PHARMACOECONOMIC STUDIES OF BREAST CANCER EARLY DETECTION PROGRAMME IN MALAYSIA

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PHARMACOECONOMIC STUDIES OF BREAST CANCER EARLY DETECTION PROGRAMME IN MALAYSIA

by

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LIST OF ABBREVIATIONS

BCEDP	Breast cancer early detection programme
CBE	Clinical breast examination
HIC	High-income countries
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost utility ratio
LMIC	Low- middle-income countries
MMG	Mammography
COI	Cost-of-illness
CEA	Cost-effectiveness analysis
HRQoL	Health related quality of life
GDP	Gross domestic product
QALY	Quality-adjusted life years
WTP	Willingness-to-pay

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KAJIAN FARMAKOEKONOMI PROGRAM PENGESANAN AWAL KANSER PAYUDARA DI MALAYSIA

ABSTRAK

Insiden kanser payudara terus meningkat di Malaysia, dengan 50.5% baru didiagnosis pada peringkat lanjut III dan IV. Pelbagai kajian melaporkan hasil campuran keberkesanan kos program pengesanan awal kanser payudara di kalangan negara berpendapatan rendah dan sederhana. Kajian kami bertujuan untuk menganggarkan keberkesanan kos program pengesanan awal kanser payudara (BCEDP) melalui model Markov untuk Malaysia. Model Markov telah dibina berikutan peralihan daripada peringkat rendah kepada peringkat lanjut dengan kematian sebagai peringkat akhir, dalam ufuk seumur hidup. Kami membandingkan pemeriksaan payudara klinikal (CBE), mamografi (MMG), dan gabungan CBE dan MMG dengan tiada program untuk wanita berumur 40 tahun ke atas. Model ini digunakan untuk meramalkan kos seumur hidup dan hasil kesihatan ketiga-tiga program daripada perspektif pembayar dan masyarakat. Saiz sampel pada mulanya dikira sebagai 268 untuk kedua-dua data kos dan hasil kesihatan utiliti, dengan pelarasan dikira disebabkan penambahan tapak pengumpulan data. Data kos diperoleh daripada profil pesakit kanser payudara di Hospital Kuala Lumpur, dan tinjauan pesakit telah dijalankan untuk mendapatkan data utility di beberapa hospital. Analisis sensitiviti telah dijalankan untuk menangani ketidakpastian dalam parameter. Ambang kesanggupan membayar (WTP) bagi satu keluaran dalam negara kasar pada RM51,830 (1 USD = RM4.4497, 2023) telah digunakan dalam kajian ini. Tahun hayat pelarasan kualiti (QALY) yang diperoleh dikira mengikut kualiti hidup, dengan tempoh hayat yang diperoleh sebagai manfaat kesihatan intervensi jika dibandingkan

dengan tiada pendedahan kepada BCEDP. Saiz sampel akhir sebanyak 268 telah diperolehi untuk kedua-dua kos dan hasil. MMG melaporkan keuntungan 2.23 QALY, diikuti oleh gabungan CBE dan MMG pada 1.12 dan CBE pada 0.67. Ketiga-tiga BCEDP menunjukkan ICUR kurang daripada satu WTP. Dengan setiap perspektif pembayar dan masyarakat, MMG melaporkan RM13,011 dan RM 21826/QALY, diikuti dengan gabungan CBE dan MMG pada RM13,419 dan 23551/QALY, manakala CBE melaporkan ICUR tertinggi pada RM13,702 dan 23944/QALY. Analisis sensitiviti mengenal pasti bahawa EQ-5D utiliti, kos perubatan langsung dan kadar diskaun mempengaruhi keputusan tetapi mempunyai kesan terhad pada kesimpulan. Kajian ini mempunyai had parameter input yang diperoleh dari negara yang berbeza, yang boleh menjejaskan anggaran Markov. MMG kekal sebagai protokol pemeriksaan kanser payudara standard, manakala CBE menawarkan nilai penjagaan kesihatan untuk capaian populasi yang lebih luas dalam bajet penjagaan kesihatan yang terhad. Maklumat ini akan membantu pihak berkepentingan dasar membuat keputusan termaklum dalam BCEDP.

PHARMACOECONOMIC STUDIES OF BREAST CANCER EARLY DETECTION PROGRAMME IN MALAYSIA

ABSTRACT

The incidence of breast cancer continues to increase in Malaysia, with 50.5% newly diagnosed at stages III and IV. Various studies reported mixed outcomes of the cost-effectiveness of breast cancer early detection programmes among low- and middle-income countries. Our study aims to estimate the cost-effectiveness of breast cancer early detection programmes (BCEDP) through a Markov model for a Malaysian population. The Markov model was constructed following the transition from lower to advanced stages with death as the end stage, in a lifetime horizon. We compared clinical breast examination (CBE), mammography (MMG), and a combination of CBE and MMG to no programme for women aged 40 and older. This model was used to forecast the three programmes' lifetime costs and health outcomes from the payer's and societal perspectives. The sample size was initially calculated to be 268 for both the cost data and health outcomes of utilities, with an adjustment calculated due to the addition of data collection sites. Cost data were obtained from breast cancer patient profiles in Hospital Kuala Lumpur, and a patient survey was conducted to obtain the utility data from a few hospitals. Sensitivity analysis was conducted to address the uncertainty in parameters. A willingness-to-pay (WTP) threshold of one gross domestic product at RM51,830 (1 USD = RM4.4497, 2023) was used in this study. Quality adjusted life years (QALY) gained were calculated by the quality of life, with the length of life gained as the health benefit of an intervention when compared to no exposure to BCEDP. A final sample size of 268 was obtained. MMG reported a 2.23 QALY-gained, followed by the combination of CBE and MMG at 1.12 and CBE at

