School of Population Health

The Effectiveness and Cost-Effectiveness of Screening Strategies for Breast Cancer in Indonesia

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Author’s declaration

I declare that this thesis has been solely the result of my own work and it has not been submitted, in whole or in part, in any previous application for a degree at any tertiary education institution. This thesis contains no material accepted for the award of any other degree or diploma in any university. To the best of my knowledge this thesis contains no material previously published by any other person except where due acknowledgement has been made.

Ethics approval

This research was approved by the Curtin University Human Research Ethics Committee (Reference: HRE2018-0642). A research permit was also obtained from Indonesia's National Cancer Center — Dharmais Cancer Hospital Research Ethics Committee (Reference: LB.02.01/XXII.2/12855/2018) — and Provincial Government of DKI Jakarta Health Office (Reference: 807/AF.1/31/-1.862.9/2018).

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Abstract

Background: Breast cancer is the fifth most deadly cancer globally and the most diagnosed among Indonesian women. To achieve the highest impact in minimizing disease burden, early detection and diagnosis and breast cancer treatment must be integrated, organized and resourced appropriately within existing healthcare structures. In Indonesia, it has been more than a decade since breast cancer early detection was first introduced, and opportunistic screening remains the primary strategy in the country. An opportunistic screening strategy may pose difficulty in assessing health outcomes at the population level as its nature can potentially reduce the likelihood of systematic assessment. Today, there are limited numbers of systematic investigations into the effectiveness and cost-effectiveness of organized early-detection strategy within the Indonesian healthcare system, despite the evidence that an organized breast cancer screening is more economically attractive than opportunistic screening. The challenges researchers encounter in investigating this issue in Indonesia include the low quality of data availability, limited financial resources and inadequate technical expertise. Nevertheless, program implementers and engaged stakeholders who in this study represent the Indonesian national breast cancer early-detection program in Jakarta Province have planned to pilot organized screening services. Therefore, an informed decision-making approach based on suitable cost-effectiveness analysis is needed to inform policy options for program improvement, maximize health outcomes, and further scale up services at the national or sub-national level.

Objectives: This research aims to: 1) first collect contextual evidence from existing literature and experienced stakeholders in decision-making to understand the

decision problem in Indonesia's implementation of its breast cancer early-detection program; 2) explore the sources of accessible data to inform model development; 3) develop a decision–analytic model to examine cost-effectiveness analysis of national breast cancer screening strategies in Indonesia.

Methods: This study used an explanatory sequential mixed method design over two phases. First, a systematic literature review was used to collect quantitative parameters on the economic evaluation of breast cancer early detection in Asia to populate the cost-effectiveness model. Then, an exploratory qualitative approach was undertaken using three consecutive interrelated qualitative methods, namely document analysis, semi-structured interview and working group discussion. The findings from the qualitative component supported in the contextualization of the policy implementation of breast cancer early-detection programs in Indonesia and in gathering relevant data to inform the model developed in this study. A decision–analytic framework for cost-effectiveness analysis of breast cancer screening was developed from these accounts. The analytical decision model developed in this thesis incorporated the parameter ranges of disease progression, associated costs and health outcomes. A decision-tree approach, combined with a Markov model of breast cancer natural history, was developed to synthesize the evidence of effectiveness and cost, with or without organized screening.

Contribution to knowledge: This thesis significantly contributes to existing literature across five principal areas.

1. This research has established an evidence-informed decision-making framework for cost-effectiveness analysis of breast cancer early-detection strategies essential for Indonesia and other developing countries with limited

resources-and-capacity to provide scientific evidence of economic evaluation in policy decision-making.

2. The research presented in this thesis has demonstrated a comprehensive contextualizing process using a modified analytical framework.
   This framework can be replicated to capture salient features of complex public health issues systematically.
3. This thesis demonstrates an intertwined research process and a practical approach to forming collaborative relationships with key stakeholders, which are needed to narrow the gap between research production and research use.
4. This research produced a country-specific model structure, reference parameters, and assumptions. These results may be adapted as a baseline framework for further study in other developing countries to conduct an economic evaluation of breast cancer prevention programs.
5. The model simulated in this thesis contributes to a growing body of literature by capturing the sources of accessible data for conducting a Health Technology Assessment for the breast cancer screening in low- to middle-income countries.

Result: The published systematic literature review conducted has allowed research insights into a range of economic evaluation models on breast cancer screening developed in high-income, upper-middle-income and lower-middle-income countries in Asia. The evidence also highlighted the model parameters and assumptions used and differences in the background, for example, in inter-country health resources, breast cancer incidence, prevalence and mortality.

The local context explains the discourse of the program landscape. Important themes emerging from key-informant interviews and discussions are framed within a

logic model of an early-detection program consisting of inputs, activities, outputs, and outcomes. While the inputs component gives an overview of policy direction for national breast cancer early-detection strategies, the activities showcase program implementation in Jakarta and contextualize how the national guidelines are operationalized. The showcasing includes a description of the healthcare setting, target population, service availability, information system tiers and data availability. The knowledge translation of the barriers to the early-detection pathway and outcomes achievement of the program has addressed specific problem definitions. A policy process embracing collaborative stakeholders' commitments shaped a course of action plan relevant to quality improvement by designing an organized breast cancer early-detection program. To that end, an ex-ante decision-analytic model of cost-effectiveness analysis pertinent to the feasibility of organized service delivery within Indonesia's healthcare system was constructed to aid in decision-making for policy options.

Overall, the organized breast cancer screening yielded slightly higher quality-adjusted life-years (QALYs) compared to opportunistic breast cancer screening (20.72 versus 20.10 QALYs) but was more expensive relative to the opportunistic strategy (US$ 19,340.44 versus US$ 14,562.94). The discounted incremental cost-effectiveness ratio (ICER) was US$ 7,727.88/QALY below the threshold of three times the Indonesian gross domestic product (GDP) per capita, US$12 406.

Conclusion: The contextualization process established a relevant structure of the decision–analytic model within the Indonesian healthcare setting, attempting to use local data to populate the model. Relative to the Indonesian GDP, a cost-effectiveness analysis indicates that an organized breast cancer screening program is cost effective. This study suggests a potential benefit to community-based early-

detection programs when scaled up to a systematic screening program in Indonesia, albeit with limited resources. Therefore, strategic steps are needed for the implementation of organized screening. These include clear guidelines for referral pathways, systematic metrics, and measures of screening outcomes, developing screening registration, and scaling up of decentralized pilot sites.

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List of abbreviations

AJCC	American Joint Committee on Cancer
BC	breast cancer
BHGI	Breast Health Global Initiative
BHRS	Basic Health Research Survey
BIRADS	Breast Imaging Reporting and Data System
BPJS	Indonesian national health insurance scheme; the Social Security Management Corporation for the Health Sector
C/E	Cost-Effective
CBE	clinical breast examination
CBS	Central Bureau of Statistics
CEA	cost-effectiveness analysis
CECAP	Cervical and Breast Cancer Prevention project
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DALYs	disability-adjusted life-years
EBSCO	Cumulative Index to Nursing and Allied Health Literature
ECHO	National Cancer Institute web-based collaborative learning project

EQ-5D-5L	EuroQoL with five dimensions and five levels of severity
WGD	Working group discussions
GDB	Global Burden of Disease
HBCR	hospital-based cancer registry
HHR	health human resource
HICs	high-income countries
HRQoL	health-related quality of life
HTA	health technology assessment
IARC	International Agency for Research on Cancer
ICER	incremental cost-effectiveness ratio
IFLS	Indonesian Family Life Survey
IHME	Institute for Health Metrics and Evaluation
InaHTAC	Indonesian HTA Committee
INMB	incremental net monetary benefit
LMICs	low- and middle-income countries
LRCB	Dutch National Expert and Training Centre for Breast Cancer Screening
LYS	Life Year(s)

MISCAN	Microsimulation Screening Analysis
MST	mean sojourn time
NCCP	National Committee of Cancer Control Program
NCCPs	national cancer control plans
NCI-CGH	National Cancer Institute's Centre for Global Health
NCCN	National Comprehensive Cancer Network
NCDs	non-communicable diseases
NGOs	non-government organizations
NHRD	National Institute of Health Research and Development
OOP	out-of-pocket payments
PE	physical examination
PHCs	primary health centres
PBCR	population-based cancer registry
QA	quality assurance
QALYs	quality-adjusted life-years
RCT	randomized controlled trial
RQ	research question
SMG	mammography screening

SRIKANDI	Indonesia’s cancer registry system; Sistem Registrasi Kanker Indonesia
SUPAS	Intercensal Population Survey
SUSENAS	National Socio-Economic Survey
UK	United Kingdom
USG	ultrasonography
WHO	World Health Organization

Chapter 1: Introduction

1.1. Overview

The development, implementation, and evaluation of effective health programs and policies require the application of scientific reasoning (Frieden, 2014; Rabarison, Bish, Massoudi, & Giles, 2015). It is essential to incorporate research evidence in policy decision-making to support high-quality, effective and efficient health services that further ensure more responsible allocation of resources (Yost et al., 2014). In addition to evidence-based public health, economic evidence can provide insights into the investment value of public health to a nation's overall health system (Rabarison et al., 2015).

Chapter 2 and Chapter 5 of this thesis elaborate the fact that Indonesia faces health resource constraints and increased breast cancer incidence. Moreover, in Indonesia, cancers are generally detected when they are at advanced stages, when the treatment is less likely to be effective and cost-effective. The country's current breast cancer screening is offered opportunistically, which unfortunately reduces the possibility of the nation systematically assessing the health outcome of screening activities at the population level (Espinas et al., 2011). Therefore, it is an extremely important decision to improve the quality of screening through an organized program. Thus, making an optimal decision around improving the quality of screening is extremely important.

This thesis uses a mixed methods design to establish evidence-informed decision-making for breast cancer screening strategies in Indonesia. The model structure has simulated cost-effectiveness analysis of organized screening compared to the usual

care approach (opportunistic screening). The researcher adopted five iterative processes of model development based on Chilcott et al (2010) to construct the model, namely to: 1) understand the decision problem, 2) develop the conceptual model, 3) look at model implementation, 4) undertake model-checking, and 5) engage with the decision. These processes are reported in five interrelated individual chapters (**Chapter 3**, **Chapter 5**, **Chapter 6, Chapter 7,** and **Chapter 8**).

