Original Article

Cost Effectiveness Analysis Of Breast Cancer Screening In Upper-And Low-Middle Income Countries, Focusing On Egypt: A Systematic Review

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Abstract

Background Breast cancer is the leading cause of death among women. Screening using mammography is proposed as an effective intervention for reducing early deaths due to breast cancer. **Aim of the study** to assess the cost-effectiveness of different screening programs in upper and low-middle income economies. **Methods** We conducted a systematic review, we searched pub-med, Google Scholar, Cochrane and Embase with related search words. We screened the titles and abstracts for relevancy. Our searches yielded 366, after initial screenings and assessments, we excluded (228 studies excluded by title being irrelevant such as breast cancer treatment or awareness program), we assessed the abstracts of 121 articles and excluded 80 articles (including 7 systematic review studies), then reviewing the full-texts of 41 studies and finally we included Fourteen studies that met the minimum inclusion criteria. **Results** The majority of these studies were of poor-quality regarding cost calculation, breast cancer incidence among different age groups, mortality rate of breast cancer. Studies demonstrated the cost-effectiveness of breast cancer screening strategies. **Conclusions** This review shows that the evidence base to guide strategies for breast cancer control in upper and low-middle income countries are limited and of poor quality. There is very little evidence to provide specific recommendations on screening by mammography versus clinical breast examination, the frequency of screening, or the target population.

Keywords: Cost effectiveness, Breast cancer, Screening, low- and middle-income economies, developing countries.

INTRODUCTION

Breast cancer was reported to be the second most common cancer in the world and, by far the leading cause of death among women. 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). Breast cancer, once considered the disease of the developed countries, has slowly but surely become one of the commonest cancers among women in less developed world. (3) Increasing life span, delayed childbearing and Westernized lifestyle might have contributed to this surge in breast cancer incidence. (4) More concern is the higher mortality rate of breast cancer in lowmiddle income economies; accordingly, breast cancer is the number one killer cancer among women in developing countries (4). As regards to the World Bank countries and leading group economic classification, for the current 2020 fiscal year (5), low-income economies are defined as those with a GNI per capita, calculated using the World Bank Atlas method, of $1,025 or less in 2018; lower middle-income economies are those with a GNI per capita between $1,026 and $3,995; upper middle-income economies are those with a GNI per capita between $3,996 and $12,375 (5). 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 , the goals of screening are to reduce mortality by detecting cancer early when treatment is more effective and has less morbidity. (6) Current methods of breast screening and diagnosis include Breast Self-Examination (BSE), Clinical Breast Examination (CBE), Mammography, Ultrasonography, and Magnetic Resonance Imaging (MRI) (7). Considering the limited resources and equity concerns for health systems, the importance of making decisions about healthcare interventions based on cost effectiveness evidence is increasing every day (8).

The most important question for less developed countries now would be what is the most cost-effective screening intervention to spend their limited financial resources on. In our research we aimed to conduct a systematic review intends to evaluate the cost-effectiveness of female breast cancer screening policies in upper and low-middle income economies, through an analysis of current literature. The objective of this research paper is to declare the current breast cancer screening policies in these countries as either cost-effective or ineffective according to screening modality starting age of screening, intervals and measured outcome (i.e QALYs, DALYS ACER or ICER) with comparison to established program or no screening to make recommendations that will increase cost-effectiveness in the future. Cost effectiveness analysis can provide experts with useful information for programming and developing a breast cancer control policy. Such an analysis can provide data required for balancing the budget and fair allocation of the limited re-sources in national breast cancer control programs and subsequently determining the most effective way for providing diagnostic and therapeutic care (9).

Review of the breast cancer screening program in Egypt

In Egypt, breast cancer is the most common cancer, occurring at ate of 32 % of all cancer types among women (10). Although incidence levels in Egypt are not as high as in more developed nations (11), breast cancer mortality rates are higher in Egypt than in Western countries (19.1 deaths per100,000 compared with 14.9 deaths per 100,000 in the United States) (12).

In Egypt, several barriers to breast cancer screening, including inadequate knowledge of breast cancer in the population, low access to breast cancer screening facilities, self-care as a low priority in women, fear of breast cancer diagnosis, and other socio-demographic factors, have been identified. (13,14) 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. (15) 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 then extended to another 11 governorates on 1 September 2019, then to the remaining 7 governorates 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 for all females 18 years and over, and 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. (16) 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. (17)

The lack of data about the definite breast cancer incidence in Egypt, participation rate, stage at diagnosis as well as the health care expenditure on breast cancer diagnosis and treatment, make it difficult to conduct an economic evaluation plan to assess the cost and effectiveness of different intervention, the target population and screening modalities and intervals.