0.67. All three BCEDPs showed ICURs of less than one WTP. With each of the payer's and societal perspectives, MMG reported RM13,011 and RM 21826/QALY, followed by the combination of CBE and MMG at RM13,419 and 23551/QALY, while CBE reported the highest ICUR at RM13,702 and 23944/QALY. Sensitivity analysis identified that EQ-5D utilities, direct costs, and discounting rates influenced the results but had a limited impact on the conclusions. The study has the limitation of some input parameters being obtained from different countries, which could affect the Markov estimation. MMG remains the standard breast cancer screening protocol, while CBE offers healthcare value for a wider population reach within a limited healthcare budget. This information will help policy stakeholders make informed decision in BCEDP.

CHAPTER 1

INTRODUCTION

1.1 Brief Overview

Breast cancer is a noncommunicable disease for which the World Health Organization (WHO) supports global preventive and early detection measures in the report of the Global Action Plan for the prevention and control of noncommunicable diseases (Geneva: World Health Organization, 2013). WHO supports the notion that cancer early detection leads to better outcomes and possible cure.

Breast cancer incidence and mortality age-adjusted rates per 100,000 populations rapidly increase worldwide, with rate differences between low- and middle-income countries (LMICs) and high-income countries (HICs) (Bray et al., 2024). HICs have a significantly higher incidence of breast cancer with a lower mortality rate of breast cancer when compared to LMICs. Late diagnosis of breast cancer in the LMICs was due to the lack of cancer awareness and accessibility to health care, as reported by a few authors (Mubarik et al., 2022; Yip et al., 2015). This is an obstacle to reducing the mortality of breast cancer in LMICs.

Malaysia has been facing similar situations for more than a decade, with increasing incidence and advanced cancer stages at diagnosis (Institut Kanser Negara, 2024). Several factors influenced the late diagnosis of breast cancer among Malaysian women (Khan et al., 2015; Norsa'adah et al., 2021), including the misconceptions about cancer screening, diagnosis and treatment, along with the use of alternative medicine. Breast cancer awareness and screening campaigns would need to account for the specific factors about the community (Geneva: World Health Organization, 2013).

According to the Malaysian National Cancer Registry 2017 – 2021 (Institut Kanser Negara, 2024). Breast cancer is the most common cancer in Malaysia, with a 38.9 per 100,000 population age-adjusted incidence rate. This is an increase from 34.1 per 100,000 population in the previous report of 2012 – 2016. Over half of newly diagnosed breast cancer cases in Malaysia (50.5 percent) were in the advanced stages of stage III and IV (Institut Kanser Negara, 2024), which increased from 48 and 43.2 percent in the previous cancer registry reports. Concerted efforts are needed to detect breast cancer at earlier stages. A health economic evaluation of the current status of the breast cancer early detection programme (BCEDP) in Malaysia could provide stakeholders with informed decisions in designing future programmes.

1.2 Early detection of breast cancer

Many HICs have initiated population-based breast cancer early detection programmes, which could improve the treatment outcomes and survival of breast cancer patients as well as reduce the financial burden on the healthcare system (Sankatsing et al., 2020). The current cancer screening programmes in Malaysia are selective, opportunistic, and not population-based, and they are limited within the healthcare resources (Htay et al., 2021).

Early diagnosis and screening of the asymptomatic population are the two strategies proposed for cancer early detection. WHO's Global Breast Cancer Initiative Implementation Framework (GBCI) (World Health Organisation, 2023) was started in 2021 to guide the global health systems in reducing global breast cancer mortality. One of the key performance indicators of GBCI is to have more than 60% of breast cancer being detected at stages I and II, the early stages of breast cancer. BCEDP, which includes breast cancer awareness, clinical breast examination (CBE), and

mammography (MMG) screening, was the primary strategy discussed in GBCI. It advocates for countries to plan and initiate BCEDP in phases depending on available healthcare resources.

The Breast Cancer Clinical Practice Guidelines (CPG) of the Ministry of Health Malaysia recommends breast cancer screening for women from 50 onwards with biennial MMG screening; women between the ages of 40 and 49 are urged to get screened if they are at high risk of breast cancer (Ministry of Health Malaysia, 2019a). Women were urged to practice breast self-examination frequently and take responsibility for the early detection of breast cancer, similarly to CBE, which CPG advocates as an early clinical experience of women being conducted by healthcare professionals. Although BSE and CBE are not the standard breast cancer screening methods, they raise breast cancer awareness and earlier detection of breast cancer (Mittra et al., 2021; Yeong et al., 2023).

1.3 Late diagnosis of breast cancer

Studies indicated that Malaysian women have a good awareness of breast cancer but lack self-action in going for mammography (Mahmud & Aljunid, 2018; Norsa'adah et al., 2011). Norsa'adah et al. found that the misconceptions that breast cancer cannot be cured and that mastectomy disfigures the body were among the factors that prohibited early diagnosis (Norsa'adah et al., 2011). It further reported the social-cultural perception of the fear of women being abandoned by their husbands if they were diagnosed with breast cancer. The studies suggested that breast cancer programmes with the awareness component will help to reduce these misconceptions of women (Norsa'adah et al., 2011).