1.2. Aims and objectives

This research aims first to collect evidence from existing literature and engage with stakeholders to better understand the decision problems of the breast cancer screening program before representing them in the model structure. Secondly, the decision–analytic approach examines the cost-effectiveness analysis of Indonesia's national breast cancer screening strategies. These aims will be fulfilled by undertaking two interrelated objectives, each with the guided research questions (RQ) as follow:

Objective 1. To undertake a systematic review of the effectiveness and cost-effectiveness of breast cancer screening in Asian countries that focuses on
a) reviewing the evidence from different approaches to breast cancer screening;
b) assessing plausible parameter requirements for the development of the economic model.

- RQ 1: What is the effectiveness of breast cancer screening strategies investigated by studies and countries in Asia?

- RQ 2: To what extent has economic evaluation been conducted for breast cancer screening strategies in various health-system settings in Asia?

Objective 2. To contextualize the decision problem of breast cancer early detection in the Indonesian healthcare setting to align between relevant model structure and the decision needs of the end users.

- RQ 1: What is the government's policy to address early detection of breast cancer?
- RQ 2: How is national policy operationalized at national and sub-national levels?
- RQ 3: What policy options are used to strengthen the current breast cancer early-detection program?
- RQ 4: To what extent are the availability and quality of the existing screening data sufficient to inform the development of an economic evaluation model?

Objective 3. To develop cost-effectiveness analysis for breast cancer screening strategies in Indonesia.

- RQ 1: For the healthcare system setting in Indonesia, should the program implement systematic or organized screening proven to cover a more target population and, therefore, provide greater effectiveness at the population level than opportunistic screening?
- RQ 2: Under what circumstances may systematic or organized screening be more economically attractive than opportunistic screening?

- RQ 3: What the cost-effectiveness of organized versus opportunistic screening?

1.3. List of manuscripts

There are currently three manuscripts written which include a systematic literature review on the economic evaluation of breast cancer early detection strategies in Asia, published in 2020. Contextualizing breast cancer early detection program in Indonesia, submitted to BMC health services on 16th July 2022. Meanwhile, one manuscript is in progress to be submitted.

Manuscript 1: Systematic literature review

Popy Yuniar, Suzanne Robinson, Rachael Moorin, Richard Norman (2020). ***Economic Evaluation of Breast Cancer Early Detection Strategies in Asia: A Systematic Review.*** Value in In Health Regional Issue, 21 (C): 253-263. doi:10.1016/j.vhri.2020.01.003

Manuscript 2: Contextualizing breast cancer early detection program in Indonesia

Popy Yuniar, Kardinah, Dian Sinulingga, Anggi Kartikawati, Widyastuti, Lady M.F. Sirait, Budi Utomo, Marshall Makate, Richard Norman, Rachael Moorin, Suzanne Robinson. **Contextualising policy implementation, challenges, and plans for improvement of breast cancer early detection program in Indonesia.**

Manuscript 3: Establishing evidence-informed decision-making (in progress to final manuscript)

Popy Yuniar, Suzanne Robinson, Rachael Moorin, Marshall Makate, Richard Normal. ***Establishing* ex-ante *evidence-informed decision-making of organized breast cancer screening in Indonesia toward quality improvement.***

1.4. Outline of the thesis

This thesis consists of nine chapters divided into four parts, as illustrated in **Figure 1. 1.** The first chapter sets the concept for this research using iterative processes in the decision–analytic model's development. The chapter provides descriptions of the aims, objectives, research questions addressed within each objective, and the thesis outline.

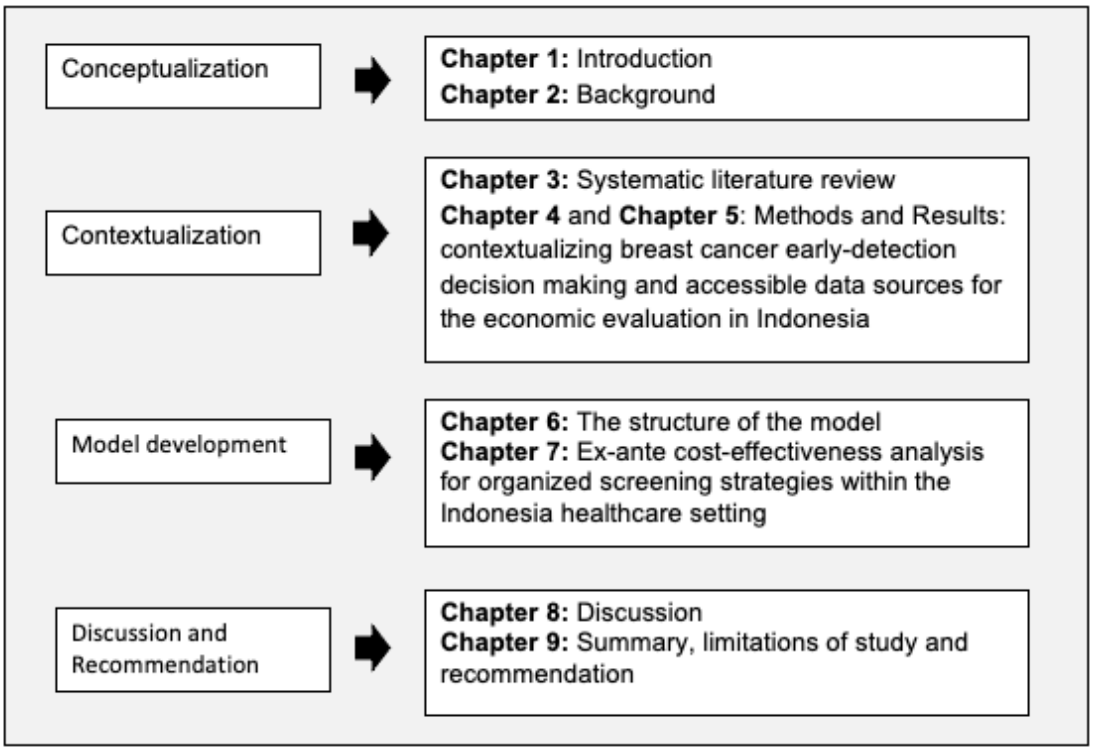

Figure 1. 1 Outline of the thesis

The second chapter presents the theoretical and practical basis for organized versus opportunistic screening, describes the decision analytic models for cost-effectiveness analysis, and outlines their use to compare the costs and health consequences of competing healthcare interventions.

The third chapter commences a systematic literature review, exploring evidence on economic evaluations of breast cancer early detection in Asia. The review establishes the essential foundation for this thesis, providing the core elements for constructing the structure, plausible parameters, and assumptions to build an economic evaluation model with a similar programmatic setting of breast cancer early-detection among selected Asian countries.

The fourth chapter details the preparatory methods framing the local contexts. This is considered the initial phase of knowledge translation of the decision problem for the model development. Stakeholder identification, informants' recruitment, data collection and analysis have been undertaken using document analysis, semi-structured in-depth interviews.

The fifth chapter presents the synthesized evidence. It focuses on the findings of the semi-structure in-depth interviews, the participatory workshop, and documents review. These findings are organized under the themes that emerged from the qualitative analysis, including the policy environment, showcasing policy implementation, problem structure and accessible data sources for breast cancer–related data.

The sixth and seventh chapters present the empirical work undertaken within the model implementation phases. **Chapter 6** focuses on defining the decision-problem components of the model (that is, the perspective used, the comparator, eligible

population, time-horizon) and structuring the model of natural disease of breast cancer. Meanwhile, **Chapter 7** elaborates on the parameters used in the model and presents a base case for a cost-effectiveness model.

The eighth chapter discusses the important contribution of the study, policy implications for a breast cancer screening program and research limitations.

The ninth chapter summarises the study and highlights the significant and original contribution that the study has given. The strength and limitations of the three research objectives are also provided. The chapter concludes with a range of recommendations for future policy and research.

Chapter 2: Background

2.1. Overview

This chapter will present the rationale for the overall aim of this thesis, using current knowledge surrounding breast cancer early-detection strategies. The current management system of breast cancer screening programs in Indonesia arguably, remains inadequate to prevent the late detection of breast cancer among women in Indonesia, as evidence shows high percentage of late stage at diagnosis. This, therefore, adds further to the rationale, that reforming the republic's systematic screening strategy is imperative to address significant public health issue in Indonesia, a country that is both large and has crammed with substantial burden of disease associated with breast cancer. This research provides new knowledge regarding the cost-effectiveness of organized breast cancer, and it serves as a platform of evidence to support the decision-making model and the development of policies promoting a systematic breast cancer screening model in the Indonesian healthcare system setting.

This chapter will begin by outlining the disease landscape and risk factors of breast cancer, including the global burden of disease, and different features of epidemiological background between developed and developing countries.
Then, the chapter's second section on the continuum of breast cancer screening care contains the reviewed of the process of identifying the specific types of care in screening implementation and its transitions will be undertaken to emphasize the important role of an organized set of processes in improving breast cancer quality of care.

The chapter's third section presents a detailed comparison between organized and opportunistic screening, followed by Breast Health Global Initiative (BHGI) guidelines for the management of breast cancer in low- and middle-income countries (LMICs). Lastly, the decision-analytic approach will be described, and cost-effectiveness analysis of breast cancer screening will be described, along with the country profile and known historical data on breast cancer screening programs in Indonesia.

2.2. Disease landscape and risk of breast cancer

Breast cancer is a significant global issue (Bennett et al., 2018; Fan, Goss, & Strasser-Weippl, 2015a; Francies, Hull, Khanyile, & Dlamini, 2020a; Torre et al., 2015). BC remains the most common cancer diagnosed among women worldwide (Bray et al., 2018). There were two million new cases in 2018 which resulted in 14.8 million disability-adjusted life years (DALYs), making breast cancer one of the main causes of mortality and morbidity in females around the globe (Bray et al., 2018; Sharma, 2019). The incidence and mortality of breast cancer were expected to increase by 50% between 2002 and 2020 (Anderson et al.,2008)

Developed countries typically display a high incidence and low mortality of breast cancer and, comparatively, developing countries demonstrate low incidence and high mortality rates for breast cancer (Bray et al., 2018; da Costa Vieira, Biller, Uemura, Ruiz, & Curado, 2017). The rising incidence of breast cancer, coupled with inadequate resources for early-detection-and-treatment programs as well as high fatality rate, have made breast cancer a notable cause of premature death in less-developed countries (Francies, Hull, Khanyile, & Dlamini, 2020b). In addition, regarding financial burden, a study in Taiwan by Chu et al. (2008) asserts that breast

cancer is associated with the highest total lifetime medical cost compared to other cancer.