Throughout our systematic search we could not find any significant study to assess the CEA of breast cancer screening or prevention in Egypt apart from a study addressed Cost-Effectiveness of Clinical Breast Assessment-Based Screening in Rural Egypt (Denewer Adel et al 2010) (18) which was excluded from our review for not meeting the inclusion criteria and quality CEA study.

The chances of success of this initiative are great, as it has full support of the government and is not expected to face any financial constraints, yet it needs dedicated economic evaluation to measure the cost and outcomes. It is also important to ensure sustainability of the program. (16)

Methods

Study Design A systematic search of any cost effectiveness studies on breast cancer screening program in upper and lower middle income countries, was conducted. We included population-based programs, cost-effectiveness studies alongside randomized controlled trials, or studies using modeling techniques to estimate cost-effectiveness ratios (8). Our search included studies published in English language only. Data bases searched were pub-med, Google Scholar, Cochrane and Embase with related search words.

Inclusion and exclusion Criteria

1. The research studying the cost effectiveness of breast cancer screening in population based average risk women in Upper and lower-Middle-Income countries.
2. We included cost-effectiveness studies CEA alongside trials as well as those studies that used modeling techniques based on routine data or data from previous studies (the total number of studies was 366). The systematic reviews studying the cost effectiveness of breast cancer screening using mammography and studies of other screening approaches like Clinical breast examination (CBE) and breast ultrasound, all were eligible for inclusion.
3. The exclusion criteria were: studies on mammogram techniques (comparing different mammogram technologies), studies of screening in women with special diseases, high risk screening interventions, studies of other screening approaches (e.g. selfexamination and MRI) studies of higher income economies ,studies with ambiguous target age groups, studies which calculate cost per case and studies of opportunistic screening approaches.

Search strategy

We systematically searched international databases of PubMed ,Google Scholar Cochrane and Embase web pages in the last 10 years (from 2010 to 2020) As an exception to this time-frame we included a study being conducted in India, (Quirine Lamberts Okonkwo et al, 2008) due to limited studies in this category, search was limited to English language publications with full text available. We also searched the reference lists of the identified studies.In order to find all the related articles. Keywords used were: “cost effectiveness analysis OR cost benefit analysis OR economic evaluation, breast cancer screening program OR breast cancer early detection OR breast malignancy screening, AND developing countries”.

Selecting studies, quality assessment and data extraction

The titles of the resulted 366 articles were screened by all reviewers to identify papers and exclude those that were obviously unrelated to our review as a step one. Step two the abstracts of the remaining 121 articles were assessed for inclusion and exclusion criteria. Based on reviewer’s consensus, the studies which do not meet the inclusion criteria or were unrelated to our study objective were omitted. The full texts of 41 articles were assessed to finally include 14 articles in our review. Extracted data from included studies into the data extraction sheet and it was checked by two authors.

Quality assessment using the CHEERS instrument

We assessed the quality of each reviewed study using the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist(19) This checklist is composed of 24 items suggested for inclusion when reporting economic evaluations of health care interventions, we assumed that studies containing over a half of contents in each item would be assessed as “Yes”, or, conversely, the result was “No”. This was done by two reviewers read the selected articles and then examined differences on items’ ratings.

Table 1 presents the evaluation of our 14 research studies fulfilling each recommendation of CHEERS. Among twenty four recommendations, there are some items presented by high percentage of studies whereas some items were almost neglected.

Results

Our searches yielded 366 articles after duplicate removal the remaining number was 349 (17 duplicate articles in the search). After initial screenings and assessments, we excluded (228 studies excluded by title being irrelevant and breast cancer treatment awareness program) we assessed the abstracts of 121 articles and excluded 80 articles (including 7 systematic review studies) reasons for exclusion, not a CEA, including other cancers, wrong population, screening high risk population, genetic testing or MRI screening modalities. Then reviewing the full-texts of 41 studies and finally we included 14 studies that matched the inclusion criteria, being population based CEA in upper and low-middle income countries by CBE and or mammography with comparison with no screening interventions or already established ones. **(Fig.1).** Studies on cost-effectiveness of screening programs in upper and low middle-income 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 other studies estimated the DALYs and the QALYs.

