

Review Article

Cost-Effectiveness of National Breast Cancer Screening Programs in Developing Countries, with Reference to the Recent Egyptian Initiative

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Abstract

Breast cancer was the second most common cancer in the world and the most common cancer in women both in developed and less developed world. It ranked the fifth cause of death from all cancers and caused the greatest number of cancer related deaths among women in 2018. A variety of factors have been shown to impact an individual's risk of developing breast cancer and its ultimate prognosis. Screening for breast cancer will help to reduce mortality, to confer lifetime protection, and to protect those with high risk factors.

Cost-effectiveness analysis refers to the economic evaluation in which the costs and consequences of alternative interventions are expressed in cost per unit of health outcome. Studies on cost-effectiveness of screening programs in developing countries used different methods and calculated different outcome measures. They studied different tools used for screening. Some studied the cost-effectiveness of clinical breast examination and others studied that of mammography. The outcome measures varied, some studies calculated the cost-effectiveness ratio, while others calculated the incremental cost-effectiveness ratio, the disability adjusted life years and the quality adjusted life years. It is concluded that although population-based mammography has been widely adopted in high-income countries, it is less cost-effective in low- and middle-income countries which face some challenges such as the problem of investment in screenings .

In developing countries, further research to study the cost-effectiveness of breast cancer screening, covering a comprehensive set of interventions and resulting in clear policy recommendations, is required.

Keywords: Breast cancer; Screening; Challenges; Cost-effectiveness; Egyptian initiatives.

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MAGNITUDE OF BREAST CANCER

Breast cancer was reported to be the second most common cancer in the world and, by far the most common cancer in women both in the developed and less developed world. In 2012, 1.67 million new cases of breast cancer were diagnosed (25% of all cancers).⁽¹⁾ This number increased to 2.09 million new cases (11.6% of all cancers) in 2018.⁽²⁾ In Egypt, breast cancer is the most common female malignancy accounting for 35.1% of female cancer. It was also reported to carry an unfavorable prognosis with 29% mortality and 3.7:1 incidence to mortality ratio.⁽²⁾

As regards mortality due to breast cancer, the World Health Organization (WHO) estimated that worldwide over 508 000 women died in 2011 due to breast cancer.⁽³⁾ The WHO in 2013 estimated that the number of deaths due to breast cancer globally will reach 560,000 by 2015⁽⁴⁾ and

626,679 in 2018.⁽²⁾ Breast cancer ranked the fifth cause of death from all cancers and causes the greatest number of cancer related deaths among women (15% of all cancer deaths among women) worldwide in 2018. Although breast cancer is thought to be a disease of the developed world, almost 50% of breast cancer cases and 58% of deaths occur in less developed countries.⁽⁵⁾ In Egypt, breast cancer was the leading cause of cancer related mortality, accounting for 29.1% of the total mortality from cancer in 2012⁽⁴⁾ while in 2018, it became the second leading cause of cancer related mortality accounting for 21.3% of the total deaths from cancer.⁽²⁾

RISK FACTORS OF BREAST CANCER

A variety of factors have been shown to impact an individual's risk of developing breast cancer and its ultimate prognosis. Some of the well-established risk

factors are non-modifiable such as age, gender, family history, estrogen exposure, nulliparity, hormone replacement therapy, age at menarche, first full-term pregnancy, and menopause. Other factors are modifiable and include both lifestyle and environmental factors.⁽⁶⁾

Breast cancer incidence rate increases sharply with age, becoming substantial before the age of 50 years.⁽⁷⁾ In Egypt, breast cancer occurs at a relatively earlier age compared with other populations. The median age of breast cancer is 46 years, a full decade below the western populations.⁽⁸⁾

Regarding gender, being a woman is the most significant risk factor for developing breast cancer. Men can develop breast cancer, but it is 100 times more common in women than men because women's breast cells are constantly changing and growing, mainly due to the activity of the female hormones estrogen and progesterone.⁽⁹⁾

Family history of breast cancer is a well-established risk factor for breast cancer and is used to identify women at higher risk. A woman's risk of breast cancer at a young age is increased if she has a first-degree relative (mother, sister, or daughter) with breast cancer, or if she has more than one relative with breast cancer. The commonly mutated tumor suppressor genes are BRCA1 and BRCA2, which are the only known high penetrance genes involved in breast cancer susceptibility.⁽¹⁰⁾

The risk of breast cancer is affected by several reproductive and hormonal factors.⁽¹¹⁾ Menarche at age 15 years or older was associated with reduced risk for breast cancer. Late menopause is known to be a risk factor for breast cancer because of both the longer duration and higher level of exposure to estrogen and progesterone.⁽¹²⁾

Pregnancy and breast feeding have dual effects on breast cancer development. Although early age of first full-term birth is highly protective against late occurrence of hormone-dependent breast cancer, each successive pregnancy of multiparous women has a progressive effect on breast cancer irrespective of hormone dependency. Multiple pregnancies can potentially decrease the breast cancer risk probably due to the process of breast tissue differentiation following pregnancy.⁽¹³⁾

There is a consistent and significant increased risk of developing breast cancer in women who have taken combined hormone replacement therapy for more than 5 years compared with women who have never taken HRT.⁽¹⁴⁾