Risk factors related to the increased probability of developing breast cancer include age (Feng et al., 2018), environment and lifestyle changes, reproductive and hormonal factors, and genetic predispositions such as familial or hereditary cases (Howell et al., 2014; Sun et al., 2017). Aging inevitably increases one's risk of breast cancer as evidenced by the fact that most breast cancers are diagnosed in women aged 55 and older (Andermann, Blancquaert, Beauchamp, & Déry, 2008; H. J. de Koning, Boer, Warmerdam, Beemsterboer, & van der Maas, 1995). However, in Asian countries, female breast cancer is more likely to appear in women of younger ages than in women in non-Asian countries (Fan et al., 2015a; Yu et al., 2021). Although the diagnosis of breast cancer is much less common in women who are younger than 40 years old, it can have a greater impact on their health than in older women because it tends to present at a later stage, is more aggressive, and has a poorer prognosis (Assi et al., 2013; Brennan, French, Houssami, Kirk, & Boyages, 2005).

Breast cancer is a potentially curable disease if diagnosed and treated early (IARC, 2002). Breast cancer screening in asymptomatic at-risk populations has the highest impact or most effect in minimizing the burden of the disease in the population (Tsu, Jeronimo, & Anderson, 2013a) when accompanied by accurate diagnosis and effective treatment (WHO, 2002). As an early detection strategy, screening can impact the prevalence of breast cancer by 1) reducing the length of time an individual might suffer from the disease and 2) affecting the development of new cases or both (Haddix, Teutsch, & Corso, 2003). Additionally, the diagnosis and

treatment of invasive breast cancer at an early stage in its natural history are associated with a shorter duration of disease and higher cure rates (Lauby-Secretan et al., 2015). Therefore, the fundamental interventions of screening, diagnosis and treatment must be integrated, organized, and resourced appropriately within existing healthcare structures (Panieri, 2012; WHO, 2002).

2.2.1. Principle and practice of screening for disease

In 1968, Wilson and Jungner published Principles and Practice of screening for Disease, highlighting ten principles that should be considered when making screening decision (Box 1) (Jungner, 1968). These screening principles were set out as normative statements regarding what should be known about the relative importance of a health problem, the natural progression of the disease condition, the characteristics of available screening tests and follow-up treatments, and the cost-effectiveness of screening before proceeding with a screening decision. Despite the popularity of Wilson and Jungner's original principles, screening decision remain challenging. Using the Delphi approach, Dobrow et al. provide an additional focus to the Wilson and Junger principles, particularly on the evolving complexity required of program or system considerations to develop and implement the necessary infrastructure for population-wide screening (Dobrow, Hagens, Chafe, Sullivan, & Rabeneck, 2018).

Box 1. Wilson and Jungner's principles of screening

1. The condition sought should be an important health problem.
2. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
3. There should be a recognizable latent or early symptomatic stage.
4. There should be a suitable test or examination.
5. The test should be acceptable to the population.
6. There should be an agreed policy on whom to treat as patients.
7. There should be an accepted treatment for patients with recognized disease.
8. Facilites for diagnosis and treatment should be available.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

2.2.2. Breast cancer screening pathways and failures to transition

Screening processes are performed differently across countries according to their health care and financing system (IARC, 2002). Nevertheless, screening must be organized in such a way that follows the pathways illustrated in **Figure 2. 1 .**

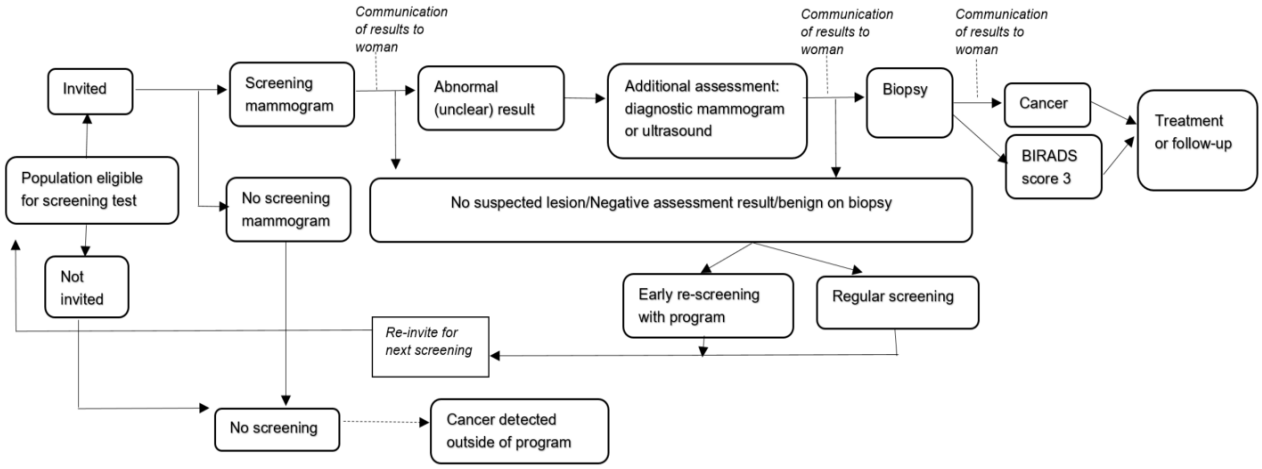

Figure 2. 1 Breast cancer screening pathway

(Muratov et al., 2020)

In addition to focusing on the continuum of breast cancer care, the Muratov screening process displayed above focuses on two types of care (detection and diagnosis) and the transition between them (**Figure 2. 2**). The framework also illustrates three types of failure during the processes of care — failure to screen, failure to detect, and failure to follow up.

Before detection of cancer can occur, a woman must transition from the at-risk population to the screened population (Jacklyn, Bell, & Hayen, 2017). The transition requires three conditions: an informed-and-activated target group that pursues screening, a prepared team recommends or performs screening during a routine visit, or a healthcare system identifies a woman who is eligible for screening and sends a letter recommending she schedules or attends an examination. If any of these conditions do not occur, or the woman does not follow through, It is a failure to screen. Even when screening does occur, it is still possible for late-stage disease to develop if the screening test misses cancer or premalignant condition that is present. Poor test sensitivity and poor reading of the test results can lead to a failure in detection.

If a test is abnormal, follow-up is necessary to evaluate whether cancer or a precancerous lesion exists. As shown in **Figure 2. 2** , two transitions — detection to diagnosis and diagnosis to treatment — encompass factors that could go wrong during follow-up. For instance, a provider could misinterpret the screening results or not adequately communicate the need for additional evaluation. The diagnostic work-up could incorrectly conclude that no cancer is present and give inappropriate reassurance, or a patient could choose not to pursue the recommended biopsy.

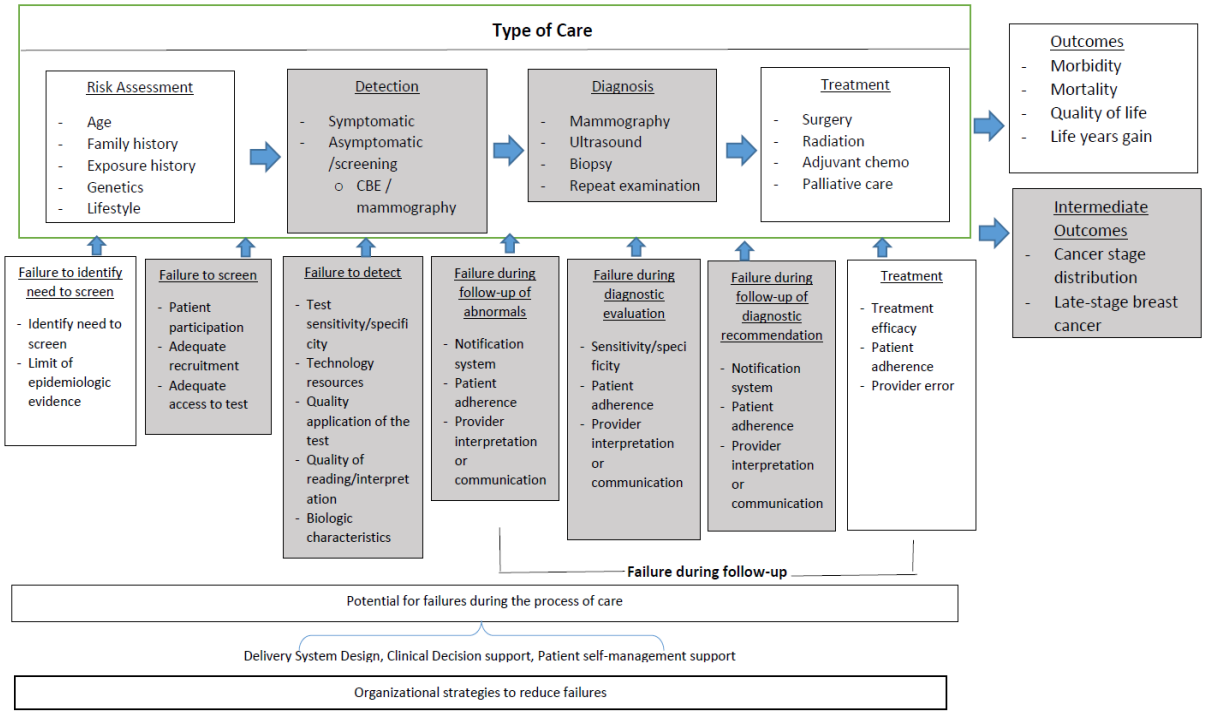

Figure 2. 2 The continuum of breast cancer screening care

(IARC, 2002; Zapka, Taplin, Solberg, & Manos, 2003)

2.3. The forms of screening delivery services

The screening process can be perceived as a continuum, from organized national programs to opportunistic screening (Anderson et al., 2008). The World Health Organization (WHO) has provided the following definition (World Health Organization, 2002) to distinguish between organized screening and opportunistic screening programs. Organized or systematic screening refers to the establishment of a formal screening program for a specific population by a facility, institution, regional government of national healthcare ministry; while opportunistic screening is when an individual woman who has no symptoms of breast pathology is referred to screening outside of a formal program.