Table (2) CHEERS Checklist Quality Assessment

Section	Item No	Rural Iran	Hong Kong	India	Iran	Peru	Vietnam	Mexico	Costa Rica & Mexico	Korea	Vietnam	Morocco	Kazakhstan	Turkey	China	No.	Yes %	No.	No %
Title & abstract																			
title	**1**	√	√	√	√	√	√	√	√	√	√	√	√	√	√	14	100	0	0
abstract	**2**	√	√	√	√	√	√	√	√	√	√	√	√	√	√	14	100	0	0
introduction																			
Background & objectives	**3**	√	√	√	√	√	√	√	√	√	√	√	√	√	√	14	100	0	0
methods																			
Target pop	**4**	√	√	√	√	√	√	√	√	√	√	√	√	√	√	14	100	0	0
location	**5**	√	√	√	√	√	√	√	√	√	√	√	√	√	√	14	100	0	0
perspective	**6**	√	-	√	-	√	√	-	√	√	√	√	√	√	√	11	78.6	3	21.4
comparators	**7**	-	-	-	-	-	-	-	√	√	√	√	√	√	√	7	50	7	50
Time horizon	**8**	√	√	√	√	√	√	√	√	√	√	√	-	√	√	13	92.8	1	7.2
Discount rate	**9**	√	-	√	√	√	√	√	√	-	√	√	√	-	√	11	78.6	3	21.4
Health outcome	**10**	√	√	√	√	√	√	√	√	√	√	√	√	√	√	14	100	0	0
Measurement of	**11**	√	√	√	√	√	√	√	√	√	√	√	√	√	√	14	100	0	0

effectiveness																			
Measurement & valuation of preference based outcome	**12**	√	√	√	√	√	√	√	√	√	√	√	√	√	√	14	100	0	0
Estimating resources & costs	**13**	√	√	√	√	√	√	√	√	√	√	√	√	√	√	14	100	0	0
Currency, price date & conversion	**14**	√	√	√	√	√	√	√	√	-	√	√	-	√	√	12	85.7	2	14.3
Choice of model	**15**	√	√	√	√	√	√	√	√	√	√	√	√	√	√	14	100	0	0
assumptions	**16**	√	√	√	√	√	√	√	√	√	√	-	-	√	√	12	85.7	2	14.3
Analytical methods	**17**	√	√	√	√	√	√	√	√	√	√	√	√	√	√	14	100	0	0
results																			

Study parameters	18	√	√	√	√	√	√	√	√	√	√	√	√	√	√	14	100	0	0
Incremental costs & outcome	**19**	√	√	√	√	√	√	√	√	√	√	√	√	√	√	14	100	0	0
Characterizing uncertainty	**20**	√	-	√	√	√	√	√	-	√	√	√	√	√	√	12	85.7	2	14.3
Characterizing heterogeneity	**21**	√	-	√	√	√	√	√	-	√	√	√	√	√	√	12	85.7	2	14.3
discussion																			
Study finding, limitation	**22**	√	√	√	√	√	√	√	√	√	√	-	√	√	√	13	92.8	1	7.2
other																			
Source of funding	**23**	-	√	-	-	-	√	-	√	-	-	-	-	√	√	5	35.7	9	64.3
Conflicts of interest	**24**	-	-	-	-	√	√	-	-	-	-	-	-	-	-	2	14.3	12	85.7
total	21	18	21	20	23	23	20	21	20	22	20	19	22	23					