According to several studies, MMG is the most cost-effective breast cancer early detection programme in Western countries; it is most cost-effective for women aged 50 to 69 years old (Capri & Russo, 2017; Mandrik et al., 2019). However, other options, such as CBE and BSE, play a role in increasing rates of earlier breast cancer detection in LMICs (Yuniar et al., 2020). The diverse nation-specific resources, breast cancer incidence, prevalence, and mortality rates affect the early detection of breast cancer in these countries.

There is a need to determine which BCEDPs are most suitable and cost-effective for Malaysians. Before a cost-effectiveness analysis (CEA) can be conducted, the parameters of the cost-of-illness (COI) of breast cancer and the health-related quality-of-life (HRQoL) weights (utilities) of each cancer stage must be determined.

1.4 Factors affecting early diagnosis of breast cancer

Various factors were reported to influence the late diagnosis of breast cancer in LMICs, which include women's awareness of breast cancer symptoms, negative attitudes and perception towards the disease, cultural and social beliefs, and the influence of complementary and alternative medicine (Khan et al., 2015; Norsa'adah et al., 2021). The importance of health education and awareness programmes in promoting early identification, diagnosis, and treatment of breast cancer needs to be emphasised among Malaysian women for the early detection of breast cancer (Dahlui et al., 2011).

Financial difficulties were mentioned as a factor for the delayed diagnosis of breast cancer (Gebremariam et al., 2019). Financial toxicity refers to the adverse financial impacts on patients due to cancer management (PDQ Adult Treatment Editorial Board, 2002). Advanced cancer stages, high out-of-pocket costs, productivity

loss and medical debts are often associated with financial toxicities of cancer patients. A high percentage of patients with financial difficulties have a lower quality of life (PDQ Adult Treatment Editorial Board, 2002) and either consider delaying their treatment or quitting treatment (Liu et al., 2022).

1.5 Health economic evaluations

Health care systems face the challenge of cost-containment within limited health resources (Arnold, 2020). Health economic evaluations, including pharmacoeconomic evaluations, identify and compare the costs and consequences of pharmaceutical products and services, disease management and health care programmes as a significant and important field of research to aid policymakers in formulating and prioritising healthcare policies to achieve the most cost-effective use of limited resources (Arnold, 2020; Jayasekera & Mandelblatt, 2020).

There are four basic types of health economic evaluations, including cost minimisation analysis (CMA), cost benefit analysis (CBA), cost-effectiveness analysis (CEA) and its branch of the cost utility analysis (CUA) (Glied & Smith, 2011; Rascati, 2013). They examine the differences in costs between two or more interventions concerning the health outcomes achieved in one intervention compared to the other comparators. They differ in the unit of measurement of the outcomes. CMA adopts the assumption of equivalent outcomes in both the intervention and the comparator, to compare the costs. CBA has the outcomes unit of measurement converted to monetary terms. CEA has the unit of natural measurement of outcomes, for example, units of mmol/L of glucose levels, or mmHg units of blood pressures. If the natural unit of measurement is the utility values of the quality of life (QoL), it is called CUA. CUA is a branch of the CEA.

1.6 Cost-effectiveness analysis (CEA)

CEA compares the costs and health outcomes of two interventions in a situation of limited health resources (Briggs et al., 2006). The outcomes in CEA are measured in the natural units and are expressed as either life-years (LY) saved in CEA or quality-adjusted life years (QALY) gained in CUA.

CEA describes the cost to outcome differences between at least two interventions. The ratio of costs to outcomes differences in CEA is measured by the incremental cost-effectiveness ratio (ICER) (Briggs et al., 2006), i.e. the incremental amount of health outcomes obtained (or not obtained) from each unit of costs invested in the resources. One of the disadvantages of measuring health outcomes in their natural units is that they cannot be compared directly, for example, the resources used by the hypertensive patients versus the diabetic patients when the outcomes are measured in the natural units of mmHg and mmol/L (Rascati, 2013). To overcome this, HRQoL and its utility values are derived. The following section further explains these concepts. Both COI and HRQoL utility values are essential data inputs in CEA.

1.7 Cost-of-illness (COI) for CEA

COI, also known as burden of disease, is a way to measure the costs of healthcare resource utilisation resulting from a disease or condition (Banegas et al., 2018; Horton & Gauvreau, 2015). Costs could include direct, indirect and intangible costs (Arnold, 2020). Direct costs include investigation costs, treatment costs, medications, follow-up visits, transportation, and accommodation, among others, which are directly related to managing a health condition. Indirect costs are the productivity loss incurred due to a health condition. Intangible costs include costs incurred due to such things as pain, emotional depression and other sufferings. They

are often not included in a COI analysis due to the challenges in data collection. COI analysis could be conducted from the payer's and the societal perspectives. Payers are often the funder of health resources who require the cost information in planning effective use of health resources.

1.8 Health-related quality of life (HRQoL) for CEA

Quality of life (QoL) is the overall perception of people over their lives (Rascati, 2013). QoL and HRQoL are used interchangeably in health economics. In health economic evaluations, HRQoL is a tool for gauging patients' disease experiences and the impact of a disease on their functioning (Arnold, 2020). HRQoL is multi-dimensional, encompassing areas such as physical, mental, emotional, and social functioning. It focuses on the influence of health status on quality of life rather than direct measurements of patients' clinical parameters (Chean et al., 2016; Gandhi et al., 2015). HRQoL data is often collected from participants of a study directly through some form of survey or self-assessment (Arnold, 2020), which is a part of patient-reported outcomes (PROs). PROs capture the experience of individual patients in disease management, and it is highly influenced by the patients' own health beliefs and intrinsic values in looking at a health situation (Arnold, 2020).