Obesity is associated with greater tumor burden and higher grade of tumors at diagnosis. The relative risk of breast cancer increases from 1.5 to 2.5 among obese women (body mass index (BMI) (kg/m²) > 30).⁽¹⁵⁾ Fatty diet is suggested to be a factor in the development of breast cancer. Diets rich in fruits and vegetables have been linked to the decrease in risk of several chronic diseases, including several types of cancer.⁽¹⁶⁾

Alcohol consumption has negative impact on health and social consequences. Women who drank more than 45

grams of alcohol per day (approximately three drinks) had 1.5 times risk of developing breast cancer than non-drinkers.⁽¹⁷⁾

Tobacco smoking is among the leading preventable risk factors for cancer. Tobacco smoke contains potential human breast carcinogens which pass through the alveolar membrane and into the blood stream.⁽¹⁸⁾

The primary environmental factor that has been shown to have a direct link with breast cancer is ionizing radiation. Women exposed to ionizing radiation due to nuclear war and medical diagnostic or therapeutic procedures are at an increased risk of developing breast cancer.⁽¹⁹⁾

IMPORTANCE OF EARLY DIAGNOSIS OF BREAST CANCER

Early diagnosis is defined by WHO as the awareness (by the public or health professionals) of early signs and symptoms of cancer in order to facilitate diagnosis before the disease becomes advanced. This enables more effective and simpler therapy. The concept of early diagnosis is sometimes called "down-staging."⁽²⁰⁾ Early diagnosis remains an important early detection strategy, particularly in low- and middle-income countries where the disease is diagnosed in late stages and resources are very limited. There is some evidence that this strategy can produce "down staging" (increasing in proportion of breast cancers detected at an early stage) of the disease to stages that are more amenable to curative treatment.⁽²¹⁾

The WHO indicates that there are two early detection methods: early diagnosis or awareness of early signs and symptoms in symptomatic populations in order to facilitate diagnosis and early treatment, and screening that is the systematic application of a screening test in a presumably asymptomatic population to identify individuals with an abnormality suggestive of cancer.⁽²⁰⁾

BREAST CANCER SCREENING

The goals of screening are to reduce mortality by detecting cancer early when treatment is more effective and has less morbidity, to confer lifetime protection by repeating the screening test at regular intervals that allow identification of any suspicious changes, and to particularly protect those with high risk factors.⁽²²⁾

Current methods of breast screening and diagnosis include Breast Self-Examination (BSE), Clinical Breast Examination (CBE), Mammography, Ultrasonography, and Magnetic Resonance Imaging (MRI).⁽²²⁾

There is no evidence on the effect of screening through BSE. However, the practice of BSE has been seen to empower women, taking responsibility for their own health. Therefore, BSE is recommended for raising awareness among women at risk rather than as a screening method.⁽²²⁾ Although there is evidence that organized population-based mammography screening programs can reduce breast cancer mortality by around 20% in the screened group versus the unscreened group across all age

groups, in general there appears to be a narrow balance of benefits compared with harms, particularly in younger and older women. There is uncertainty about the magnitude of the harms particularly overdiagnosis and overtreatment.⁽²⁰⁾ Ultrasonography is typically used as a complementary method for the assessment of mammographically or clinically detected breast masses and for supplemental information on dense tissue. However, there is limited data supporting the use of ultrasonography in breast cancer screening as an adjunct to mammography.⁽²²⁾ Indeed, MRI is indicated for resolving findings on mammography and

staging of breast cancer. The results of nonrandomized prospective studies in United Kingdom⁽²³⁾, Canada⁽²⁴⁾, Germany⁽²⁵⁾, United States⁽²⁶⁾, and Italy⁽²⁷⁾ to detect MRI efficacy in breast cancer screening for high risk women populations demonstrated an average sensitivity of 87.5% and specificity of 92.8%. Several agencies working in cancer prepared guidelines for screening for breast cancer with few differences with regards to the age of starting screening and recommended methods for women at average risk and women at higher than average risk (Table1).

Table 1: Summary of different breast cancer screening guideline recommendations

Risk/Age	Guideline Recommendation					
	ASC (2015)	IARC (2015)	USPSTF (2016)	AAFP (2016)	NICE (2017)	CTFPHC (2018)
Average						
40-49 yrs	Annual MS	Insuff. Evid.	Biennial MS	Individual decision	Annual MS	MS not recom.
50-54 yrs	Annual MS	MS	Biennial MS	Biennial MS	MS every 3 yrs	Biennial MS
55-74 yrs	Biennial MS	50-69 yrs: MS 70-74 yrs: MS not recom.	Biennial MS	Biennial MS	MS every 3 yrs	Biennial MS
75 + yrs	Cont. screen.	Not address.	Balance betw. Harm/Benefit	Balance betw. Harm/Benefit	Not address.	Not address.
Higher than average	Annual MS and MRI	MS and MRI at earlier age may be beneficial	May benefit from begin. Screen. in 40s	Not addressed	30-90 yrs: annual MS 60 + yrs: MS every 3 yrs	Not address.