Organized screening is not only the most resource-intensive the approach for detection but also the most likely to achieve early detection for a broad segment of

the population (Anderson et al., 2003, 2011). Meanwhile, opportunistic screening may facilitate early diagnosis of non-palpable breast cancer, but only for individual women who have both the resources and the need to undertake the screening test and any follow-up diagnostic testing (Bulliard et al., 2009; Panieri, 2012). Although both screening processes are likely to yield favourable health benefits to the population, a comparison in relative terms for both strategies is relevant for public health decision-makers to establish an appropriate screening policy guideline (Neeser, Szucs, Bulliard, Bachmann, & Schramm, 2007) and a meaningful measure of quality that promotes improved screening outcomes (Zapka et al., 2003).

2.3.1. Comparing organized and opportunistic screening system

Different outcomes observed between countries offering organized screening programs and those providing screening on an opportunistic basis only are often underpinned by their differing philosophies on healthcare provision, as well as their healthcare infrastructure (Miles, Cockburn, Smith, & Wardle, 2004).

Organized screening programs consist of elements that form a coherent structure offering a standardized system of care (Chamot, Charvet, & Perneger, 2007; Madlensky, Goel, Polzer, & Ashbury, 2003), with nationally implemented guidelines defining who should be invited, how frequently they should be screened, and how any screen-detected abnormalities should be followed and treated (Amendoeira et al., 2013). Furthermore, the quality of the overall program and its various parts need to be monitored through Quality Assurance (QA) (Giorgi Rossi, Federici, & Zappa, 2013). This involves the setting and monitoring of key targets for several performance parameters, such as population uptake rates, cancer detection rates,

false positive, and false negative (Edward A. Sickles, Dulcy E. Wolverton, & Katherine E. Dee, 2002).

In contrast, opportunistic screening depends on individual members of the public to request screening or on their health advisors to recommend screening (Anderson et al., 2008). It involves fewer formal decisions regarding whether to screen, who to screen, and at what interval screening should be performed. In addition, QA may be more variable, and few opportunities exist to monitor the achievements and failures of the service as a whole (Giorgi Rossi et al., 2013). The information in **Table 2. 1** presents the similarities and differences between organized screening and opportunistic screening (A. Miles et al., 2004).

Table 2. 1 Similarities and differences between aspects of organized screening and opportunistic screening

Aspect of screening	Organized screening	Opportunistic screening
Screening method for a particular type of cancer	Fixed: chosen by government/health department	Variable: chosen by the individual and individual healthcare providers
Aim	Reduce cancer incidence/mortality at the population level	Reduce cancer incidence/mortality at the individual level
Sensitivity of test	The most sensitive test may not be chosen for the nationwide program. Sensitivity targets for practitioners and programs are established and monitored to improve test performance	The most sensitive test is usually chosen. Sensitivity at the practitioner and program levels is not generally monitored
Specificity of test	High specificity is important for reducing avoidable costs due to unnecessary workup of false-positive results and associated adverse effects	High specificity is less important at the individual level
Screening interval	Fixed: chosen to maximize population benefit at a reasonable cost	Variable: chosen to maximize an individual's protection against cancer morbidity/mortality; usually more frequent than in organized programs
Available financial resources	Limited at the population level to policies about health spending, taking into account all aspects of health care	Limited at the level of the individual, and limited to health plan–level decisions; depends primarily on the finances and insurance status of the individual
Health technology assessment	Must be confirmed to yield more benefit than harm	Efficacy does not necessarily have to be demonstrated

Aspect of screening	Organized screening	Opportunistic screening
Quality assurance	Set targets have to be met and are monitored. Targets are continually reviewed to ensure that the screening delivered is of the highest quality possible	Target may be set and may or may not be monitored
Target uptake rates	Specified and monitored: lower rates result in organized effort for improvement	May or may not be specified (by health plans or health agencies) or monitored; few opportunities for systematic application for population-based improvements
Person invited	Fixed: all people within all specified age ranges	Variable: people in contact with healthcare professionals who recommend screening; people with particular jobs in which their healthcare coverage may include reimbursement for screening; anyone exposed to direct-to-consumer marketing
Invitation strategy	Active: everyone in the eligible population is invited	Passive: no consistent strategy
Aim for equality of access	Equality of access is built into the organization of the program	Equality of access is desired, but resource allocations limit the potential of outreach efforts
Relation between people invited and cancer risk	Those people invited for screening are not necessarily the people at highest risk but represent the age group most likely to receive the greatest benefit from screening	Those people invited for screening are not necessarily a person at the highest risk; this feature may lead to over-screening of low-risk people and under-screening of high-risk people
Benefits	Maximized for the population within available resources	Maximized for the individual
Harm	Minimized for the population within available resources	Not necessarily minimized

2.3.2. Performance indicators of breast cancer screening programs

Monitoring and evaluation of breast cancer screening programs are necessary to ensure that the programs are as effective as expected (Perry et al., 2008) Based on the 88 articles reviewed by Muratov et al. (2020) in the scoping review study, the performance indicators of organized screening can be elicited for monitoring and evaluation of breast cancer screening programs according to the domains of clinical effectiveness, safety, facilities, and resources.

2.3.3. Lessons learned from countries using organized screening programs

Developed countries, including the United Kingdom (UK), Sweden, Austria, Australia, France, and Switzerland, have implemented organized screening programs to mitigate the incidence of breast cancer among their female populations (de Gelder et al., 2009; Espinas et al., 2011; Hofvind, Vacek, Skelly, Weaver, & Geller, 2008). Drawing from their experience, some invaluable lessons can be learned for the potential implementation of screening programs for Indonesia.

First, compared to the opportunistic approach, organized screening efforts have greater potential to reduce cancer incidence and mortality due to the higher achievable levels of population coverage and quality assurance in screening activities. Secondly, organized screening programs aim to achieve population-level benefits and greater protection from harm. Also, narrowing the gap of equity of access is a main principle adopted by healthcare providers in countries with organized screening (Espinas et al., 2011). In organized programs, the opportunity to be screened is determined by health policy and by the adequacy of the call–recall system. Meanwhile, in opportunistic screening, the opportunity is determined to a

greater extent by individual factors, such as the knowledge and behaviour of the patients and providers, insurance coverage, and the patient's pattern of encounters with health services. Lastly, introducing an organized system of screening presents many challenges related to the existing versus the required infrastructure, people's vested interests, and public and provider acceptance of centralized health care.

2.4. Global initiative to strengthen implementation of breast cancer early-detection programs in limited-resources countries

In response to the increase of global breast cancer death in low-income and middle-income countries, the World Health Assembly resolution on Cancer Preventions and Control in the Context of an Integrated Approach calls on the WHO for the development of resource-stratified guidance to scale up strategic cancer prevention and controls program development (Catherine Duggan et al., 2020). Strategic investment in cost-effective and equitable programs for breast cancer early detection and management is expected to strengthen the healthcare system and advance progressive implementation of universal health coverage, particularly for low- and middle-income countries (LMICs), where cancer and non-communicable disease program are often inaccessible and under-resourced (Anderson et al., 2011).

The Breast Health Global Initiative (BHGI) is one global commitment dedicated to improving breast health care and cancer treatment for women in economically disadvantaged countries through three pillars of global strategies. These strategies include the early presentation, timely breast cancer diagnosis, and comprehensive breast cancer treatment management (Anderson et al., 2011; Duggan et al., 2017). Monitoring early presentation may shed light on the effectiveness of patient management strategies to downstaging disease to a point at least 60% of the

cancers that are stage I or II at diagnosis. Early diagnosis aims to reduce the time delay between the time a patient presents to the healthcare system and the initiation of breast cancer treatment, which contributes to late-stage diagnosis. A comprehensive breast cancer treatment is focused on timely access, and stage-appropriate and multidisciplinary cancer treatment (such as surgery, radiotherapy, and systematic treatment). Further, these three pillars should be translated into an implementation framework to manage breast cancer cases in a resource-appropriate fashion, with the associated process, quality, and outcome metrics (for example, effectiveness and reach) (Catherine Duggan et al., 2020).

Organized mammographic screening evidence reduces the proportion of late-stage disease to the point that at least 60% of invasive breast cancers are diagnosed at stage I or II of their development, which concomitantly reduces breast cancer mortality by more than 20% (Lauby-Secretan et al., 2015). **Figure 2. 3** illustrates the crucial healthcare system to prepare a resource-appropriate organized screening program.

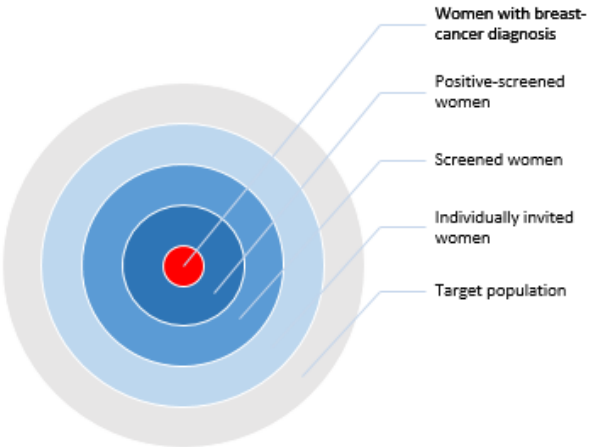

Figure 2. 3 A paradigm of early breast cancer detection using population-based screening programs

Source: (Ginsburg et al., 2020)

However, a stepwise implementation model for systematic management of clinically detectable (palpable) breast disease is required before a jurisdiction can embark on a population-based screening program. This model addresses the system requirements of low- and middle-income countries (LMICs) through the integration and organization of multidisciplinary care at the primary level (such as a community), secondary level (such as a district), and tertiary level (such as regional or national levels) of the healthcare system in a functional triage pathway (Allison Dvaladze, Catherine Duggan, Julie R. Gralow, & Benjamin O. Anderson, 2016). The courses or phases people go through include a clinical breast examination, breast cancer awareness and education, clinical diagnosis, tissue sampling, anatomical pathology diagnosis or surgery, chemotherapy or endocrine therapy, and radiotherapy when available (Allison Dvaladze et al., 2016).