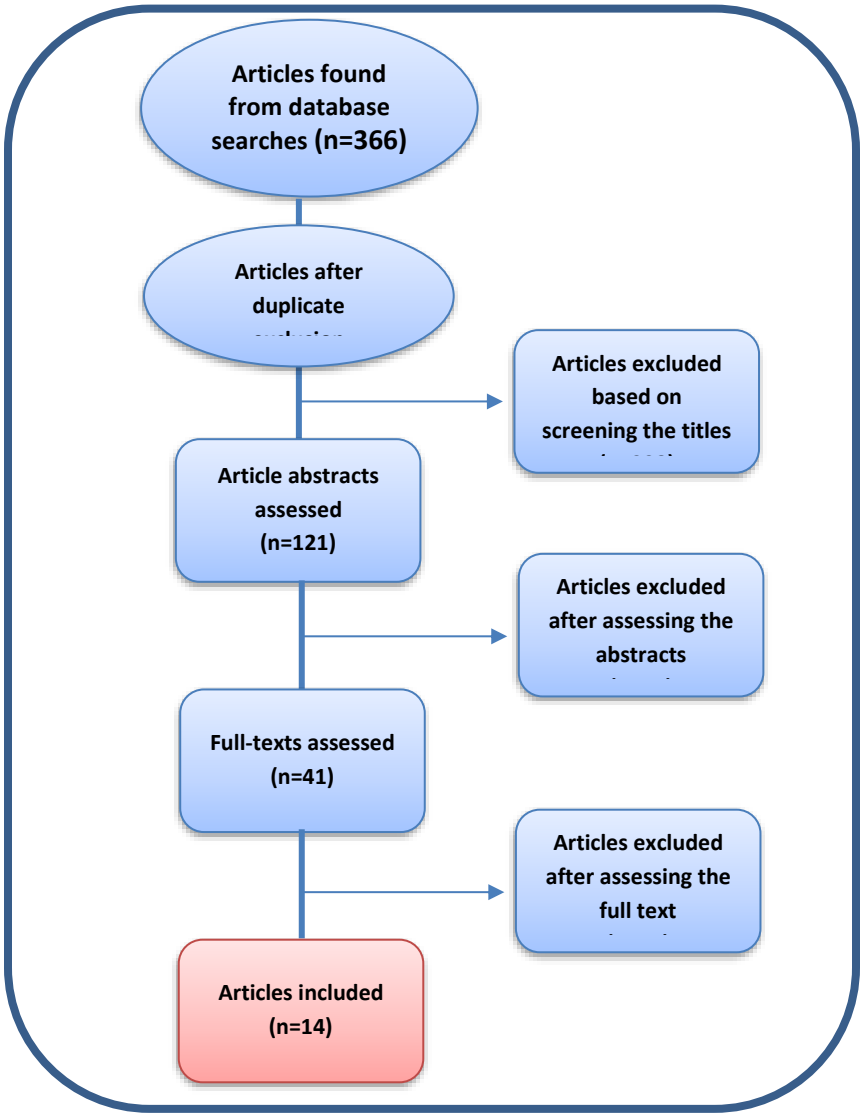

Fig (1) PRISMA diagram of literature review process for PubMed Search and Screening

Table (2) Summarizes the findings of fourteen studies of CEA of different screening methods of breast cancer

Author	Country	Perspective	Model	Screen.	Comp.	Pop.	Freq. of	Effect.	Measure	Conclusion
Okonkwo et al, (2008)	India	Health care payer perspective	MISCAN	CBE&MS	No screening	40-60 yrs	Every 5 years	LYG, LYS	ICER	CBE is CE compares with that of MS
Nguyen et al, (2013)	Vietnam	Health care payer perspective	Markov Model	CBE	No program	40-55 yrs	Yearly	LYS	ICER	CBE is very CE
Kang et al, (2013)	Korea	Government expenditure perspective	NA??	MS	No screening	≥40 yrs	Biennially	LYS	ICER	NCSP seems CE

Nguyen et al, (2018)	Vietnam	NA	Decision tree model and Markov model	MS	No screening	45-64yrs	Annual	YLG	ICER	MS is CE
El Mahi et al, (2018)	Morocco	Health care payer perspective	Markov Model	CBE	No screening	45-69 yrs	Biennially	LYS	ICER .	Biennial CBE is not CE
Wong et al., (2012)	Hong Kong China	NA	Markov Model	MS	No screening	40-69 or 79yrs	Biennially	QALYs	ICER	Biennially MS is CE
Zelle S. G (2013)	Peru	Healthcare perspective	Mathematical modeling	MS and CBE	No screening	40-69yrs	Triennially or biennially	DALYs	ACER ICER	MS and CBE is CE
Niens, L. M.,(2014)	Costa Rica and Mexico	NA	Simple modeling	CBE& MS	No intervention.	40-70 yrs	Biennially	DALYs	ICER	CBE is CE MS is CE if more resources available
Haghighat, S(2016)	Iran	NA	Markov model and decision tree	MS	No screening	40-70yrs	Annual	QYALYs	ICER	MS is CE
Zehtab, N(2016)	Iran	Policy-makers of insurance	Decision tree modeling	MS	No screening	35-69 yrs	Annual	DALYs	ACER ICER	MS is CE
Ulloa-Perez et al, (2016)	Mexico		Simulation model	MS	No program	25-75 yrs	Annual Biennially Triannual	DALYs	ACER	MS is highly CE when performed every 3 years
Ozmen et al, (2017)	Turkey	Health care perspective	Simple modeling	MS	(TNBCRP) No organized screening	40-69 yrs	Biennially	LYS	ICER	Biennial MS is highly CE
Li Sun et al, (2018)	Rural of China	Societal perspective	Markov Model	CBE and US	No screening	Rural women 35-64	Every 3 years	QALYs	ICER	MS Not cost effective
Salikhanov,2019	Kazakhstan	Health care perspective	Cross sectional?	MS	No screening	50-60 yrs	Biennially	LYS& QALYs	ICER	Biennially MS is CE