Yrs: years; MS: Mammography screening; MRI: Magnetic Resonance Imaging; Cont. screen.: continue screening; Insuff. evid.: Insufficient evidence; recom.: recommended; address.: addressed; betw.: between; screen.: screening.

COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis (CEA) in healthcare refers to the economic evaluation in which the costs and consequences of alternative interventions are expressed in cost per unit of health outcome. The objectives of CEA are to identify the most cost-effective option for achieving a pre-set objective or criterion that is not measurable in monetary terms for example some health outcomes. It can determine the most effective option for a fixed amount of funding that has been allocated to achieve a policy objective. CEA is a method of assessing whether the current mix of interventions is efficient as well as whether a proposed new technology or intervention is appropriate.⁽²⁸⁾

Before conducting CEA, four preliminary considerations need to be identified. The first consideration is to determine the baseline to which the alternative program will be compared. Secondly is to select appropriate outcome. The third consideration is to decide whose cost perspective will serve as the basis for the analysis. The fourth or final preliminary consideration is to determine the time frame that is defined as amount of time over which the analysis is projected.⁽²⁸⁾

There are five essentials steps in conducting CEA⁽¹⁾ namely: developing research questions⁽²⁾, designing decision analysis tree⁽³⁾, measuring cost and outcome⁽⁴⁾, calculating cost-effectiveness ratio (CER) and incremental

cost-effectiveness ratio (ICER)⁽⁵⁾ and testing for uncertainty.⁽²⁸⁾

Step 1: Developing research question

In CEA, a research question should be clearly defined that compares the consequences of various treatment options in terms of costs. The formulation of research question depends on the perspective that can be societal/provider/clinician/program/funding source perspective. Apart of that, it is also important to consider the time frame, effectiveness measures such as cases of disease detected and cases successfully treated, relevant treatment options and relevant outcomes.⁽²⁹⁾

Step 2: Designing decision analysis tree

Decision analysis is a process of quantifying programmatic alternatives for systematic analysis. It graphically describes the sequence in which interventions occur, how the course of a health condition is affected, complications, and health outcomes.⁽²⁸⁾

Step 3: Measuring cost and outcome

Measuring costs of a resource is depending on whether it is financial costs (i.e. actual money spent on the resources) or economic costs (value of a resource in its most productive alternative use or the best foregone use of the resources). Measuring program costs involves two major components which are identifying type of costs and quantifying costs. All these activities need to be further categorized under program development, program implementation, or both.

This is to be able to separately measure start-up and ongoing costs.⁽²⁸⁾

Measuring outcome or estimating health effects can be done directly such as by calculating number of disease-prevented or incident cases of a specific disease in an intervention group compared to a control group over a given follow-up period. There are several ways of measuring health outcomes in CEA. It can be categorized into single measure (natural unit) or combined measures of health outcome. The combined measures include the disability adjusted life years (DALYs) and the quality-adjusted life years (QALYs). Using QALYs or DALYs as outcome measures provide a variant of CEA termed cost utility analysis. The DALYs is most common outcome metric used to explain CEA and WHO has recommended it is best to express population effectiveness in terms of DALYs.⁽³⁰⁾ In general, DALYs refers to the total of years of potential life lost due to premature mortality and the years of productive life lost due to disability. The QALYs is a measure of health outcome which incorporates the impact on both the quantity and quality of life. QALYs are calculated simply by multiplying the duration of time spent in a health state by the health-related quality of life weight associated with that health state.⁽³⁰⁾

Step 4: Calculating cost-effectiveness ratio (CER) and incremental cost-effectiveness ratio (ICER)

Cost-effectiveness analysis seeks to recognize how much dollars are the costs of an intervention/program. Linking costs and effects can be achieved in the form of a ratio, to provide an overall indication of cost-effectiveness in a way that will inform decision-making. CER can be calculated once cost and outcome data are gathered. CER is obtained by dividing costs by units of effectiveness. CER simply represents a measure of how efficiently the proposed intervention can produce an additional unit of effect, e.g. DALY averted or QALY gained. The ICER is more important than CER value to determine the cost-effectiveness of interventions because economic analysis is concerned with how much we are paying for each extra unit of effectiveness by undertaking the new intervention. The ICER is calculated by ordering the interventions from least to most effective in terms of outcomes achieved, then for each intervention dividing the change in cost from the next-least-effective intervention by the change in outcomes achieved.⁽³¹⁾

Step 5: Test for uncertainty (Sensitivity analysis)

All estimates of costs and effects are subject to uncertainty. Therefore, good health economic evaluation studies should involve assessing the impact of the uncertainties in the parameter values used and factors that determine how model outputs depend on model inputs. The principal method for handling uncertainty is by conducting a sensitivity analysis.⁽³⁰⁾

Decision making

Each CEA represents the magnitude of additional health gained per additional unit of resources spent. A cost-effectiveness threshold represents the willingness to pay

per QALY gained and is a vital component of decision making involving economic evaluation. Cost-effectiveness thresholds allow CERs that represent good or very good value for money to be identified. In 2001, the World Health Organization's Commission on Macroeconomics in Health suggested cost-effectiveness thresholds based on multiples of a country's per-capita gross domestic product (GDP). If the cost/DALY is less than 3 times the GDP, the intervention is cost-effective.⁽³⁰⁾