In the absence of population-wide mammographic screening in LMICs, selected countries like Peru and Tanzania have experienced the phased implementation model of breast cancer early detection through a four-steps approach as a prerequisite to screening. These steps include 1) establishing a systematic triage approach to the diagnosis of palpable breast disease; 2) strengthening resource-adapted, stage-appropriate treatment planning using navigation processes to reduce access barriers; 3) scaling up targeted educational interventions for both public and private healthcare staff audiences to promote the down-staging of clinically detectable disease; and 4) systematically upgrading image-based diagnostic systems for the management of non-palpable disease, as a prerequisite to mammographic screening programs (Catherine Duggan et al., 2020). Once these strategic goals have been addressed, a healthcare system can be prepared to

initiate a resource-appropriate screening program (Catherine Duggan et al., 2020; Ginsburg et al., 2020) **(Figure 2. 3).**

2.5. Cost-effectiveness analysis for breast cancer screening

As resources are limited, any decision about healthcare interventions based on cost-effectiveness analysis (CEA) should help decision makers to evaluate the comparative investment in health care relative to health improvement from healthcare strategies that compete for similar resources (Gold, 1996; Haddix et al., 2003). CEA involves estimating an intervention's net or incremental costs and effects (Siegel, Weinstein, Russell, & Gold, 1996). The results are presented in the form of a cost-effectiveness ratio that compares two alternatives and is calculated as the difference in costs between the alternatives divided by the one or multiple differences in health outcomes (Claxton, Sculpher, & Drummond, 2002).

International studies on the cost-effectiveness of breast cancer screening show a substantial discrepancies in cost per life-year gained between well-organized screenings and spontaneous screening activity (IARC, 2002). The probable explanation is that dedicating one organization only for screening may keep the costs low and promotes more efficient use of resources, while having a high attendance of invited women and good-quality screening which leads to health benefits (Miles, Huberman, & Saldana, 2014). However, comparing cost-effectiveness between programs in different countries is complex because differences may exist not only in the epidemiology of breast cancer but also in the organization and costs of health care in general that affect both effectiveness and the costs (Michael Drummond et al., 2009a). In addition, to evaluate the complete economic and clinical consequences, cost-utility analysis (CUA), as a special case of

CEA, can be used to compare health outcomes across disease areas whose benefits may differ (Gray, Clarke, Wolstenholme, & Wordsworth, 2012). A systematic review of the evidence on this issue will be explored further in **Chapter 3**.

2.6. Decision–analytic modeling for economic evaluation

In order to make decision on breast cancer policy decision-makers need information on both effectiveness and cost-effectiveness of the various screening options. These data can be collected through a primary research design can be used, where economic and additional health outcomes are piggybacked onto an existing randomized controlled trial (RCT) (O'Sullivan, Thompson, & Drummond, 2005). However, the approach of relying on a single RCT to inform economic evaluation has been criticized because the clinical trial is unable to accomplish three aspects: compare all relevant interventions for the treatment of a disease, incorporate all important evidence to decide resource allocation, and compare the long-term costs and outcomes associated with competing interventions (Petrou & Gray, 2011; Philips, Bojke, Sculpher, Claxton, & Golder, 2006). In addition, costs and effects that include costs to the patients and their family, and the ostensible variations in treatment that are seen between settings of care occur after non-mortality endpoints are reached (Bonsel, Rutten, & Uyl-de Groot, 1993).

The decision-analytic approach has manifested as a complementary approach to trials-based economic evaluation (Arrospide et al., 2016). Decision–analytic models are therefore recommended as a vehicle for economic evaluation, due to their ability to provide a platform to compare all relevant treatment options and synthesize all relevant data over an extended time horizon (Buxton et al., 1997; Kassirer, 1976). Decision analytic model allows a rational, feasible, scientific and timely approach to

measure the efficiency of new medical technologies in health care using the best available evidence of different resources to produce detailed estimates of the clinical and economic consequences of different healthcare intervention (Petrou & Gray, 2011).

A decision–analytic model is essentially a mathematical structure that can represent the health and economic outcomes for all patients populations receiving a particular medical interventions (Claxton et al., 2002; Sculpher, Fenwick, & Claxton, 2000). The model uses mathematical relationships to express the likelihood of particular health consequences occurring within each of the interventions compared. The nature of these consequences informs the structure of the model. Each consequence has inherent cost and outcome which, when weighted with the probability of its occurrence, enable researcher or decision makers to calculate both expected costs and expected outcomes associated with each intervention under evaluation (Briggs, Sculpher, & Claxton, 2006). Researchers generally consider there are three key aspects to build decision-analytics model construction: structuring the model, populating the model (identifying and collecting appropriate data), and assessing uncertainty within the model and its results (Drummond, Manca, & Sculpher, 2005; Gray, Clarke, Wolsthenholme, & Wordsworth, 2012). These three actions are taken after defining the decision problems, such as the setting, perspective, and disease area of focus.

The process of defining the decision problem of a breast cancer screening program in an Indonesian setting is described in **Chapter 4** and **Chapter 5.** A detailed explanation regarding the model structure, parameterization of the model, and any assessment of uncertainty will be given in **Chapter 6** and **Chapter 7.**

2.7. Scoping out the problem of breast cancer early-detection programs in Indonesia

Given Indonesia is the setting for this research, it is important to understand the country context. This section describes Indonesia's socio-demographic and epidemiological characteristics, economic context, and current policy on early detection of breast cancer, which may reflect the challenges specific to the country's implementation of a national quality-assured breast cancer screening program.

2.7.1. Geography, socio-demography, and economic context

Indonesia is the largest archipelago country in the world with an estimated 17 504 islands found in two oceans, the Pacific and the Indian oceans, scattered across two continents, Asia and Australia. There are five main islands and four groups of smaller islands in Indonesia. The nation's capital is Jakarta, a city-province of 10.56 million people. The country is ranked fourth globally in terms of population, with more than 270 million inhabitants (Central Bureau of Statistics Republic of Indonesia, 2021). One of the characteristics of the Indonesian population is uneven economic growth between islands and provinces (Mahendradhata et al., 2017).

The majority of the population lives on the island of Java (58%), where Jakarta rests on the northwest coast. In 2010, about 56.7% of the Indonesian population lived in urban areas while the reminder lived in rural areas. The median age of Indonesia's population is 27 years, which is 10 years younger than that in most major developed countries, thus making Indonesia the third-youngest nation in East Asia (Central Bureau of Statistics Republic of Indonesia, 2021). In 2010, about 65.2% of the population were aged 15 to 64 years old, indicative of a large working-age large.

The nation is in the midst of a fundamental demographic shift as the working-age population increases in age relative to the rest of the population (Mahendradhata et al., 2017).

Indonesia has emerged as a low- and middle-income country. The gross national income per capita in the LMIC steadily rose from US$3836, US$3894, and US$3896, in 2018, 2019, and 2020 The World Bank (2022). Despite the steady decline of poverty rate in Indonesia's rural and urban areas, about 31 million people still live below the poverty line (US$21 a month) and 40% of total households live just above the national poverty line. In fact, the number poor urban people in cities is currently on the rise, largely due to rapid urbanization in the country, and Mahendradhata et al. (2017) predicted that urban population will rise by 67% by 2025.

2.7.2. The burden of breast cancer

Indonesia is undergoing an epidemiological transition, in which the burden of disease shifts from communicable disease and early-life mortality to non-communicable diseases (NCDs) which reflect increases in people's life expectancy and increases to the median age at death (Bloom et al., 2015). In Indonesia, breast cancer has become a major public health problem. It accounts for 30.5% of all cancers diagnosed and 21.5% of cancer-related deaths among women (Choridah et al., 2019; Mardela, Maneewat, & Sangchan, 2017). The costs associated with the five domains of NCDs (cardiovascular disease, cancer, chronic obstructive pulmonary disease, diabetes, and mental health conditions) will cost Indonesia an estimated US$4.47 trillion (or US$17 863 per capita) from 2021 through to 2030, a period over which breast cancer is expected to cause 15.7% of the total loss of gross-domestic-product output (Bloom et al., 2015).

Although the incidence of breast cancer is lower in Indonesia and other LMICs than that in high-income countries (HICs) (Michael Drummond et al., 2015), the typical breast cancer incidence in Indonesia is characterized by late presentation, young age, and low survival rate (Fan, Goss, & Strasser-Weippl, 2015; Mittra, 2011; C. Ng et al., 2011; Tsu, Jeronimo, & Anderson, 2013). These aspects are the results of a lack of cancer prevention and screening programs, as well as limited resources to treat cancer (Mahendradhata et al., 2017; Shah, Kayamba, Peek, & Heimburger, 2019). In addition, a low percentage of women are aware that a painless lump on their breast may be symptomatic of breast cancer, and even if suspicious of any abnormality of their breast, they will first reach out to a local traditional healer, and hence delaying the proper diagnosis and producing poor prognosis (Anwar et al., 2018; Sharma, 2019). The details of epidemiological context of breast cancer in Indonesia are described in **Chapter 5**.

2.7.3. Breast cancer screening in Indonesia

In Indonesia, breast cancer screening is offered as an opportunistic activity rather than an organized program. Breast cancer screening in the country is delivered at the primary healthcare level known as the SADANIS program. In Jakarta province, SADANIS takes place at fixed units located at tertiary hospitals and with mobile mammography units temporarily housed at outreach services. In addition, most of the cancer-care units are located in urban areas, making it more difficult and more costly for rural patients to access quality care (Kardinah, Anderson, Duggan, Ali, & Thomas, 2014).

Clinical breast examination (CBE) is the selected screening technique for the SADANIS program, while mammography-and-ultrasonography (USG) is the

screening modality used at secondary and tertiary hospitals. CBE is considered a cost-effective alternative to screening mammography, despite the inconclusive efficacy in early diagnosis and improved survival (Corbex, Burton, & Sancho-Garnier, 2012; Mathew et al., 2011; Sharma, 2019).

Following a pilot project in six provinces of Indonesia started in 2008, the Indonesian government expanded the implementation of the SADANIS to 180 districts in 32 provinces, engaging 500 out of 9500 health centres across the country. Trained practitioners in public primary healthcare centres provided screening services along with nurses and volunteers who were undertaking community awareness campaigns to encourage people in the targeted groups to come forward for screening (Mahendradhata et al., 2017). In several regions in Indonesia, cultural factors, values, and beliefs remain the determinants in the utilization of medical services, such as the use of contraceptives in family plang programs and vaccines. However, regarding breast cancer screening, a previous study by (Solikhah, Ratu, Fitriana Putri, Lina, & Tri Ani, 2021) found that the primary inhibitors for low attendance of breast cancer screening were lack of knowledge, fear, anxienty, and discomfort following a diagnosis of breast cancer.