Further to HRQoL, patients are asked about the values they would assign to their preferences in their own health (Rascati, 2013). These values are compared to the average value of the healthy population, and the utility values are assigned. If these HRQoL utility values are multiplied by the length of life gained from an intervention, quality-adjusted life years (QALYs) are obtained. CUA can then be performed with the ratio of the cost differences over QALY-gained between the intervention and the comparator.

1.9 Markov state transition model

Pharmacoeconomic evaluation involves the use of decision modelling techniques to guide evidence-based decision making in the cost-effectiveness of treatments or interventions (Arnold, 2020; Rascati, 2013). Decision tree, Markov model, simulation model, and mechanistic model are commonly used modelling techniques.

A decision tree is a classic model that uses branches and nodes to represent decisions and outcomes in a process, with terminal nodes indicating single events or outcomes (Rascati, 2013). A study from Iran (Zehtab et al., 2016) chose the decision tree model in looking at the cost-effectiveness of MMG with women registered in a national screening programme. It was a single outcome analysis without follow-up periods or a time horizon.

In comparison, cost-effectiveness studies from Vietnam (C. P. Nguyen & Adang, 2018), India (Okonkwo et al., 2008), Iran (Barfar et al., 2014), and China (Sun et al., 2018) were conducted with a Markov model to compare BSE, CBE and MMG. These were CEA studies with breast cancer health states and transition between the cancer stages, looking at a lifetime horizon.

The Markov state transition model is a CEA decision analysis tool that can be used when there are multiple possible health consequences of a condition or disease over an extended period (Briggs et al., 2006). Transition probabilities in Markov model are used to describe the events and accommodate the natural history of the disease or condition being analysed.

1.10 Problem statement

Breast cancer patients are diagnosed at advanced stages in Malaysia, affecting the survival rates and quality of life of cancer survivors. Pharmacoeconomic evaluations, particularly CEA, which identifies and compares the costs and consequences of pharmaceutical products and services, have emerged as a significant field of research to aid policymakers in formulating and prioritising healthcare policies to achieve the most cost-effective use of limited resources (Henry & Taylor, 2014). However, limited cost-effectiveness studies have been conducted to estimate the cost-effectiveness of BCEDP in Malaysia so far at the time of this study. In addition, there is a lack of data on COI and HRQoL of different breast cancer stages in Malaysia, which is needed for accurate CEA. The CEA will provide information to the stakeholders in the planning of BCEDP for earlier diagnosis of breast cancer.

1.11 Study aims and objectives

1.11.1 Study aims

This study aims to explore the pharmacoeconomics of early cancer detection programmes in Malaysia.

1.11.2 Study objectives

The objectives of this study were:

Objective 1: To assess the cost-of-illness of invasive breast cancer in Malaysia

Objective 2: To estimate the health-related quality of life of patients with invasive breast cancer at different stages

Objective 3: To examine the cost-effectiveness analysis of the breast cancer early detection programme, including scenarios with clinical breast examination (CBE), mammography (MMG) and a combination of CBE and MMG.

CHAPTER 2

LITERATURE REVIEW

Low- and middle-income countries (LMICs) reported higher mortality rates and more advanced stages of breast cancer at diagnosis (Bray et al., 2024; Yip & Anderson, 2007). Due to these epidemiologic trends, LMICs faced increasing economic impact from the burden of breast cancer (Mubarik et al., 2023; Yeong et al., 2024). WHO Global Breast Cancer Initiative (GBCI) emphasised the importance of a financially feasible and sustainable breast cancer early detection programme (BCEDP) relevant to countries' healthcare resources (World Health Organisation, 2023).

To understand the constraints of healthcare resources for the implementation of BCEDP, health economic evaluation provides information for an informed decision to stakeholders. Health economics examines the allocation of scarce health resources within the health system to achieve optimal outcomes in terms of cost-effectiveness (Briggs et al., 2006). Sections 1.5 to 1.9 in the previous chapter describe the various components of health economic evaluation.

A literature review on the COI, HRQoL and CEA was conducted to understand further the existing literature on the cost-effectiveness of BCEDP in Malaysia and in similar countries. The following sections 2.1, 2.2 and 2.3 will further explore the relevant literature.

2.1 COI of breast cancer: a systematic review

Treatment for breast cancer is becoming more expensive as technology advances. Understanding COI and its contributing factors is the first step to estimating the cost-effectiveness of the current programme in the earlier detection of breast cancer (Arnold, 2020). COI could include the effects of a disease or condition on the direct

costs, indirect costs and nonmedical costs in relation to a condition or disease. Direct costs include costs directly related to treatment, such as surgeries, radiation therapies, medications, hospital admissions and follow-up visits. Indirect costs are costs resulting from the impact of a disease on the activities of the patients, such as the loss of work or absenteeism from work due to treatment. Nonmedical costs would include costs incurred in the process of seeking treatment, such as transportation costs, accommodation costs and informal care costs during and after the treatment periods. COI is a part of the parameter inputs in the health economic evaluation and the CEA of a condition or a disease.

A systematic review was conducted on the COI studies of LMICs for cost itemisations, valuation, and analysis. It analysed the cost methods and determined the methodological areas that could enhance comparative studies across the countries. The systematic review was completed and reported in the PROSPERO platform, with its publication subsequently (Yeong et al., 2024).