There are several types of threshold. Individual countries may use the WHO threshold or may set their own thresholds. The following are examples of thresholds adopted by countries: The United Kingdom's National Institute for Health and Care Excellence has used an explicit cost-effectiveness threshold of between 20 000 and 30 000 pounds. If the ICER for a new technology falls below £20 000 per QALY gained, that technology is generally recommended for purchase by the national health system. In United States, the Institute for Clinical and Economic Review which has a high commitment to a CE threshold, bases the evaluation of an intervention's long-term value for money exclusively on a fixed cost-effectiveness threshold between \$50,000 and \$175,000 per QALY gained. Interventions with incremental CE ratios below \$50K represent "high" long-term value for money.⁽³²⁾

COST-EFFECTIVE ANALYSIS OF SCREENING

In breast cancer, cost-effectiveness analysis of screening is done to determine whether a screening intervention is economically efficient and to compare its costs and effects with costs and effects of all alternatives including doing nothing.⁽³³⁾

Costs included in CEA of screening depend on perspective, but should at least include all relevant medical costs: cost per person for breast cancer screening, costs of additional tests (e.g. MRI, ultrasound, biopsy) to confirm breast cancer diagnosis, costs of complications, costs of over diagnosis and overtreatment, and savings from preventing treatment of late-stage of disease.⁽³³⁾

Effects of interventions should be measured in QALY gained. The Components of QALY gained with screening are: life-years gained because of prevented cancer death, increase in quality of life because of less-invasive disease and treatment, and decrease in quality of life because of screening (burden and worry), diagnostic follow-up, complications and treatment (earlier detection and over diagnosis).⁽³³⁾

STUDIES ON COST-EFFECTIVENESS OF SCREENING PROGRAMS FOR BREAST CANCER IN DEVELOPING COUNTRIES

Studies on cost-effectiveness of screening programs in developing countries used different methods and calculated different outcome measures. They studied the different tools used for screening. Some of them studied the cost-effectiveness of CBE and others studied that of mammography. The outcome measures varied, some

studies calculated the CER, others calculated the ICER, and two studies estimated the DALYs and one study estimated the QALYs. The duration of follow up was also different. Table 1 summarizes the findings of nine studies of CEA of different screening methods of breast cancer.

A study in Ghana compared costs and effects of breast cancer control interventions. Analyses were based on the WHO-CHOICE method, with health effects expressed in DALYs, costs in US\$ and CERs in US\$ per DALY averted. It was found that biennial screening by CBE of women aged 40-69 years, in combination with treatment of all stages, seems the most cost-effective intervention. It was also reported that mass media awareness raising (MAR) is the second option. As regards mammography screening of women aged 40-69 years, it was found to be not cost-effective.⁽³⁴⁾

A study in Vietnam aimed to evaluate the cost-effectiveness of a screening program for breast cancer from the healthcare payers' perspective. Costs and effects of an annual screening program using CBE with the absence of screening on a cohort of asymptomatic women aged 40 years were compared. The model was analyzed over the cohort's lifetime under the assumption that women participated in the screening program annually for 15 years. It was concluded that breast cancer screening with CBE for women aged 40 to 55 years is considered very cost-effective in Vietnam according to the World Health Organization criteria.⁽³⁵⁾

A study was conducted in Korea to evaluate the cost-effectiveness of the National Cancer Screening Program (NCSP) for breast cancer in the Republic of Korea from a government expenditure perspective. The program recommends biennial mammography screening for women aged 40 years and older. The effectiveness of the NCSP for breast cancer was estimated by comparing 5-year survival and Life Years Saved (LYS) between the screened and the unscreened groups. Direct screening costs, indirect screening costs, and productivity costs were considered in different combinations in the model. When all three of these costs were considered together and the incremental cost to save one life year of a breast cancer patient was calculated, the NCSP for breast cancer in Korea seems to be accepted as cost-effective as ICER estimates were around the GDP.⁽³⁶⁾

A study was conducted in Mexico to estimate the cost-effectiveness of different breast cancer screening programs using mammography compared to no program. It estimated the lifetime costs and effects of three mammography screening frequencies: yearly, every 2 years, and every 3 years, in terms of DALYs, and in different age groups. The CER was also calculated for all scenarios. It was concluded that the use of mammography as a screening method for women is highly cost-effective only when the periodicity program schedule is every three, and when coverage includes only women from the age group of 40-70 years, resulting in fewer unnecessary biopsies and a decrease in over diagnosis.⁽³⁷⁾ A study on

cost-effectiveness of breast cancer screening using a population-based mammography screening in Turkey, compared two screening strategies: Bahcesehir Mammography Screening Project (BMSP) (includes three biennial screens for women between 40 and 69) and Turkish National Breast Cancer Registry Program (TNBCRP) which includes no organized population-based screening. Costs were estimated using direct data from the BMSP project and the reimbursement rates of Turkish Social Security Administration. The life-years saved by BMSP were estimated using the stage distribution observed with BMSP and TNBCRP. It was concluded that an organized population-based screening program may be cost-effective in Turkey and in other developing countries.⁽³⁸⁾