Comp: comparison, 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: (TNBCRP): Turkish National Breast Cancer Registry Program.

The results of the fourteen studies on cost-effectiveness of screening programs for breast cancer in upper and low -middle income countries

Costs included in CEA of screening depended on perspective, it included 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.(20) The most common cost effectiveness measure used in the CEA studies are cost per life years saved, calculated for alternatives based on age groups and screening intervals. Other measures used in the studies included: cost per QALY gained, cost per DALY averted, cost per cancer detected, cost per death averted and per life saved.(8) The majority of the studies
extracted the data on the quality and efficacy of the screening tests from the available ongoing screening programs, local cancer registries and routine data.

Studies on cost-effectiveness of screening programs included in our study under the inclusion criteria, used different screening methods (include mammography, clinical breast examination or combination of both) and calculated different outcome measures such QALYs, DALYs, ICER or ACER. The duration of follow up was also different as the interval screening were annual, biennial or triennial. Five out 14 studies were conducted in low-middle income countries (two studies conducted in Vietnam), and 9 studies were conducted in upper income countries among which 2 studies were CEA of screening program in China and 2 were about Iran. Two studies out of fourteen **(Vietnam Nguyen et al,(2013) and Morocco El Mahi et al, (2018))** were aimed to evaluate costs and effects of an annual or biennial screening program using only CBE compared to the absence of screening It was concluded that the annual breast cancer screening with CBE for women aged 40 to 55 years is considered very cost-effective in Vietnam according to the WHO suggests criterion for cost-effectiveness that is less than three times the GDP per capita while in Morocco It was concluded that biennial CBE of women aged 45-69 years at 32% coverage rate cannot be considered costeffective. (21,22) Only one study which launched a breast cancer screening with clinical breast examination coupled with ultrasound as the primary tool compared to no screening **in Rural of China Li Sun et al, (2018),** breast cancer screening cost $186.7 more and led to a loss of 0.20 quality-adjusted life years (QALYs). Breast screening was more expensive and did harm to health among rural women of China with an incremental cost-effectiveness ratio (ICER) of $916/QALY. (23) Three studies out of fourteen **(India Okonkwo et al, (2008),Peru Zelle S. G (2013) and Costa Rica and Mexico Niens, L. M.,(2014))** were evaluating the cost-effectiveness of screening with CBE and mammography screening are combined and

this combination considered cost-effectiveness for the three studies especially in Peru when both CBE screening and mammography screening are combined (from $4,239 per DALY averted). (24, 25, 26)

Eight studies **(Korea Kang et al, (2013), Vietnam Nguyen et al, (2018), Hong Kong China Wong et al., (2012), Iran two studies Haghighat, S(2016), and Zehtab, N (2016), Mexico Ulloa-Perez et al, (2016), Turkey Ozmen et al, (2017) and Kazakhstan Salikhanov, (2019)** out of fourteen estimated the cost-effectiveness of different breast cancer screening programs using mammography compared to no program. All the eight studies considered cost effectiveness but at different degrees (highly cost effectiveness) like the case of turkey and other which can be considered cost effectiveness with some limitation. (27,28,29,30,31,32,33)
The case of Iran we included two studies, one of them Haghighat, S (2016), its results revealed that the incremental cost effectiveness ratio (ICER) of mammography screening in Iranian women in the first round was Int. $ 37,350 per QALY gained and being cost effective yet the model showed that the ICER in the second and third rounds of screening program were Int. $ 141,641 and Int. $ 389,148 respectively which is not cost effective, the other study Zehtab, N(2016) found that although the screening intervention is more cost-effective than the alternative (no-screening) strategy, it seems that including breast cancer screening program in health insurance package may not be recommended as long as the target group has a low participation rate. Our population based in all the studies was women between (35-79) years old except in the case of the study of Mexico which was for women from (25-75) which concluded that the use of mammography as a screening method for women is highly cost-effective only when coverage includes only women from the age group of 40-70 years, resulting in fewer unnecessary biopsies and a decrease in over diagnosis.