2.1.1 Methods summary

Studies available in Cochrane, Proquest Thesis, PubMed, and Scopus were considered. Reporting criteria were evaluated using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 statement guidelines. Studies which (1) were peer-reviewed, (2) reported cost data, and (3) were full-text articles were included. The Cochrane Handbook and the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA) checklist were applied for reporting. The systematic literature search was conducted using the keywords “breast neoplasm” and combined with “cost of illness” from MESH terms. The protocol study was registered with PROSPERO with a registration number of CRD42022337861.

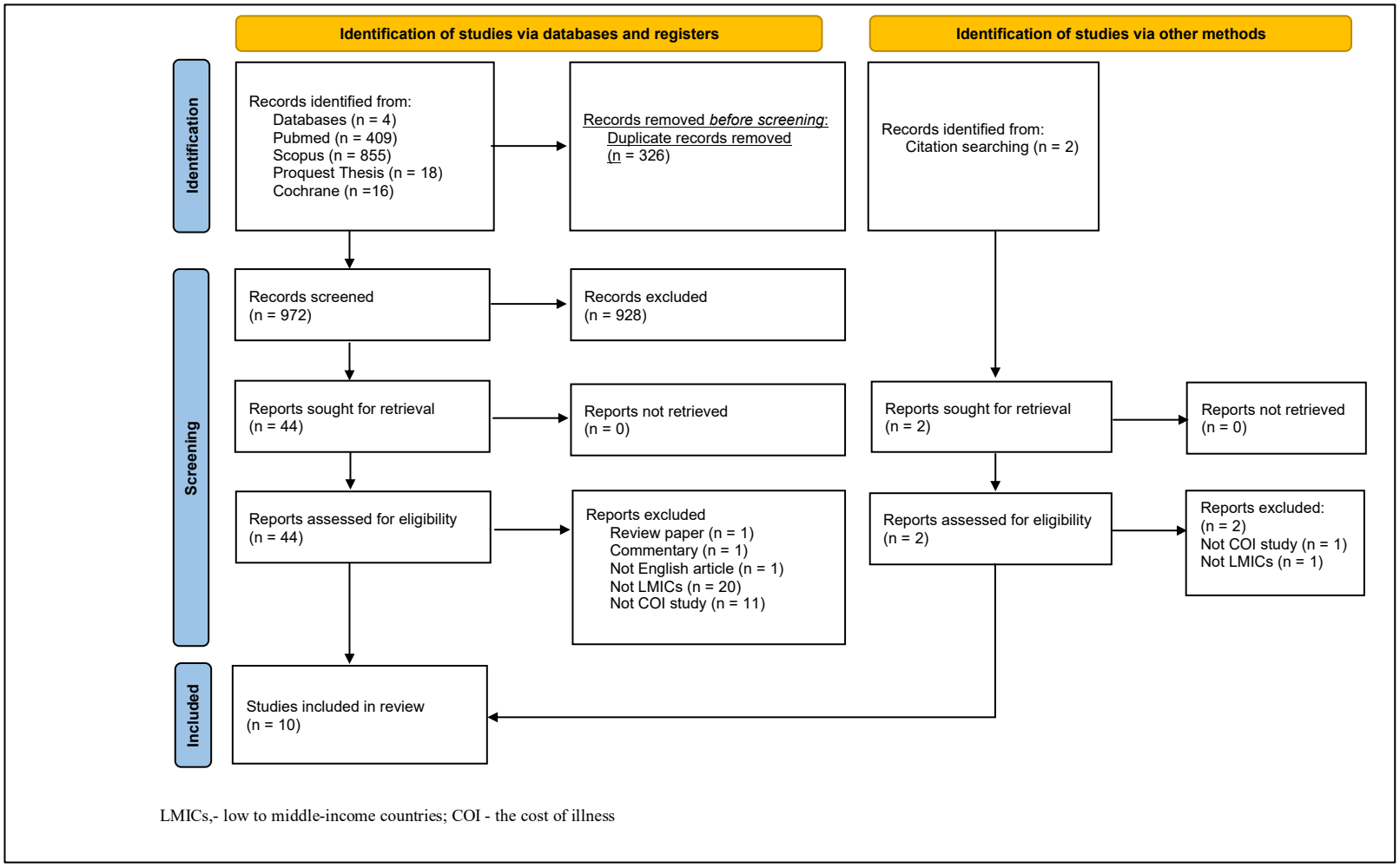

Figure 2.1 PRISMA 2020 flow chart for COI of breast cancer

2.1.2 Findings summary

A total of 10 studies of BCEDP were included in the final analysis (Figure 2.1). There were no studies from Malaysia at the time of the systematic review. The annual costs per patient ranged from USD 183 to 10,937 of direct costs, USD 188 to 1,241 of direct non-medical costs, and USD 1,091 to 24,741 of productivity losses. The ranges differ between countries due to variations in treatment types and cost differences between geographical areas and between private and public health systems. Direct costs, which accounted for hospitalisation, reported the highest costs, while the direct non-medical costs and the loss of productivity added to the financial burden of the patients.

2.1.3 Research gaps in COI of breast cancer in Malaysia

There were no COI studies on breast cancer were reported from Malaysia at the time of the systematic review. COI studies from both the payer's and societal perspectives, including productivity losses in Malaysia were needed.

