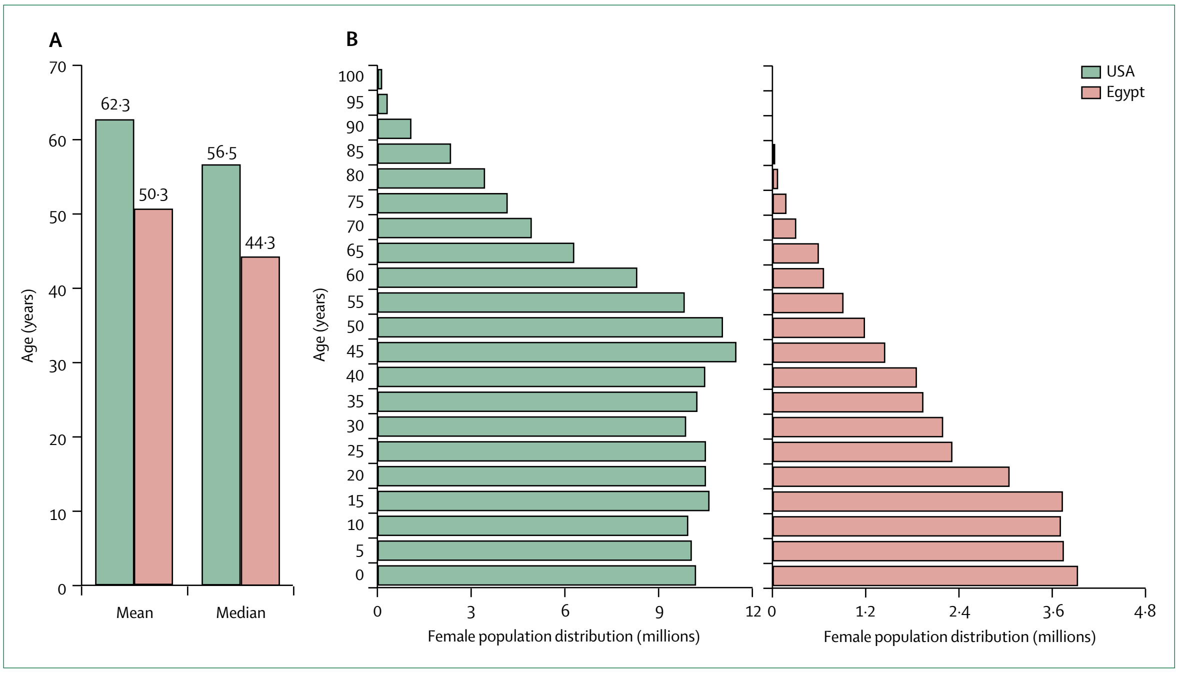

Figure 2: **Average age at diagnosis of breast cancer in the USA and Egypt, with the age distribution of women in each population**
Mean and median age of women diagnosed with breast cancer in the USA, based on data from the National Cancer Institute's Surveillance, Epidemiology, and End-Results (SEER) program, and in Egypt, based on data from the Gharbiah Cancer Registry of Tanta, Egypt (A). Age distribution of the female populations of the USA and Egypt, derived from the US Census Bureau's International Database (B).

This personal view focuses on breast-cancer control strategies in LMCs, using Egypt as a prototype. Egypt has a high-quality population-based cancer registry covering the Gharbiah district of the Nile delta. Breast-cancer data from the Jordanian Cancer Registry are very similar to the data from Egypt,[10] and similar conclusions to those drawn for Egypt and Jordan follow from breast-cancer incidence in LMCs in sub-Saharan Africa, Latin America, or southeast Asia.

Under-registration in LMCs?