Another study was done in Vietnam to evaluate the costs and outcomes of introducing a mammography screening program for Vietnamese women aged 45-64 years compared to the current situation of no screening. Decision analytical modeling was used to estimate costs and health outcomes over a lifetime horizon. Model inputs were derived from published literature and the results were reported as ICERs. It could be concluded from the study that offering the first round of mammography screening to Vietnamese women aged 50-59 years should be considered, with the given threshold of three times the Vietnamese GDP per capita.⁽³⁹⁾

A cost-effectiveness analysis of feasible breast cancer screening policies was performed in India and was aiming to compare the cost-effectiveness of feasible breast cancer screening policies. The costs of screening for breast cancer in India, its effects on mortality, and its cost-effectiveness were estimated. It was concluded that the estimated cost-effectiveness of CBE screening for breast cancer in India compares favorably with that of mammography in developed countries. However, in view of competing priorities and economic conditions, the introduction of screening in India represents a greater challenge than it has been in more developed countries.⁽⁴⁰⁾

In Morocco, more than 60% of breast cancer cases are diagnosed in late stages. A study was conducted to assess the cost-effectiveness of biennial screening program using CBE compared to the absence of screening. The study compared the cost of CBE among screened to non-screened. It was concluded that biennial CBE of women aged 45-69 years at 32% coverage rate cannot be considered cost-effective.⁽⁴¹⁾

A study was conducted in China to model the cost-effectiveness of a risk-based breast cancer screening program in urban China. It was launched in 2012. It compared screened women with non-screened and estimated the lifetime costs and effects, in terms of QALYs, of a breast cancer screening program for high-risk women aged 40-69 years. Women were screened using ultrasonography and mammography. It was concluded that high-risk population-based breast cancer screening is cost-effective compared with no screening.⁽⁴²⁾ Some studies

have focused on the value of screening but did not provide cost-effectiveness data while others provided the cost or outcome data. Examples of these studies are the following two studies: A study conducted in Egypt in 2010 revealed that the mean tumor size at diagnosis is 4.5 cm, and the median age is approximately 46 years. Both of these factors decrease the utility and cost-effectiveness of a mammography-based screening program typically designed for developed countries. The study concluded that clinical breast assessment-based screening with selective mammography is an effective modality, which improves the results of breast cancer management in Egypt.⁽⁴³⁾ However, the paper does not present any CER.

A review paper in Iran discussed the strategies that will help to reduce breast cancer burden in Iran and summarized considerations for launching a successful mass screening program in Iran using a thorough search of the literature focusing on screening activities for breast cancer in limited resource countries (LRCs). In conclusion, given the lack of quantitative information and

implementation research on breast cancer control in Iran, the ability to give a clear advice for breast cancer screening in Iran is limited. Iran should adopt a tailor-made strategy for mass screening with great emphasis on reducing the number of advanced stage tumors or “down-staging”. Combination of two approaches, CBE and mammography would be promising given the increased competence of health care professional and public awareness. Equally important, a control plan should be started small and expanded gradually.⁽⁴⁴⁾

It is concluded that although population-based mammography has been widely adopted in high-income countries for more than 30 years⁽⁴⁵⁾, it is less cost-effective in low- and middle-income countries.⁽⁴⁶⁾ Despite recent controversies about screening mammography in high-income countries and a scarcity of high-quality data for this approach in LMICs, it is often assumed that wherever mammography is available, it must benefit women.⁽⁴⁷⁾ The discussed cost-effectiveness studies are succinctly summarized in table 2.

Table 2: Summary of some cost-effectiveness studies on breast cancer screening in developing countries

Author (Year)	Country	Screen. tool	Comp.	Pop.	Freq. of screening	Effect. outcome	Measure	Conclusion
Zelle et al, (2012)	Ghana	CBE, MAR, MS	Screening modalities	40-69 yrs	Biennially	DALYs	CER	Both CBE and MAR are CE while MS is not
Nguyen et al, (2013)	Vietnam	CBE	No program	40-55 yrs	Yearly	LYS	ICER	CBE is very CE
Kang et al, (2013)	Korea	MS	No screening	≥40 yrs	Biennially	LYS	ICER	NCSP seems CE
Ulloa-Perez et al, (2016)	Mexico	MS	No program	25-75 yrs	Every 3yrs	DALYs	CER	MS is highly CE when performed every 3 years
Ozmen et al, (2017)	Turkey	MS	No screening	40-69 yrs	Biennially	LYS	ICER	Biennial MS is highly CE
Nguyen et al, (2018)	Vietnam	MS	No screening	≥45 yrs	Yearly	LYG	ICER	High risk population based screening is CE
Okonkwo et al, (2018)	India	CBE, MS	No screening	40-60 yrs	Every 5 yrs	LYG, LYS	ICER	CBE cost-effectiveness compares with that of MS
El Mahi et al, (2018)	Morocco	CBE	No screening	45-69 yrs	Biennially	LYS	ICER	Biennial CBE is not CE
Sun et al, (2018)	China	MS and US	No screening	45-69 yrs	1,3,5 yrs	QALYS	ICER	High risk screening every 3 years is CE

Screen: screening; Comp: comparator; Pop: population; Freq: frequency; Effect: effectiveness; CBE: clinical breast examination; MAR: mass media awareness raising; MS: mammography screening; US: Ultrasonography; yrs: years; DALYs: daily adjusted life years; LYS: life years saved; LYG: life years gained; QALYs: quality adjusted life years; CER: cost-effectiveness ratio; ICER: incremental-cost-effectiveness ratio; CE: cost-effective.