In 2015, SADANIS was officially regulated through a decree of the Ministry of Health which allowed free breast cancer screening available at the primary health centres (PHCs) for women aged 30–50 years under the national health insurance scheme (BPJS). However, the opportunistic strategy of delivering SADANIS program produced a low-quality screening process and reduced the possibility of systematically assessment of the screening activity outcomes of screening activities at the population level (Ballard-Barbash et al., 1999; Espinas et al., 2011). Data

collected through SADANIS consisted of the patient's demography and clinical breast examination results. Because SADANIS was a one-time screening service the data recording system was not designed to capture the longitudinal history of the screening interval period. Conclusively, SADANIS screening outcomes and the program's effectiveness were difficult to assess.

2.8. The need for cost-effectiveness analysis of breast cancer screening programs in Indonesia

Breast cancer screening programs will only make a substantial difference to population health if a sufficient proportion of the population is screened and the expected acceptable level is greater than 70% (WHO, 2020). After almost seven years of implementation, only 5% - 10% of the targeted population of SADANIS program participated in the program (Anwar et al., 2018; Ministry of Health Republic of Indonesia, 2017). Dharmais national cancer center Indonesia which monitored the stage of breast cancer at diagnosis reported that between 2003-2013 more than half of the cumulative proportion of all breast cancer patients presented with stage III-IV disease. Findings from a previous SADANIS study in Jakarta showed that of 14 women identified with breast cancer, 42.8% were lost to follow-up treatment (Kardinah et al., 2014). This evidence suggests that the current screening program has a limited effect on detecting early-stage breast cancer, which may be due to the nature of the program's opportunistic approach in SADANIS (Anderson et al., 2011). Despite strong investments in this intervention program, more evidence is needed to evaluate the ability of SADANIS to hasten breast cancer detection and improve prognosis (Fracheboud et al., 2004).

The Ministry of Health and stakeholders have called for context-specific information focused on practical and cost-effective breast cancer screening strategies. If made available, this information may result in a redesigning of the SADANIS program and reallocating its resources, and eventually helps achieve the ultimate goal of reducing the morbidity and mortality of breast cancer in Indonesia.

2.9. Applicability of health technology assessment for breast cancer screening programs in Indonesia

Health technology assessment (HTA) is a dynamic and evolving process, embracing different types of assessment that can inform decision-makers about the benefits, risks, and costs of new and existing technologies (Drummond et al., 2008). HTA considers the full spectrum of domains that include technology description, clinical effectiveness and safety, economic evaluation, social, and organizational features, and ethical and legal issues (Teljeur, Moran, Harrington, & Ryan, 2017). The health technology type in this research context is considered 'technology applied to the healthcare system", and is used to ensure access and service delivery have corresponded with regulatory and policy measures on access structures and organization, processes and healthcare outcomes (Velasco Garrido, Gerhardus, Røttingen, & Busse, 2010).

Addressing the scarcity of healthcare resources, HTA has been of growing interest in Indonesia's health care system. The Indonesian HTA Committee (InaHTAC) was established in 2014 and responsible for providing evidence-based, transparent policy recommendations. A national HTA guideline has been published to standardize Indonesia's HTA studies (Ministry of Health Republic of Indonesia, 2017). However, to the researcher's knowledge the HTA study for systematic management of the

breast cancer screening services remains very limited in Indonesia. Therefore, it is crucial to explore the current evidence on economic evaluation conducted in selected Asian countries that have implemented organized breast cancer screening programs, and then develop the country specific model for Indonesia's healthcare setting.

This research provides new knowledge regarding cost-effectiveness of organized breast cancer screening. Despite reflecting breast cancer screening program in Jakarta, this research potentially serves as a platform of evidence to support decision-making model and the development of policies promoting an organized breast cancer screening model using HTA study.

2.10. Summary

In summary, this study has provided the supporting evidence for a broader understanding of the appropriateness of strategies to improve breast cancer screening within the Indonesian health system. While current opportunistic screening program SADANIS has been improved over the years, there remains room for improvements in terms of cost and efficacy. Organized screening programs implemented in developed countries have proven some benefits that could be implemented in Indonesia, with some necessary adjustments. It is expected that the improved screening strategies would substantially raise awareness of the opportunity to build integrated pathways into the national guidelines for breast cancer screening to ensure promptness of follow up for accurate diagnosis and treatment. This chapter has elaborated the importance of using decision-analytic models in economic evaluation, particularly about the models' ability to compare the cost effectiveness of healthcare interventions over an extended time horizon.

Chapter 3: Literature review

3.1. Overview

The main purpose of this literature review is to obtain supporting data to populate the model developed as part of this research study. This chapter consists of a systematic literature study that synthesizes the availability and variability in economic analysis of breast cancer early-detection strategies undertaken in Asian countries.

The economic evaluation of early detection for breast cancer was searched from databases of Medline, Embase, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the researcher identified 15 publications in high-income countries, upper- and middle-income countries and in lower-, middle-income countries. The search findings indicated that the evaluation of economic research on breast cancer early-detection strategies was still limited in Asia. The evidence from the reviewed studies further suggested that organized mammography screening in women younger than 50 years of age may be economically attractive in Asia. However, there was relatively limited evidence regarding opportunistic screening strategies. The findings on model parameters and key assumptions in this study were used to inform the next stage of the model developed in **Chapter 6** and **Chapter 7**.

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Yuniar, P., Robinson, S., Moorin, R., & Norman, R. (2020). Economic Evaluation of Breast Cancer Early Detection Strategies in Asia: A Systematic Review. ***Value in Health Regional Issues,*** **21, 252–263. Doi:10.1016/j.vhri.2020.01.003.**

For ease of reading, the paper is reproduced for the thesis in this chapter. The PDF of the published paper can be found in **Appendix A**.

3.2. Background

Both health and financial burdens of breast cancer remain significant, despite considerable efforts to address them (Fan et al., 2015; Wagh, Chaluvarayaswamy, & Pal, 2017). Asia is facing high and increasing strain from breast cancer but is less researched than Europe or North America. This absence of region-specific evidence poses a significant threat because findings around safety, effectiveness, and cost-effectiveness may differ substantially. This absence affects both the pathway women experience in the detection and management of the disease, and the resource capacity for implementing early-detection strategies (Agarwal, Pradeep, Aggarwal, Yip, & Cheung, 2007; M. F. Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005). Given the significant prognostic benefit of detecting breast cancer at early stages, early detection is a potentially fundamental strategy for minimizing the burden of the disease. It comprises two components, early diagnosis and screening (WHO, 2007). The existing work concerning interventions across the breast cancer continuum of care are predominantly from western countries (Bhoo-Pathy et al., 2013; Lee, Mariapun, Rajaram, Teo, & Yip, 2017).

Many Asian countries have been struggling to improve the implementation of early-detection strategies due to funding barriers, an absence of evidence to guide programs, and a lack of appropriate investment in healthcare infrastructure (Singh, Pearlman, & Kostelecky, 2017). Addressing the scarcity of healthcare resources in the face of seemingly unlimited demand, economic evaluation is gaining more attention from policy-makers in Asia (Yothasamut, Tantivess, & Teerawattananon,

2009). However, some regions face challenges to using economic evaluation that include data limitations, users' minimum comprehension of economic evaluation, and political and ethical considerations in resource allocation (Moatti, 1999; Yothasamut et al., 2009).

Economic evaluation can be used as a tool to assist decision makers in allocating healthcare resources and making choices about the planning and provision of healthcare (Alastair M. Gray, Philip M. Clarke, Jane L. Wolstenholme, & Sarah Wordsworth, 2012; Crowley et al., 2018). The central principle of economic evaluation is to estimate the costs and outcomes associated with two or more approaches to care in a particular population, and to compare these costs and outcomes simultaneously to understand the trade-offs made when shifting between these competing strategies (Zwahlen, 2003).

There has been a need to develop Asia-specific body of literature around economic evaluation to support the development of practical guidelines on early detection and reduce the incidence of breast cancer and the mortality rate in Asia. Several recent reviews have summarised the evidence on the economic evaluation of different aspects of breast cancer control (Ahmadian & Abu Samah, 2012; da Costa Vieira et al., 2017; Rashidian, Barfar, Hosseini, Nosratnejad, & Barooti, 2013; Sten G Zelle & Rob M Baltussen, 2013). However, these have not been explicitly conducted in Asian countries and generally have a broader scope than the simple identification of cases. Given a considerable uncertainty when generalizing results from developed western nations to Asia, it is essential to have region-specific comparative evidence on the variability of the economic analysis of strategies for breast cancer early detection. Therefore, this review will provide new knowledge concerning the

economic studies which evaluate breast cancer early detection strategies in Asian countries and synthesize the availability and variability of the health-related economic evaluations undertaken.

3.3. Aim and objectives

This systematic review aims to assess the variability in economic analysis of breast cancer early-detection strategies in Asian setting by focusing on three specific objectives: 1) assess strategies for detecting breast cancer at an early stage; 2) assess the variability of economic evaluation methodology; and 3) assess the differences in the way the costs and effectiveness of early-detection strategies are estimated.

3.4. Study design

The protocol was designed by the authors of the Cochrane Handbook for Systematic Reviews of Interventions, which is the reporting standard checklist used by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS), and the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA-P) checklist. This protocol study is registered with the international prospective register of systematic reviews (PROSPERO, registration number CRD42018115419).

3.5. Methods

3.5.1. Search strategy

A systematic literature search was conducted in Medline (via PubMed); EMBASE, using the OvidSP platform; the Cumulative Index to Nursing and Allied Health Literature using the EBSCO platform; Scopus, the Health Economic Evaluation

Database (via EBSCO) from its inception up to September 2018, but limited to studies written in English. In addition, the grey literature was searched using the website of selected organizations and networks, including the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO). The search was expanded by identifying studies from the reference lists of identified relevant studies.

The key definitions used in this review are “economic evaluation,” “early detection of breast cancer,” “strategies,” and “Asian countries”. These definitions are shown in **Table 3. 1**.

Table 3. 1. Operational definitions and terms were used in the search strategy

Economic evaluation: articles are eligible if they were dealt with one of four main types of economic evaluation studies, namely cost ffectiveness, cost benefit, cost utility, and cost minimization.
Early detection of breast cancer: two approaches that enable timely diagnosis and treatment of breast cancer are: 1) early diagnosis (recognizing symptomatic cancer in patient), and 2) screening (identifying asymptomatic disease in a healthy target population).
Strategy: initiative, approach, or activities that aim to either: 1) strengthen national breast cancer control program by planning an effective and appropriate early-detection program; or 2) improve healthcare provision of timely diagnosis and treatment of breast cancer.