A common reaction to learning the difference in breast-cancer incidence between high-income countries and LMCs is to question the validity of lower incidence in LMCs, because of the paucity of population-based cancer registries in the developing world. Although more cancer registries are needed in LMCs,[11,12] it is implausible that the lower rates of breast cancer are merely the result of cancer registry deficiencies and under-registration. Quality-control exercises, including case finding, have been done in Gharbiah via the Middle East Cancer Consortium, and local medical experts do not believe that many women in Gharbiah are dying of breast cancer unregistered. Indirect arguments that take a global view also support a truly lower incidence of breast cancer in LMCs; registries in LMCs around the world, even those of high quality, show markedly lower incidences than reported in most high-income countries.[12] Additionally, the incidence of breast cancer in a population covered by a high-quality registry can increase substantially in a short time. For example, breast-cancer rates in Nordic countries with excellent registries have doubled since 1975.[1] This increase does not seem to be due to improved capture rate but to a true rise in incidence. Rather than ascribing low rates in LMCs to underestimation because of a lack of registry data, or to undiagnosed cases, it is more plausible that the low rates are an accurate reflection of breast-cancer incidence and are likely related to known risk factors, as described by Gail and colleagues.[13] Notably, reproductive patterns that affect sex-hormone levels (eg, later childbirth, fewer children, less breastfeeding) are termed westernisation, and are likely to result in a higher incidence of breast cancer in LMCs as the cohort of younger women who are at higher risk become older.[14,15] Factors associated with reproduction can substantially affect cancer rates. For example, it has been estimated that each birth reduces the relative risk of breast cancer by 7%, and each 12 months of breastfeeding further reduces the risk by 4%.[16]

Age distribution and breast cancer

Although women in Egypt (and in LMCs generally) have a lower risk of breast cancer than do their counterparts in high-income countries, young women in Egypt (and other LMCs) are at a higher risk today than their mothers and grandmothers were at the same age,[14,15,17] which is consistent with a classic birth-cohort effect. Much emphasis has been placed on the lower average age in Egypt and other Arab countries compared with

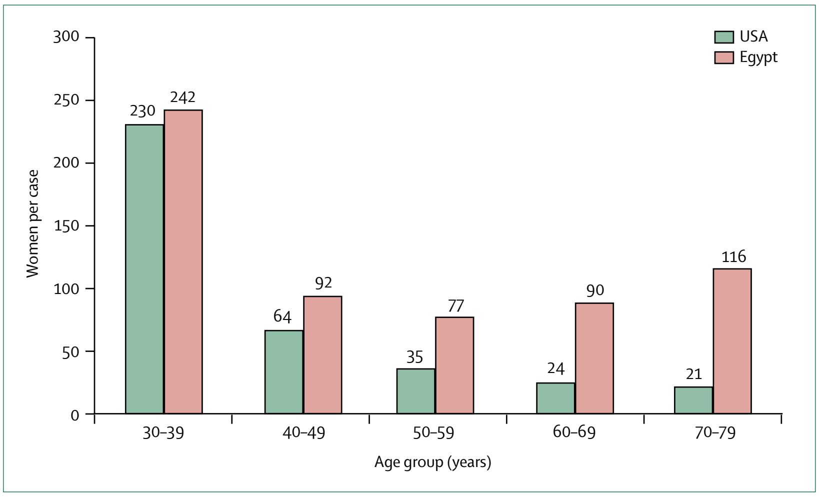

Figure 3: **Number of women in each decade of life that are needed to yield one breast-cancer case**
Plots were generated based on age-specific breast-cancer incidence with data from the Surveillance, Epidemiology, and End-Results (SEER) program, and the Gharbiah Cancer Registry.

higher-income countries.[18–20] A comparatively lower average age of the female population is a common feature in LMCs and hence diagnosis of breast cancer at younger ages is more common. Some explanations focus on a different biology for breast cancer. Since younger women do seem to have different breast-cancer biologies,[21] comparisons between women in high-income countries and LMCs should be carefully age-matched. Differences in breast cancers even within a given population are likely, depending on the age of onset of the disease. Comparing two populations with different age structures is an apples-versus-oranges comparison.

Different age distributions of the general populations in high-income countries versus LMCs makes the lower age of breast cancer seen in LMCs statistically probable, even without biological differences in the disease. Figure 2A shows the mean and median age for breast-cancer diagnosis in US and Egyptian populations. It might seem that the incidence of breast cancer in young Arab women is higher than in their age-matched counterparts in the USA, but this is not the case. For any decade of age, breast-cancer incidence is higher in US women than in Egyptian women of the same age.[10] Figure 2B shows the overall age distributions for the US and Egyptian female populations. With these age distributions, the mean age for nearly any characteristic would likely be lower in Egypt.