CHALLENGES FACING COST-EFFECTIVE ANALYSIS STUDIES OF BREAST CANCER

Screening strategies may be economically attractive in LMICs - yet there is very little evidence to provide specific recommendations on screening by mammography versus

CBE, the frequency of screening, or the target population.⁽⁴⁷⁾ Health care systems in LMICs may face strong incentives and pressure to adopt health care interventions such as screening mammography that are well established in high-resource settings. Factors that

could reduce efficacy of breast cancer screening in LMICs include a younger population with lower breast cancer incidence, shorter life expectancy, more prevalent competing causes of death, and higher prevalence of biologically aggressive subtypes for which patient outcomes are less likely to be affected by screening.⁽⁴⁷⁾ Another important challenge is the problem of investment in screenings; governments of today should pay for the benefits partially measurable by subsequent governments.⁽⁴⁷⁾

EGYPTIAN INITIATIVES FOR BREAST CANCER

The launching of the first Egyptian national screening program "Women Health Outreach Program" (WHOP) was announced on October 30th 2007. This project is a government-funded program that offers free breast screening for all Egyptian women above the age of 45 years. In addition to free mammograms, the program gives the participants a chance to be screened for diabetes, hypertension and obesity as well. Positively detected cases are also offered the option of free management. During the period from October 30th, 2007, up to February 9th, 2009, 20,098 women in Cairo, Alexandria and Suez governorates were screened for breast cancer, diabetes, hypertension and obesity through the program.⁽⁴⁸⁾

In Cairo in 2007, four mobile mammography vans were launched, to screen women over 45 years in the underserved areas. Each van was equipped with a full field digital mammography (FFDM) machine, dedicated computer system linked to the National Breast Screening Center, sphygmomanometer, blood glucose measuring kit, and spring scale and meter to measure weight and height. Based on positive findings, patients were directed to Cairo University Hospital to receive appropriate treatment. Mobile units continued to operate through October, 2008.⁽⁴⁹⁾

With launching of the National initiative of 100 million healthy individuals, breast cancer control became one of the main elements of this initiative. A nationwide campaign started in July 2019 in 9 governorates (Alexandria, Port Said, Matrouh, Qalyubia, Beheira, Assiut, Fayoum, South Sinai and Damietta) and extended to another 11 governorates (Cairo, North Sinai, Red Sea, Ismailia, Suez, Kafr el Sheikh, Menoufia, Beni Suef, Sohag, Luxor, and Aswan) on 1 September 2019 then to the remaining 7 governorates (Giza, The New Valley, Gharbia, Dakahlia, Sharkia, Minya, and Qena) on 1 November 2019. This campaign mainly aims to address breast cancer among women 18 years and over free of charge for those having family history of any cancer and those suspected of having breast cancer by CBE. The first step is to promote BSE. All females 18 years and over will have the chance to be trained on BSE. In addition, health education material (pamphlets) on how to do BSE will be provided to them. For those aged 40 years and over and to females aged 18-39 who have high risk factors, CBE will be offered and those found to be suspected of having breast

cancer will be referred to the special centers for further investigation and management. The outcome measures for the first phase will include decreasing the average size of the breast cancer tumor from 2.4 cm to 2cm, improving the rates of detection of first and second stages of cancer more than stage 3 and 4. It will also increase the average survival overall and the average survival free disease for patients diagnosed as having breast cancer tumors.⁽⁵⁰⁾

The chances of success of this initiative are great, particularly as the public is keen for it especially as it is linked with other screening initiatives including diabetes and hypertension. Although, the initiative is having the full support of the government and is not expected to face any financial constraints, it merits an economic evaluation by measuring the cost and outcomes. It is also important to ensure sustainability of the program.

CONCLUSION AND RECOMMENDATIONS

To conclude, it is to be noted that developing countries are very diverse with respect to culture, societal values, political arrangement but they all share the fact of limited resources to protect the health of their citizens. They still struggle with endemic diseases including tuberculosis, malaria, and nutritional deficiencies, high rates of infant and child mortalities, and premature deaths. Even where substantial economic development has taken place as in Thailand, Malaysia, China, India, it has not succeeded to effectively control long term burden of prevalent diseases and health problems, together with the rise in health threats such as cancer. In the situation of budgetary constraints and competition with the demand of other diseases, cancer control programs such as that of breast cancer in women need to make wise choices to maximize the efficacy of their investments. These choices should be driven primarily by the feasibility and cost of the different interventions in the local/national setup. In developing countries, further research to study the cost-effectiveness of breast cancer screening, covering a comprehensive set of interventions and resulting in clear policy recommendations, is required.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in Globocan 2012. *Int J Cancer*. 2015; 136(5): 359-86.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
3. National Cancer Registry Program of Egypt. [Internet]. Cairo: Cancer Registry; [Cited 2019 Oct 28]. Reports and statistics. Available from: <http://www.cancerregistry.gov.eg/>
4. World Health Organization. Global Health Estimates. [Internet]. Geneva: WHO; 2013. [cited 2019 Jun 10]. Available from: https://www.who.int/healthinfo/global_burden_disease/en/
5. World Health Organization. Projections of mortality and causes of death, 2015-2030. [Internet]. Geneva: WHO; 2013. 9p. [cited 2019 Apr 4]. Available from: https://www.who.int/healthinfo/global_burden_disease/projections/en/