2.2 HRQoL of breast cancer

A literature search was conducted with studies on PubMed, Google Scholar and Scopus up to October 2024. The literature search was conducted using the keywords "breast neoplasm" and combined with "quality of life" and "HRQoL" from the MESH terms. The literature search was conducted using the keywords "breast neoplasm" and combined with "quality of life" and "HRQoL" from the MESH terms.

A systematic review and meta-analysis by Fukushima et al presented that QoL was significantly associated with the mortality risk of several cancer, including breast cancer (Fukushima et al., 2024). The team further investigated the timepoints which QoL has an impact on cancer mortality and it was found that QoL was significantly

associated with mortality at the pretreatment phases, followed by the posttreatment phases and patients in the palliative care phases of their cancer. QoL was further reported to be a prognostic factor in breast cancer survival in the nonmetastatic stages (Efficace, Therasse, et al., 2004), metastatic stages (Efficace, Biganzoli, et al., 2004) and posttreatment phases (De Aguiar et al., 2014). It was suggested that HRQoL studies to be incorporated as a part of cancer clinical trials and to be reported for the clinical management of patients. These studies reported the association of QoL and breast cancer mortality specific to the populations of the respective countries. Generalisation to LMIC like Malaysia may not be possible, as the demographics of the breast cancer population vary significantly.

A study by Browall et al (Browall et al., 2013) reported that women had significantly lower QoL if they receive chemotherapy for their breast cancer treatment. However, age did not significantly influence the QoL of breast cancer patients. Further to this, clinical treatment, adverse drug effects, anxiety and depression were found to be negatively associated with QoL in two other studies, including a study from Malaysia (Haidari et al., 2020; Ng et al., 2015). The study from Malaysia further reported that the anxiety levels of newly diagnosed breast cancer patients significantly reduced at 6-month and 12-month after diagnosis, attributed to the completion of clinical management at those time points and the perceived social support by the patients throughout their diagnosis and treatment. These studies pointed out that attention should be given to the QoL of patients amid their breast cancer management.

The literature search found a few reports related to Malaysia. Yusuf et al. (Yusuf et al., 2013) conducted a study with QLQ-C30 questionnaires in Kelantan, which reported that QoL was comparable among the Malay and Chinese breast cancer patients, except that the newly diagnosed Malay patients reported a lower mean QoL score with

breast cancer symptoms. They further discussed that the fear of breast cancer challenging their marital relationship, concerns about body image and reproductive health and the practice of restrictive diet after diagnosis were among the factors of Malay women having lower QoL scores.

2.2.1 HRQoL of breast cancer in Malaysia

Ganesh et al (Ganesh et al., 2016) found that the QoL C-30 scores were lower by 10-point scale in stage IV cancer compared to stage I cancer, although the difference was insignificant. When comparing QLQ C-30 scores across the cancer stages, advanced stage patients reported worse functional scales, with higher levels of pain and constipation.

In other studies, the authors (Chui et al., 2015) reported no differences in QoL between users of complementary medicine and Chinese medicine breast cancer compared to non-users. Liew et al (Liew et al., 2019) concluded that although complementary medicines helped to reduce negative symptoms of chemotherapy, the effects were not significant. This might have been affected by the relatively small sample size in the study. The authors reported a sample size based on validated assumptions and past clinical experience. Sample size estimation based on calculation and previous proportions affected by published studies would have provided more accurate numbers for data collection.

Mental well-being of breast cancer patients was further reported by the QoL studies of Matalqah et al (Matalqah et al., 2011). Ng et al (Ng et al., 2015) with the former reported lower QoL in relation to higher depression when breast cancer survivors were compared to women without breast cancer while the latter reported

satisfactory scores in depression among the newly diagnosed patients. The studies did not report differences across cancer stages.

These studies reported various factors which affect the QoL of Malaysian breast cancer patients, including cancer stages, treatment factors which affect the functionality of patients, and the influence of ethnicity and health beliefs. For instance, some ethnic groups may have different cultural attitudes towards illness and treatment, and these beliefs can significantly impact a patient's QoL during their cancer journey.

2.2.2 Research gaps in HRQoL of breast cancer patients

Ganesh et al. (Ganesh et al., 2016) reported decreasing QLQ C-30 scores with advancing stages of breast cancer among Malaysian breast cancer patients. However, no EQ-5D studies were found in different breast cancer stages among the Malaysian population. Further studies were needed to gauge the QoL of breast cancer patients in Malaysia at different cancer stages with EQ-5D questionnaires, as EQ-5D utilities are the standard measure as inputs in CEA (Briggs et al., 2006).

2.3 CEA of breast cancer: a systematic review

Malaysia is an upper-middle income country classified by the World Bank (Fantom & Serajuddin, 2016), which faces challenges in its healthcare system with limited healthcare resources (Hong Phua et al., 2011). With the increasing breast cancer incidence in Malaysia over the years and the majority of patients being diagnosed at the advanced stages of stage III and IV (Institut Kanser Negara, 2024), payers need to carefully allocate healthcare resources for increasing breast cancer awareness and screening among the public. CEA of BCEDP is an important inputs in the design of an early detection programme. We conducted a systematic review on the CEA of BCEDP in LMICs to further understand the available literature. Following completion, the

systematic review was published and reported on the PROSPERO website (Yeong et al., 2023).