3.5.2. Eligibility criteria

Types of early-detection strategies

For this review, early detection was defined either as early diagnosis or screening. Early detection without screening entails education of the population and for healthcare providers to respond to the first signs or symptoms of breast cancer. Since screening modalities can be delivered through either organized or opportunistic approaches depending on the country's setting, this review employed opportunistic and/or organized screening using screening modalities such as: clinical breast examination (CBE), magnetic resonance imaging (MRI), mammography; ultrasonography (USG), a combination of two or more of four modalities above, health promotion of the symptoms and signs of breast cancer, and breast-self-examination (BSE).

Types of studies

Studies were included if they used one or more of the following types of full economic evaluation: 1) cost effectiveness, cost benefit, cost utility, or cost minimization, evaluating any of the strategies for early detection of breast cancer noted above, focused on populations in Asian countries; 2) economic analyses measuring the performance of national breast cancer control programs, programmatic approaches (such as organized or opportunistic), the benefit of particular screening modalities to reduce morbidity, mortality or any other intermediate outcome, as well as the evaluation of specific diagnostic imaging equipment to support early-diagnosis strategies; and 3) inclusion of the outcome indicators from experimental studies, observational studies, or mathematical models.

Studies were excluded if they met any of the following criteria: 1) did not present original data; 2) were not a full-text publication; 3) were in the form of comments, letters to the editor, descriptive studies, case reports or conference papers; 4) did not include information on health outcomes; 5) did not include information on intervention costs (only gross economic benefit was estimated); or 6) was not published in English.

3.5.3. Data extraction

The study characteristics were extracted from all reviewed studies. These were the country or region, the base year of cost, year of publication, and study population. The extracted methodological characteristics were type of economic evaluation, study design, perspective, time-horizon, and outcome measure for effectiveness. Also listed information on cost, discount rate, the source of estimation effectiveness, the source for estimation of resource utilization, value, and references used for the study parameter. The results of the studies were captured using the economic evaluation results obtained by the authors.

3.5.4. Data synthesis

Descriptive characteristics of the eligible studies, together with the results of their standard reporting appraisal, were extracted and reported in a systematic format. A variety of early-detection strategies and epidemiological backgrounds was explored to frame the policy consideration in the implementation of breast cancer early-detection programs. Across the studies, based on the authors' description, the researcher identified the common themes of early-detection strategies, namely screening programs, or early diagnosis. The study design for the economic evaluations was also discussed to consider the methodological approaches. To

facilitate data synthesis, the results of the economic evaluation was converted to US dollars (USD) and inflated to 2018 prices sourced from the U.S. Bureau of Labor Statistics (http://www.bls.gov/cpi).

3.5.5. Quality assessment of reviewed studies

The quality of study reporting was examined using the Consolidated Health Economic Evaluation Reporting Standards statement (Husereau et al., 2013). It contains a 24-items checklist intended to establish the minimum information that should be included when reporting on economic evaluations of health strategies; each publication included in this review was assessed against these criteria (Husereau et al., 2013).

Three-scale responses were used to appraise each item. Publications scored 1 point for each point fully met, 0.5 for each partially met, and 0 for very little or no information was reported. A percentage score was then generated, and the sum of scores was divided by the total domain scores, giving all criteria equal weight. Studies that scored 75% or more were categorized as high quality, scores in the 50–74% were ranked medium, and scores below 50% were ranked low (Mangham-Jefferies, Pitt, Cousens, Mills, & Schellenberg, 2014). As two of the reporting criteria may depend on the publishers (source of funding and conflicts of interest), the percentage scores excluding these criteria were also generated, but this had minimal impact on the categorizations.

3.6. Result

3.6.1. Search results

The systematic selection criteria for the articles are shown in **Figure 3. 1 .** The articles were exported to EndNote X7 (Clarivate Analytics, Philadelphia, PA), with duplicates removed. The title and abstract of the retrieved articles were then uploaded to Rayyan, a free web app for systematic review (Ouzzani, Hammady, Fedorowicz, & Elmagarmid, 2016). The research strategy initially yielded 1 445 studies, including 556 from Medline, 36 from EMBASE (Ovid), 117 from Cumulative Index to Nursing and Allied Health Literature (EBSCO), and 736 from PubMed. After excluding any duplicates, the total number of hits was reduced to 988 records. The application of filters to the titles, abstracts, and full texts resulted in 15 articles that fully met the criteria.

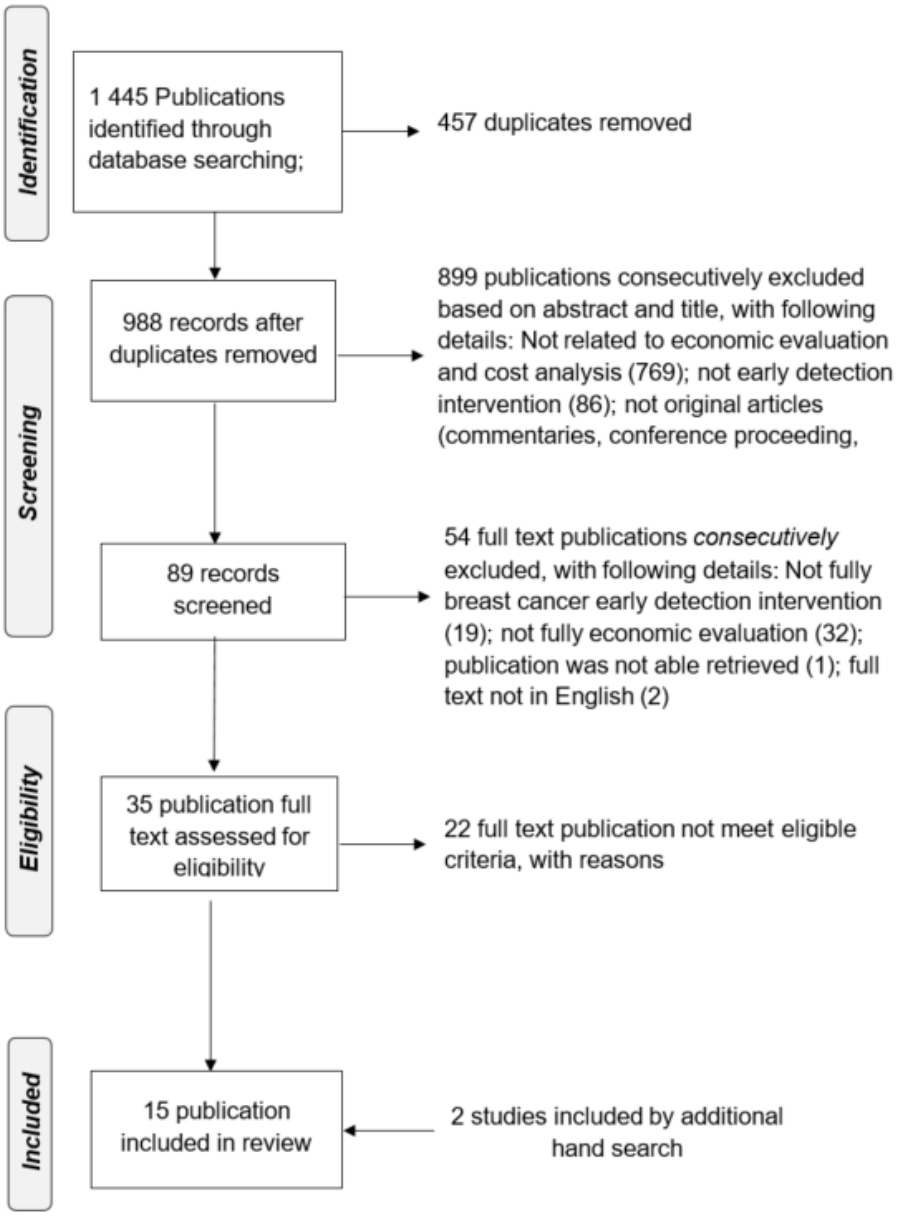

Figure 3. 1 Flow diagram of the study selection phases

3.6.2. Study characteristics

The literature review retrieved eight studies based in East Asia, five in West Asia, and one each in South Asia and Southeast Asia. Based on the income classification by the World Bank, three of the East Asian countries were categorized as high income (Japan, Korea, and Hong Kong), three were categorized as upper-middle-

income (China, Turkey, and Iran), and two were lower-middle-income (India and Vietnam).

Table 3. 2. shows the characteristics of the studies based on the elements of economic evaluation reported in them, all of which conducted a full economic evaluation and cost-effectiveness analysis. A variety of perspectives were used, including that of the payer (Hatam, Ahmadloo, Vazirzadeh, Jafari, & Askarian, 2016; Nguyen & Adang, 2018; Okubo, Glick, Frumkin, & Eisenberg, 1991; Zehtab et al., 2016a); society (Özmen et al., 2017; Sato et al., 2014a; Sun, Legood, Sadique, Dos-Santos-Silva, & Yang, 2018; Wong, Cowling, Schooling, & M Leung, 2007) ; healthcare provider (Barfar et al., 2014; Lee et al., 2009); health system (Haghighat, Akbari, Yavari, Javanbakht, & Ghaffari, 2016a); government (Ishikawa et al., 2012a; Kang et al., 2013; Ohnuki et al., 2006a); and program perspective (Okonkwo, Draisma, der Kinderen, Brown, & de Koning, 2008a).

Time horizons to capture benefit, cost, and resources were reported in 13 studies, in a range of five months to a lifetime. Nine of the studies included information on the cost and outcome in future years over specific time-horizons, discounted at 3% for both cost and effect. One study only discounted cost at an annual rate of 5%, while the discounted rate percentage was not specified in four studies. The base year of the cost data was generally from 2000 onward, in which only one study before 2000 and one that could unidentified.

Twelve studies included only direct and recurrent costs, excluding any start-up costs (Hatam, Ahmadloo, Vazirzadeh, Jafari, & Askarian, 2016b; Nguyen & Adang, 2018; Okonkwo, Draisma, der Kinderen, Brown, & de Koning, 2008; Okubo, Glick, Frumkin, & Eisenberg, 1991; Özmen et al., 2017; Sato et al., 2014; Wong et al.,

2007a; Zehtab et al., 2016a), while three studies were considered to have included indirect costs in their analysis (Ishikawa et al., 2012b; Özmen et al., 2017a; Sun et al., 2017). In terms of health outcomes, nine studies reported one of the following primary health outcomes: year of survival, life expectancy, the number of breast cancer deaths averted, mortality reduction, or disability-adjusted life years.