6. McPherson K, Steel CM, Dixon JM. ABC of breast diseases. Breast cancer epidemiology, risk factors, and genetics. *BMJ*. 2000; 321(7261):624-8.
7. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *Am J Epidemiol*. 2000;152(10):950-64.
8. Omar S, Khaled H, Gaafar R, Zekry AR, Eissa S, el-Khatib O. Breast cancer in Egypt: a review of disease presentation and detection strategies. *East Mediterr Health J*. 2003;9(3):448-63.
9. Sun YS, Zhao Z, Yang ZN, Xu F, Lu HJ, Zhu ZY, et al. Risk factors and preventions of breast cancer. *Int J Biol Sci*. 2017;13(11):1387-97.
10. Sadiqovic B, Al-Romaih K, Squire JA, Zielenska M. Cause and consequences of genetic and epigenetic alterations in human cancer. *Curr Genomics*. 2008;9(6):394-408.
11. Endogenous Hormones, Breast Cancer Collaborative Group. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. *Lancet Oncol*. 2013;14(10):1009-19.
12. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118,964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol*. 2012;13(11):1141-51.
13. Kobayashi S, Sugiura H, Ando Y, Shiraki N, Yanagi T, Yamashita H, et al. Reproductive history and breast cancer risk. *Breast cancer*. 2012;19(4):302-8.
14. Beral V, Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*. 2003;362(9382):419-27.
15. Gershuni VM, Ahima RS, Tchou J. Obesity and breast cancer: A complex relationship. *CurrSurg Rep*. 2016;4(4):1-9.
16. Key TJ, Schatzkin A, Willett WC, Allen NE, Spencer EA, Travis RC. Diet, nutrition and the prevention of cancer. *Public Health Nutr*. 2004;7(1A):187-200.
17. Dhull AK, Atri R, Kaushal V, Malik G, Soni A, Dhankhar R, et al. Alcohol as a risk factor in HNC, an enormous toll on the lives and communities. *J. Evid. Based Med. Healthc*. 2016;3(12):354-60.
18. Terry PD, Rohan TE. Cigarette smoking and the risk of breast cancer in women. *Cancer Epidemiol Biomarkers Prev*. 2002;11(10):953-71.
19. Brody JG, Moysich KB, Humblet O, Attfield KR, Beehler GP, Rudel RA. Environmental pollutants and breast cancer. *Cancer*. 2007;109(12):2667-711.
20. World Health Organization. Cancer control: Knowledge into action. WHO Guide for Effective Programs. Geneva: WHO, WHO Press; 2007.
21. Yip CH, Smith RA, Anderson BO, Miller AB, Thomas DB, Ang ES, et al. Guideline implementation for breast healthcare in low- and middle-income countries: early detection resource allocation. *Cancer*. 2008;113(8):2244-56.
22. Institute of Medicine (US) Committee on new approaches to early detection and diagnosis of breast cancer; Herdman R, Norton L, editors. Saving women's lives: Strategies for improving breast cancer detection and diagnosis: A Breast Cancer Research Foundation and Institute of Medicine Symposium. Washington (DC): National Academies Press (US); 2005.
23. MARIBS Study Group. Screening with magnetic resonance imaging and mammography of a U.K population at high familial risk of breast cancer: a prospective multi-centre cohort study (MARIBS). *Lancet*. 2005;365(9473):1769-78.
24. Warner E, Plewes DB, Hill K, Causer P, Zubovits JZ, Jong RA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA*. 2004;292(11):1317-25.
25. Kuhl C, Schrading S, Leutner CC, Morakkabati-Spitz N, Wardelmann E, Fimmers R, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *J Clin. Oncol*. 2005;23(33):8469-76.
26. Lehman CD, Blume JD, Weatherall P, Thickman D, Hylton N, Warner E, et al. Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. *Cancer*. 2005;103(9):1898-905.
27. Sardanelli F, Podo F. Breast MR. imaging in women at high risk of breast cancer. Is something changing in early breast cancer detection? *Eur. Radiol*. 2007;17: 873-87.
28. Noor Haslinda I, Juni MH, Abdul Manaf R, Faisal I. Designing and conducting cost-effectiveness analysis studies in healthcare. *Int J Pub Health Clin Sciences*. 2017;4(5):62-7.
29. Stothers, L. Cost-effectiveness analyses. In: Penson DF, Wei JT. (eds). *Clinical research methods for surgeons*. Totowa, New Jersey: Humana Press; 2006. p. 283-96.