Screening and health-care systems

The age distribution and age-specific incidence of breast cancer have implications for health-care system managers who are considering breast-cancer screening or early detection programmes. The success and efficiency, in terms of mortality reduction, of screening an asymptomatic population depends partly on the incidence of the disease. Although the incidence of breast cancer in young women is not higher in LMCs than in high-income countries, young women do constitute a larger percentage of breast-cancer cases in LMCs, because there is a higher proportion of young women in the population (figure 2B).

Figure 3 compares the number of women in each decade of life necessary for a breast-cancer case in the USA and in Egypt, on the basis of data from their respective population-based cancer registries. These numbers are essentially the inverse of the incidence. Several features of this comparison are noteworthy. At all ages, screening would have a lower yield in Egypt than in the USA (ie, more women would need to be screened to find a case). Some organisations in the USA recommend that screening begins at 50 years of age, and others at 40 years. For US women in their fifties, the chance of having breast cancer is about one in 35, whereas the comparable figure for Egypt is one in 77. Therefore, for Egyptian women in their fifties, roughly 76 of 77 women will not have breast cancer in that decade. It has been suggested that screening should start even earlier for women in Egypt, since the average age for breast cancer is lower than in the USA.[18,20] This strategy does not fit well with the facts. Although the average age of diagnosis is lower (figure 2A), the yield in a screening programme for younger women will also be lower. Roughly 91 of 92 Egyptian women in their forties will not have breast cancer in that decade (based on data from Gharbiah). In the first attempt at organised screening in Egypt, fewer than 90 true cases of cancer were found as a result of 20 000 mammograms.[19]

Based on data from the USA, we know that younger women have a greater likelihood of developing cancer after a recent negative mammogram.[22,23] This means that mammographic screening programmes are less effective in reducing mortality in younger women (40–49 years) than in older women (>50 years).[23,24] Screening programmes are more likely to detect slower growing tumours at an early stage than those that grow more rapidly, and tumours that occur at younger ages tend to grow faster.[8,25] Another possible contributor to missed tumours is the higher breast density that is more common in younger women. Among younger women with tumours detected within 24 months of a negative mammogram, breast density accounts for roughly 38% of reduced sensitivity, whereas more rapid growth of tumours accounts for about 31%.[23]

Harm-to-benefit ratio

It has been said that all screening programmes do harm, but some do good as well.[26] In the case of breast-cancer screening by mammography, harms can include false positives or suspicious findings that cause anxiety for the woman and her family, and that require follow-up by the health-care system.[27] Although small, there is also a possible harm from radiation exposure that would be higher if mammography were begun at an earlier age or done more often. Overdiagnosis, another form of harm, refers to histologically confirmed cancers that would never have clinically surfaced in the individual's lifetime. Although estimates of the magnitude of overdiagnosis vary widely and are controversial,[28–30] to the extent that it occurs, overdiagnosis leads to overtreatment of cancers that would not result in morbidity or mortality if left undiscovered.

As mammography screening programmes are promoted, it is common for the benefits to be emphasised and harms de-emphasised or omitted.[31] One metric of success that is often used for screening is how many women go through the programme. In one study done in nine European countries, 92% of women overestimated the benefits of mammography screening by at least one order of magnitude, or stated that they did not know the benefits.[32] Frequent consulting with doctors and health pamphlets tended to increase rather than reduce overestimation. The question of whether women are giving informed consent to screening has also been raised.[33,34] For any population, the harm-to-benefit ratio depends on incidence, since there are more women who are exposed to the harm but receive no medical benefit when the incidence is lower.