Five of our studies, the screening programs were implemented every 2 years ,four studies were implemented yearly ,one study was implemented every 3 years and another was implemented every five years and the rest of the studies one of them (Peru) study which implemented triennial or biennial screening strategies and (Mexico) which 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 and which concluded that the use of mammography as a screening method for women is highly costeffective only when the periodicity program schedule is every three years. The outcomes estimation of six studies out of fourteen was LYS (life years saved) ,LYG(life years gained) all these studies can be considered cost effectiveness like the case of Vietnam 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 WHO suggests criterion for costeffectiveness that is less than three times the GDP per capita, According to these criteria, the CBE screening program in Vietnam is ‘‘very cost-effective’’ in the other hand in Morocco study it showed that CBE was not cost effective. Four studies estimated (DALYs) which all were cost effective except a study of Costa Rica and Mexico, For Mexico, if more resources are available in Mexico, biennial mammography screening for women 50–70 years (ICER US$12,718/DALY), would be cost effective. Three studies estimated (QYALYs) and all of them were cost effective except the study of rural of China, and only one study estimated both QYALYs and LYS. A study of India was the only study which measure the costs of screening for breast cancer and its effects on mortality. All the studies measured (ICER) except only one studies which measured (ACER) and two studies which measured both ICER and ACER.

As we can see most of the upper middle-income economies found that screening programs of breast cancer is cost effectiveness with some exceptions like in Hong Kong and Iran duo to limited resources or low participant rate. Each CEA should be assessed on a country-by-country basis. There is no data shows exactly what amount of “incremental cost” is acceptable for individual upper middle-income economies, definitely not as much as that identical to the £20,000– 30,000 per QALY established in the UK (National Institute for Health and Care Excellence 2014). In a longitudinal comparison, we can use of the cost-effectiveness (CE)/GDP per capita ratio, (Yoo et al. 2013) as well as CE/yearly health expenditures per capita ratio, (van Ineveld et al. 1993) to balance the differences among countries. If the CE/GDP per capita ratio is greater than 1, then MS can be deemed inefficient, as the cost per life year saved exceeds the per capita GDP. Based on the 14 articles we found that there is an 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 different age groups, in general there appears to be a narrow balance of benefits compared with harms, particularly in younger and older women. (7) Ultrasonography is typically used as a complementary method for the assessment of mammographically or clinically detected breast masses and useful added tool in dense breast and resolving equivocal mammographic. (6).

Conclusion and Recommendations

Findings of our review suggested that further studies of cost-effectiveness of breast cancer screening must be conducted on country basis and along with clinical trials, it might be of value that pilot programs alongside with comprehensive evaluation plan to be adopted. Health care systems in upper and low-middle income countries 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 upper and low middle income countries 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.(35) Another important challenge is the problem of investment in screenings; governments of today should pay for the benefits partially measurable by subsequent governments.(35). Due to the lack of breast cancer awareness among the population, the inadequate identification of appropriate target populations, the low likelihood of up-take and compliance, the scarcity of mammography resources, unaffordable screening costs and overall sub-optimal outcomes in survival benefit, the best interventions to be taken for mortality reduction of breast cancer must be customized to accommodate local conditions, and making the best use of limited resources is essential according to each country specific characteristics (social, economic and cultural context).

Limitations to our study

With the large scope of the searched literature, it is possible that we missed some of the important information, despite the comprehensive approach applied in this review. We also deviated from the protocol, including a study published in 2008 in India due to deficient studies addressing our research aspect. The AMSTAR tool was not fully applicable to assess the quality of the systematic reviews with cost and cost-effectiveness outcomes. In addition, the applied transferability metric was not validated, and the use of a standard validated tool specific for systematic reviews of economic evaluations was not also included.

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