30. Edejer TT, Baltussen R, Adam T, Hutubessy R, Acharya A, Evans DB, et al (eds). *Making choices in health: WHO guide to cost-effectiveness analysis*. Geneva: WHO Publication; 2003.
31. Cellini SR, Kee JE. Cost-effectiveness and cost-benefit analysis. In: Wholey JS, Hatry HP, Newcomer KE (eds). *Handbook of practical program evaluation*. 4th ed. Hoboken, NJ, USA: John Wiley & Sons, Inc; 2015. p. 636-72.
32. Bertram MY, Lauer JA, De Joncheere K, Edejer T, Hutubessy R, Kienya MP, et al. Cost-effectiveness thresholds: pros and cons. *Bull World Health Organ*. 2016;94:925-30.
33. Maw AM, Shen NT, Fletcher DR. Updated recommendations for cost-effectiveness studies. *JAMA*. 2017; 317(1): 89.
34. Zelle SG, Nyarko KM, Bosu WK, Aikins M, Niëns LM, Lauer JA, et al. Costs, effects and cost-effectiveness of breast cancer control in Ghana. *Trop Med Int Health*. 2012;17(8):1031-43.
35. Nguyen LH, Laohasiriwong W, Stewart JF, Wright P, Nguyen YTB, Coyte PC. Cost-effectiveness analysis of a screening program for breast cancer in Vietnam. *Value in health regional issues*. 2013;2(1):21-8.
36. Kang MH, Park EC, Choi KS, Suh M, Jun JK, Cho E. The National Cancer Screening Program for Breast Cancer in the Republic of Korea: Is it Cost-Effective? *Asian Pac J Cancer Prev*. 2013;14(3):2059-69.
37. Ulloa-Perez E, Mohar-Betancourt A, Reynoso-Noveron N. Estimation of the cost-effectiveness of breast cancer screening using mammography in Mexico through a simulation. *Rev Inves Clin*. 2016; 68:184-91.
38. Ozmen W, Gurdal SO, Cabioglu N, Ozcinar B, Ozaydin AN, Kayhan A, et al. Cost-effectiveness of breast cancer screening in Turkey, a developing country: Results from Bahçeşehir Mammography Screening Project. *Eur J Breast Health*. 2017;13(3):117-22.
39. Nguyen CP, Adang EMM. Cost-effectiveness of breast cancer screening using mammography in Vietnamese women. *PLoS ONE*. 2018;13(3):e0194996.
40. Okonkwo QL, Draisma G, der Kinderen A, Brown ML, de Koning HJ. Breast cancer screening policies in developing countries: A cost-effectiveness analysis for India. *JNCI*. 2018;100(18):1290-300.
41. El Mahi T, Messoudi W, Sanchiz MD, Saadani G, Zidouh A, Nejjarri C, et al. Cost-effectiveness analysis of a screening program for breast cancer in Morocco. *Revue d'Épidémiologie et de Santé Publique*. 2018; 66(3):S160.
42. Sun L, Legood R, Sadique Z, dos-Santos-Silva I, Yang L. Cost-effectiveness of risk-based breast cancer screening programme, China. *Bull World Health Organ*. 2018;96(8):568-77.
43. Denewer AT, Hussein O, Farouk O, Elnahas W, Khater AA. Cost-effectiveness of clinical breast assessment-based screening in rural Egypt. *World J Surg*. 2010;34(9):2204-10.
44. Kolaei FAZV, Broeders MJM, Kiemeny LALM, Verbeek ALM. Opportunity for breast cancer screening in limited resource countries: a literature review and implications for Iran. *Asian Pac J Cancer Prev*. 2011;12(10):2467-75.
45. Shen S, Zhou Y, Xu Y, Zhang B, Duan X, Huang R, et al. A multi-centre randomised trial comparing ultrasound vs mammography for screening breast cancer in high-risk Chinese women. *Br J Cancer*. 2015;112(6):998-1004.
46. Lauby-Secretan B, Scoccianti C, Loomis D, Benbrahim-Tallaa L, Bouvard V, Bianchini F, et al. Breast-cancer screening—viewpoint of the IARC Working Group. *N Engl J Med*. 2015;372(24):2353-8.

47. Zelle SG, Baltussen RM. Economic analyses of breast cancer control in low- and middle-income countries: a systematic review. *Syst Rev.* 2013;2(1):20.
48. Salem DS, Kamal RM, Helal MH, Hamed ST, Abdelrazek NA, Said NH, et al. Women Health Outreach Program; a new experience for all Egyptian women. *J Egypt Natl Cancer Inst.* 2008;20(4):313-22.
49. Salem DS, Kamal R, Said NH, Adel I, Talaat S, Adel L, et al. The Egyptian National Breast Screening Program: Priorities, challenges, and results of the pilot phase. *J Clin Oncol.* 2009;27(15):1523.
50. Ministry of Health and Population. [Internet]. Cairo: MOHP; [Cited 2019 Oct 28]. The initiative of the president of the republic to support the health of Egyptian women. [about 4 screens]. Available from: <http://www.100millionseha.eg/>