Compliance

It is simply not the case that if you build it, they will come. Making mammography available is one thing and having all eligible women participate in screening is another. The WHO has suggested that participation of at least 70% is needed for screening programmes to substantially reduce mortality.[35] Low compliance is a main barrier to answering research questions and achieving maximum benefit from a screening programme. For example, a screening trial involving clinical breast exam in the Philippines was stopped because of an apparent reluctance for women to participate in follow-up, to obtain a definitive diagnosis and treatment, despite offers of counselling, transportation, and home visits.[36]

In the first attempt at screening mammography in Egypt, 2·1% of women (433 of around 20 000 screened) were recalled, but more than half of these were lost to follow up.[19] The situation of women refusing follow-up is not unique to LMCs. In the USA, even women with prepaid health-care coverage sometimes refuse recommended diagnostic tests for breast cancer. Although the reasons for refusal were not well documented, one study found that the most frequently stated reasons were avoidance, denial, and fatalism,[37] which are often suggested as reasons for non-compliance in LMCs. More research is needed to understand low participation and drop-out.[38]

Cost-effectiveness

Screening programmes based on mammography are expensive to initiate and sustain at the levels of compliance that are needed for screening and treatment to have a measurable effect in terms of breast-cancer mortality. Many cost-effectiveness studies of breast-cancer screening programmes have been done.[24,39] Although estimates vary depending on assumptions in the modelling, the cost-effectiveness of mammography depends on the age of women being screened and the screening frequency, with the cost per year of life saved in several scenarios examined ranging from US$16 100 to US$18 800.[40] A cost-effectiveness study[41] based on lower assumed mortality reductions than were used in the previous study[40] and actual screening patterns in the USA during the 1990s yielded a cost per quality-adjusted life year gained that was roughly two-times higher—ie, US$37 000. Using the average cost of a bilateral screening mammogram as a base, the cost of a unilateral diagnostic mammogram is roughly the same and a breast biopsy is ten-times higher.[42] This means that if diagnostic mammography and biopsies were to be done for 10% of those screened, the costs of the programme would double compared with the cost of just the screening mammograms.

Cost-effectiveness analyses serve as a basis for priority setting within a health-care system, or for the country. Use of economics in priority setting is based on the principles of limited resources and necessary choices, leading to what, in some ways, is a zero-sum game. The choice to do something or to do more of something means taking resources from other things, the resources must come from somewhere.

Two prominent issues for implementing a screening programme are what age to start and stop and how frequently to screen. These decisions should be based on evidence regarding the local burden and distribution of breast cancer and the resources available. An extensive modelling study that compared various screening schedules found that screening biennially maintained 67–99% of the benefit of annual screening, with almost half the number of false-positive results that require additional resources for follow-up.[43]

In some LMCs, total annual per-capita spending on health is less than US$100; in Egypt, total per-capita health spending was **INT$**310 in 2007.[44] By comparison, in the USA, Medicare reimbursement is US$82 for a film screening mammogram and US$130 for a digital screening mammogram. Although some costs (eg, labour) are much lower in LMCs, costs of mammography equipment and consumables (eg, radiograph film) are not relative to the status of the economy in which they are used. Even if film or digital mammography could be done for half of the Medicare reimbursement, the cost would still be high compared with total health spending in many LMCs. Despite limited resources, there is substantial interest in LMCs to initiate mammographic breast-cancer screening. In many cases, this interest is being driven by national and international advocacy groups that seem to believe that if something is done in New York, it should be done in New Delhi.

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An international dollar has the same purchasing power as the US dollar has in the USA