2.3.1 Methods summary

For the systematic review, PubMed, Cochrane, Proquest, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched for papers related to the keywords of the MeSH terms, including: (a) Breast neoplasm, (b) CEA, (c) Early detection of cancer and (d) LMICs. PRISMA checklist and the Cochrane Handbook were used for reporting. CHEERS 2022 criteria were used to assess the criteria of the selected studies. Articles with original data and full text were included. Theses, dissertations and conference proceedings were the main types of grey literature found in this additional search. Further searches were conducted based on the reference lists of the identified relevant studies. The search was limited to articles published from January 2000 to August 2021. Non-LMICs and non-English articles were excluded.

The titles and abstracts of the peer-reviewed articles located were first screened using synonyms and MeSH terms. The main subjects searched for include: (a) breast neoplasm, (b) CEA, (c) early detection of cancer and (d) LMICs. A systematic literature search was conducted using the keywords “breast neoplasm” combined with “cost-effectiveness”, “early detection of cancer” and “LMIC”. This protocol study was registered with PROSPERO under the registration number CRD42021271360.

2.3.2 Findings summary

The systematic selection process utilised for extracting relevant articles from the databases is shown in Figure 2.2. The initial search found 711 records and was reduced to 552 after removing duplicates. After the titles and abstracts were screened, it was found that 138 records did not study early breast cancer detection, 43 records were not

on breast cancer, 189 records did not conduct CEA, 152 records were not based on LMICs and 10 records were not in English. The final list consisted of 12 studies which met the inclusion criteria and successfully passed the exclusion criteria. The reasons for excluding the other studies are listed in Figure 2.2.

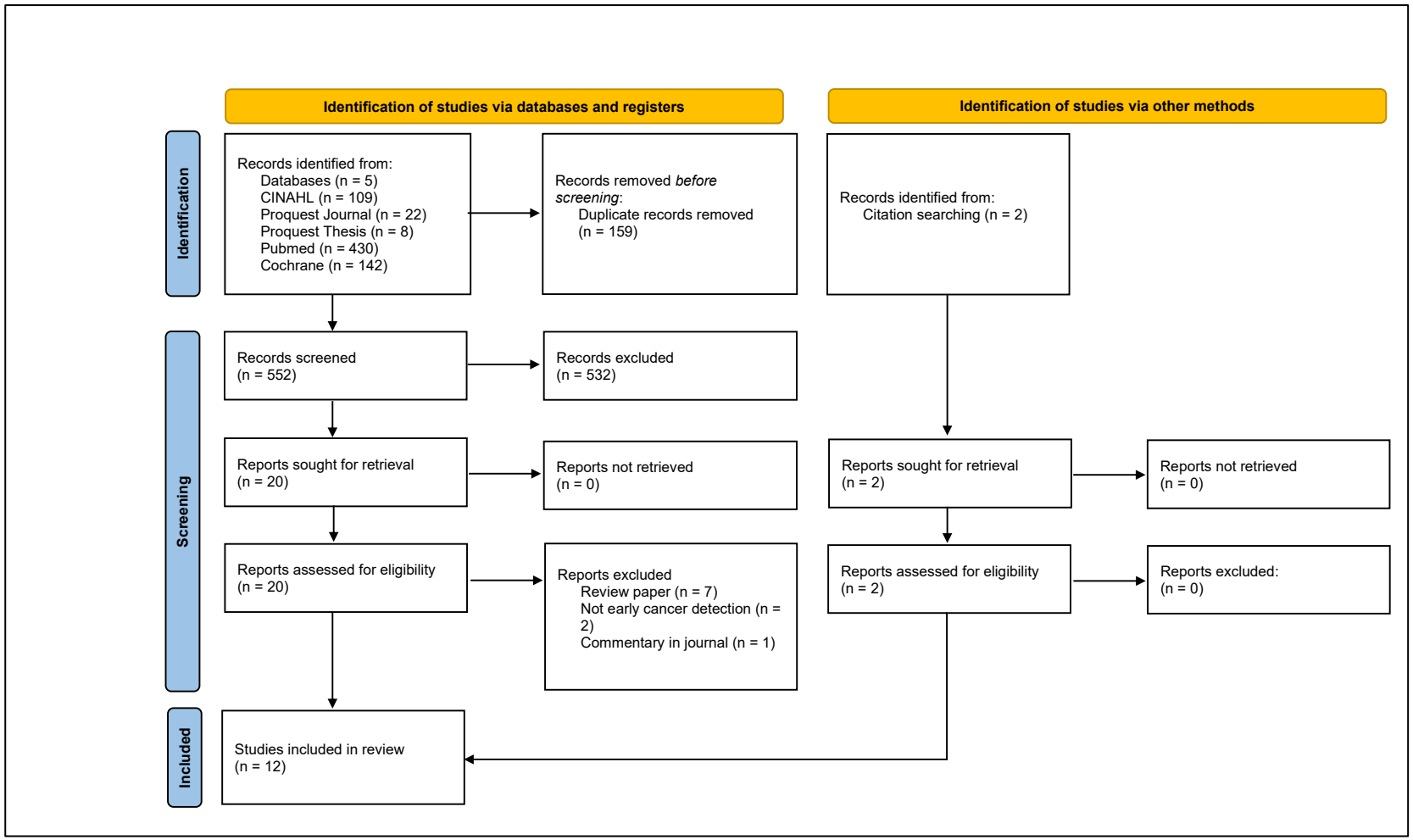

Figure 2.2 PRISMA 2020 flow chart for CEA of breast cancer

A total of 12 selected studies were included for final analysis (Yeong et al., 2023). In studies that included MMG as a screening method, all were reported to be cost-effective, except for two studies: one by Zelle et al. in Ghana (Zelle et al., 2012) and another study in a low-economic group women in Iran (Zehtab et al., 2016). High costs for the equipment and the need for trained human resources for MMG screening were the main reasons of MMG being non-cost-effective in Ghana. Zehtab et al. used case findings to gauge the success of MMG screening among women aged 35 to 69 years old. Low MMG screening rates and the inclusion of women below 40 years old could be the reasons for MMG to be non-cost-effective in the study. MMG screening in women less than 40 years old could bring more harm than benefit, as the incidence of breast cancer is low, false-positive results are more frequent in young women due to the dense breast tissue, and the possibility of overdiagnosis (Witten & Parker, 2018).

Two separate studies in China reported different results, with one study in a rural setting reported CBE to be not cost-effective. In contrast, another study with a simulated population reported CBE to be cost-effective. Similar findings were made by Yoo et al. in another systematic review comparing the cost-effectiveness of mammography in Western and Asian countries, which found that MMG could be effective in Western countries, but not in Asian countries due to the lower incidence in Asian countries and women with denser breast tissues (Yoo et al., 2013). This systematic review showed that early cancer detection programmes depend on the epidemiology, geography, and locations of the particular population, as well as the modalities of early breast cancer detection methods in LMICs, and these differ by country and may not be appropriate for a population with a low incidence of breast cancer.

In this systematic review, BCEDP with MMG, CBE, and mass media awareness raising (MAR) were investigated for their cost-effectiveness. Although MMG is the

primary technique for detecting breast cancer early in LMICs, several studies have suggested that CBE and MAR are more cost-effective. Different CEA results are seen between LMICs as well as between rural and urban areas of the same country, depending on screening methods, breast cancer incidence, and geo-social-economic levels. While Barfar et al. (Barfar et al., 2014) showed that mammograms were not cost-effective in the cities of Iran, Zehtab et al. (Zehtab et al., 2016) reported the opposite in the rural areas. However, a direct comparison of the two studies should be done with caution because Barfar et al employed case-finding while Zehtab et al used ICER as the cost effectiveness evaluation. Sun et al (Sun et al., 2019) reported that the early breast cancer programme in the rural areas was not cost-effective, attributing it to the lower incidence of breast cancer in the rural areas. No Malaysian CEA study on BCEDP was reported in this systematic review.

2.4 Breast cancer early detection programme (BCEDP) in Malaysia

While breast cancer was diagnosed at later stages with 50.5% at stage III and IV in Malaysia, it was diagnosed at earlier stages in other high-income countries, e.g. 39% at Stage 1 and 34% at Stage 2 in England (Statistics, 2016). To achieve the WHO's GBCI's target of first diagnosis at 60% stage I and II, efforts towards early breast cancer detection are needed.

Many high-income countries have initiated population-based BCEDP, which could improve the treatment outcomes and survival of breast cancer patients as well as reduce the financial burden to the healthcare system (Christensen et al., 2017; Institute for Public Health, 2019; Zahl et al., 2020).However, current cancer screening programmes in Malaysia are selective, opportunistic and not population-based due to the limitation of healthcare resources (Htay et al., 2021). The limitations of breast cancer

screening in the Malaysian context include the inequality of access to screening, the lack of trained radiologists, and the disconnect between screening, referrals and follow-up services.

With limited resources, public health tries to maximise health outcomes in the population. Malaysia reported 54.63% expenditure on health out of the total public expenditure in the year 2020 (Ministry of Health Malaysia, 2022b). The Ministry of Health and numerous non-governmental organisations in Malaysia provide breast cancer awareness and early detection programmes (NGOs). The Ministry of Health's breast cancer programmes are primarily based in public healthcare facilities such as public hospitals and government clinics; NGOs provide breast cancer programmes in communities with some mobility to rural areas (Dahlui et al., 2011)(Dahlui et al., 2011).

A systematic review reported that Malaysian women have a good awareness of breast cancer, but lack self-action in going for mammography examinations due to culture and perceptions (Dahlui et al., 2011; Khan et al., 2015). It further suggested that the availability of breast knowledge, awareness of breast health, and breast cancer screening by healthcare personnel through the breast cancer programmes will help to reduce the misconception of women about mammography (MMG) while being sensitive to the cultural aspects. However, the uptake rates for MMG screening offered by MOH were only 21% among women 40 years and above according to the National Health and Morbidity Survey.

Participation in BCEDP in Malaysia is ad-hoc, voluntary and opportunistic in the context. There is no population-based screening programme to date. Other than MOH, the Malaysia Ministry of Women, Family and Community Development (Kementerian Pembangunan Wanita, Keluarga dan Masyarakat), abbreviated KPWKM administer a breast mammogram subsidy programme which further offers a free

mammogram programme to women from a household of less than RM5,000 monthly income (Lembaga Penduduk dan Pembangunan Keluarga Negara, 2007). Other than MOH and KPWKM, NGOs offer cancer awareness and prevention programmes through community-based health campaigns. These programmes are based in the communities and mainly offer knowledge, awareness and survivor support programmes. One of the NGO has full-time nurses to offer clinical breast examination while the other NGO is with facilities to offer in-house mammogram (Dahlui et al., 2011).

Resources for public health are limited and must be utilised to the fullest extent with optimised outcomes. A pharmacoeconomic model with cost-effectiveness analysis (CEA) of breast cancer early detection programmes is therefore crucial for demonstrating the value propositions.