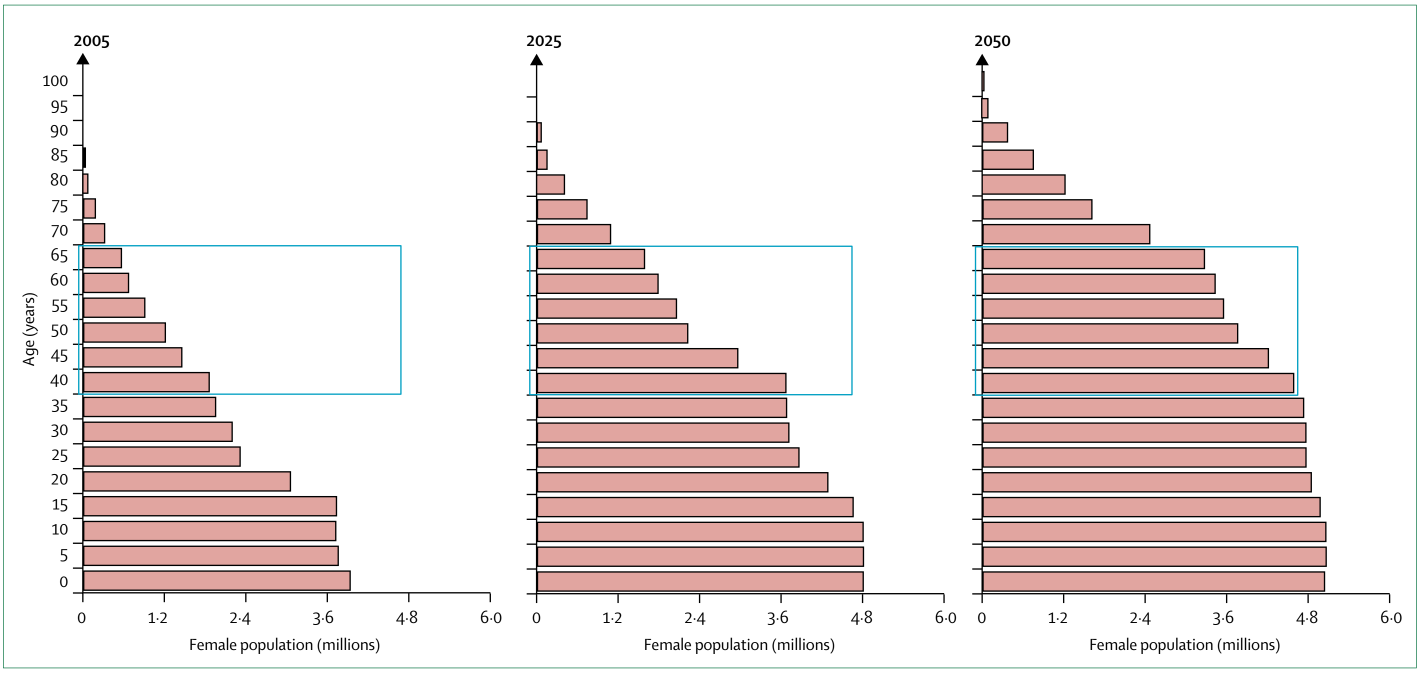

Figure 4: **Age distribution for the female population of Egypt, projected to 2050**
Age-distribution plots were derived from the US Census Bureau's International Database for Egypt, for the years 2005, 2025, and 2050. The box superimposed on the distribution graphs surround ages 40–69 years, to show the substantial increase expected in this group, representing one potential target group for screening.

The cost-effectiveness of health interventions is traditionally seen as a context-dependent issue. WHO has suggested that a health intervention can be considered cost effective if it yields savings of one disability-adjusted life year for less than three-times a country's GDP.[45] In view of the worldwide differences in GDP, mammography could be deemed cost effective in one country (with a higher GDP) but not in another (with a lower GDP). Indeed, an analysis of breast screening in India concluded that it is not cost effective,[46] based on the lower incidence (therefore lower yield in screening) and the lower resources available for the health care in India, where total health spending is only INT$81 per capita[44]—about the same as the cost of a single screening mammogram in the USA.

Practicalities

The limited studies of breast-cancer screening in LMCs suggest that organised screening of asymptomatic women might be an impractical undertaking for the health-care systems of many, if not most, LMCs. Cultural and economic barriers to participation are one issue, but the magnitude of effort required to screen a large population is another. For example, the female population of Egypt is increasing in number and in average age. By 2025, the number of Egyptian women aged 40–69 years will likely be around 15 million, and will reach about 24 million by 2050 (figure 4). A screening programme would need to be built for rapid expansion of services to meet the increase in the screen-targeted population. For an annual mammography programme for the entire population, more than 250 000 mammograms would need to be done each week (ie, 15 million women screened in 52 weeks). The current capacity of Egypt's government-funded mammography screening programme is less than 4000 per month,[19] meaning that an increase in capacity of about 250-times would be needed to screen the target population in 2025. If four mobile vans equipped for mammography screening are in use today, 1000 will be needed in 2025 (calculations are based on a hypothetical 100% coverage).

In the USA, recall rates average 11% after a first round of screening with mammography.[47] Mammograms in screening programmes can yield a suspicious finding that requires follow-up (eg, clinical breast examination, repeat mammogram, ultrasound, or biopsy). Recalling women for follow-up substantially increases the cost of breast-screening programmes. The cost of the work-up and biopsies generated by a screening programme might be roughly equivalent to the screening mammography itself, even before treatment costs begin.

For mammography to be effective in reducing breast-cancer mortality by 25–30%, women who are found to have breast cancer have to receive timely and appropriate treatment; it is early treatment rather than early detection per se that saves lives. It is difficult to envision that the already stretched Egyptian health-care system could increase from around 200 mammograms per day to 50 000 mammograms and 5000 follow-up procedures per day, as well as add state-of-the-art treatment, to reduce breast-cancer mortality by around 30% as in high-income countries. Based on the recent Norwegian analysis, only a third of this effect might be due to mammography.[6,7] If a mammogram were to cost US$40 (about half of the Medicare reimbursement in the USA), the current rate of about 4000 mammograms per month in Egypt would cost US$160 000 per month before any additional costs of follow-up or treatment are added. For a country whose current gross national income is less than INT$6000,[44] this would not seem to be a very cost-effective use of health resources since coverage is much less than that needed to have an effect on mortality in the population based on WHO guidance.[35]

Conclusions

What should Egypt and other LMCs do about breast cancer? The answer is not simple. There is an increasing demand for health-care systems in LMCs to emulate high-income countries by adding mammographic screening, and policy makers are feeling pressure from national and international advocacy groups to pay for a mammography programme. As discussed, such a programme would be a difficult undertaking and the cost–benefit analysis is questionable at best. The Breast Health Global Initiative has provided guidance for how countries with different resource levels can incrementally upgrade early detection, diagnosis, and treatment services.[17,48] One approach is to shift the focus from large asymptomatic populations—who make up the participants in a screening programme in LMCs, and most of whom will never have breast cancer—to the much smaller populations of women with breast symptoms.

In Egypt and other LMCs, women are typically diagnosed at a later stage when curative therapies are less effective. For women who are first diagnosed with large palpable tumours, it is likely that their breast-health problem has been apparent for some time. Why are these women not diagnosed earlier? It is important to understand the barriers that lead women to delay seeking care for breast symptoms, as well as the barriers within health-care systems that contribute to failure to diagnose breast cancer earlier and that delay timely treatment. Qualitative and quantitative research is necessary to understand these barriers; too often there is speculation regarding the barriers rather than research-derived evidence. Raising breast awareness is a laudable goal and one that should be aggressively pursued by advocacy groups and health-care systems in LMCs, without necessarily seeking population-based mammographic screening. For example, in Malaysia, a programme that trained health staff in skills associated with earlier detection of breast tumours and raising public awareness resulted in a decrease in stage III–IV tumours from 60% to 35% in 4 years.[49] The addition of patient navigator services in LMCs, which aim to help women access their health-care system and receive better care once in the system, could be more cost effective than attempts to screen the asymptomatic masses. Navigators improved outcomes in the USA, including within disadvantaged segments of the population that have similarities to populations in LMCs.[50]

Around 100 years ago, US President Theodore Roosevelt said, “Do what you can, with what you have, where you are”.[51] The adoption of this notion would likely improve breast-cancer outcomes in LMCs. In my view, the do-what-you-can approach is far better than the one-size-fits-all approach that characterises attempts in resource-constrained LMCs to impose programmes or breast-cancer strategies that have proven somewhat effective in a very different context.

Search strategy and selection criteria

This Personal View is partly based on a presentation from the Global Summit of the Breast Health Global Initiative in June, 2010. The examples used are taken from my experience, but also from purposive search of the published work to highlight these issues and possible solutions.

Conflicts of interest

The author declared no conflicts of interest.

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