The measured intermediate outcomes included the number of detected cases (Barfar et al., 2014; Hatam et al., 2016a; Lee et al., 2009) and participation rate (Ishikawa et al., 2012a). One study in Japan used economic evaluation alongside a randomized control trial (RCT) (Ishikawa et al., 2012a). Two studies in Iran and one in Turkey used pilot studies as their primary data source to calculate the parameters of cost, and effectiveness of screening programs (Barfar et al., 2014; Özmen et al., 2017b; Zehtab et al., 2016a). In addition, other studies combined data sources from existing datasets, including cancer registries, hospital data, and the International Agency for Cancer Research (Kang et al., 2013; Lee et al., 2009; Ohnuki et al., 2006a; Sato et al., 2014).

Table 3. 2. Elements of economic evaluation reported in the reviewed studies

No.	Authors	Country	The base year of cost data	Economic evaluation type	Study design	Perspective	Time-horizon	Result
1	(Ohnuki et al., 2006)	Japan	1996	Cost-effectiveness analysis	Mathematical simulation model	Government	50 years	Biennial CBE and mammography screening (SMG) resulted in 833.8 lives saved or C/E 2 025 100 yen/year (US$21,021) compared to annual CBE (815.5 lives saved or C/E 3 669 900 yen/year / US$38 095.37) during 15 years of follow-up among 100 000 women aged 40–49 years
2	(Okonkwo, Draisma, der Kinderen, Brown, & de Koning, 2008)	India	2001	CEA	Microsimulation Screening Analysis (MISCAN) models)	Screening program	Lifetime	The incremental cost-effectiveness ratio increased to US$1612.9 a life-year gained for every 5-year CBE (age 40–60) and Int.$1341 (US$1905.68) for biennial CBE in the same age group; the corresponding reduction in BC mortality was 8.2% and 16.3%.

No.	Authors	Country	The base year of cost data	Economic evaluation type	Study design	Perspective	Time-horizon	Result
3	(Wong, Kuntz, Cowling, Lam, & Leung, 2007)	Hong Kong	2005	CEA	Markov model	Societal	50 years	The least costly, non-dominated option was to screen from ages 40 years to 69 years, with an incremental cost-effectiveness ratio of $64 400 (US$83 845) per LYS. By extending screening until age 79 years, the ICER would increase fourfold to $260 300 (US$338 898) per LYS. The ICER is $61 600 (US$80 200) per quality-adjusted life-year saved
4	(Lee. et al., 2009)	Korea	2007	CEA	Stochastic model	Healthcare system	30–85 years	A 2-year interval for the 40–65-year-old age group had an ICER of US$241 869 per one case found.
5	(Barfar et al., 2014)	Iran	2008	CEA	The cost-effectiveness ratio was calculated as an intervention cost for each case identified during the program	Healthcare provider	NA	The total cost of the breast cancer screening program was estimated at US$444 217. The cost per cancer detected was calculated as US$18,509

No.	Authors	Country	The base year of cost data	Economic evaluation type	Study design	Perspective	Time-horizon	Result
6	(Kang et al., 2013)	Korea	2009	CEA	Costs and effectiveness outcomes were compared between the screened and non-screened groups	Government	5 years	The incremental cost to save one life year of a breast cancer patient was 42 305 000 Korean Won (US$60 380) for the screened group compared to the non-screened group
7	(Ishikawa et al., 2012)	Japan	2010	CEA	The cost-effectiveness of the intervention was analyzed by dividing the cost by the number of mammograms performed	Government	5 months	The cost of one increase in mammography screening was 2544 Japanese yen (JPY) or US$34 in the tailored intervention group and 4366JPY or US$59 in the non-tailored intervention group, respectively
8	(Sato et al., 2014)	Japan	2011	CEA	Decision tree and Markov model	Societal	2 years	The computer-aided detection used in screening mammography was cost effective. The ICER was 310 805 yen/life-year (US$3261) gained, compared with the expected cost and life expectancy for double reading

No.	Authors	Country	The base year of cost data	Economic evaluation type	Study design	Perspective	Time-horizon	Result
9	(Haghighat, Akbari, Yavari, Javanbakht, & Ghaffari, 2016)	Iran	2012	CEA	Decision-tree and Markov model	Health system	Lifetime	The incremental costs per quality-adjusted life-year were Int.$141 350 (US$154 687) and Int.$389 148 (US$425 866) in the second and third rounds of screening
10	(Zehtab et al., 2016)	Iran	2013	CEA	Decision-tree model	Policy-makers of insurance	NA	The incremental cost-effectiveness ratio DALY averted was US$6 740 per DALY averted for screening intervention compared with no screening intervention.
11	(Hatam, Ahmadloo, Vazirzadeh, Jafari, & Askarian, 2016)	Iran	2014	CEA	Decision-tree model	Patients and insurance companies	5 years	The incremental cost-effectiveness ratio with its threshold revealed that with each unit of increased effectiveness, the intensive model would cause a US$156 931 increase in costs, compared to the standard model

No.	Authors	Country	The base year of cost data	Economic evaluation type	Study design	Perspective	Time-horizon	Result
12	(Özmen et al., 2017b)	Turkey	2014	CEA	An ICER approach was employed to calculate incremental cost per life-years saved	Societal	Lifetime	The biennial screens for women aged 40–69 are expected to save 279.46 life-years compared to no organized population-based screening, with an additional cost of US$717.85 which implies an ICER of $2 565 per saved life-year
13	(Sun, Legood, Sadique, Dos-Santos-Silva, & Yang, 2018)	China	2014	CEA	Markov model based on breast cancer natural history	Societal	Lifetime	Annual screening yielded an incremental cost-effectiveness ratio of US$8739/QALY. A scenario of annual screening, but where only 70% of detected cases are treated, yields a higher incremental cost-effectiveness ratio of US$11 844/QALY, which is still lower than the threshold. Screening every 3 years and every 5 years achieves an incremental cost-effectiveness ratio of US$7064/QALY and US$7324/QALY, respectively

No.	Authors	Country	The base year of cost data	Economic evaluation type	Study design	Perspective	Time-horizon	Result
14	(Nguyen & Adang, 2018)	Vietnam	2016	CEA	Decision tree and Markov chain analysis	Healthcare payer	Lifetime	The first round of mammography screening in the 50-54 age group had the lowest ICER (US$3816.81 per life-year gained) and the highest incremental net monetary benefit (INMB) (US$811 777). Mammography screening for women aged 55-59 years was estimated to gain 289 life-years per 100000 women and resulted in an ICER of US$4610.49 when compared to no screening Screening for the 45-49 age group and the 60-64 age group could not be considered cost effective since INMBs were negative
15	(Okubo, Glick, Frumkin, & Eisenberg, 1991)	Japan	not clear	CEA	A mathematical model to estimate the cost and effect of five screening strategies	The payer of medical care	50 years	The cost per year of life-year saved during the period modelled (50 years) was US$89 552 for physical examination (PE), US$25 766 for SMG, US$72 795 for PE followed by SMG, US$32 794 for PE + SMG

Table 3. 3 Elements of economic evaluation reported in the reviewed studies (*continued*)

No	Authors	The effectiveness of outcome measure	Sources for estimation of effectiveness	Cost categories	Sources for estimation of resources utilization	Value and references of the study parameter reported	Sensitivity analysis reported
1	(Ohnuki et al., 2006)	Life-year saved	Literature, cancer registry, secondary data, life table	The direct cost of a screening test, diagnostic test, and treatment	Literature, survey	Yes	Yes (scenario analysis)
2	(Okonkwo et al., 2008)	Number of breast cancer death averted; the number of life-years gained; the percentage reduction of annual mortality	Cancer registry, GLOBOCAN 2002, United Nations population division	The direct cost of screening activities	Extrapolated from Dutch unit costs	Yes	Yes (One-way analysis)
3	(Wong et al., 2007)	Life expectancy, mortality, QALY	Literature	Direct medical cost for mammography screening, evaluating the abnormal result, treatment for DCIS, invasive and terminal care	Local public sector and private sector charges	Yes	Yes (probabilistic sensitivity analysis)
4	(Lee. et al., 2009)	Breast cancer cases found in the pre-clinical state	Central Cancer Registry, Census	The direct cost of the mammography and the confirmative examination	National Health Insurance	Yes	Yes (One-way sensitivity analysis)
5	(Barfar et al., 2014)	The number of detected cancer cases (case finding)	Primary data	Direct medical cost (mammography screening, sonographic assessment, biopsy); direct non-medical cost	Actual expenses of the screening program, the actual tariff, or unit cost.	No	Yes (scenario analysis)

No	Authors	The effectiveness of outcome measure	Sources for estimation of effectiveness	Cost categories	Sources for estimation of resources utilization	Value and references of the study parameter reported	Sensitivity analysis reported
6	(Kang et al., 2013)	Life-year saved	Cancer registry, national health insurance, national statistics office	Direct screening cost, indirect screening cost, productivity cost	The internal screening units, published studies, and national statistics	Yes	Yes (One-way sensitivity analysis)
7	(Ishikawa et al., 2012)	Participation rate	Primary data	Direct cost involving the implementation of the intervention program	Primary data	No	No
8	(Sato et al., 2014)	Life expectancy	Cancer registry, hospital data, literature	The direct cost of breast cancer screening and installation costs	Primary and hospital data	Yes	Yes (One-way analysis, scenario analysis, and multi-way analysis)
9	(Haghighat et al., 2016)	QALY	Literature, expert opinions	The direct cost of screening, assessment, treatment, and work-up cost	National tariff of public and private sector	Yes	Yes (One-way sensitivity analysis, Probabilistic sensitivity analysis)
10	(Zehtab et al., 2016)	DALY	Literature, domestic and foreign resources	The direct cost of screening	Primary data	Yes	Yes (One-way and multi-way sensitivity analysis)
11	(Hatam et al., 2016)	Case-detection ratio of recurrences and metastasis	Primary data (patient's records)	The direct cost of follow-up including diagnostic and laboratory testing	The private fees published by the Ministry of Healthcare and Medical Education	No	Yes (One-way sensitivity analysis)

No	Authors	The effectiveness of outcome measure	Sources for estimation of effectiveness	Cost categories	Sources for estimation of resources utilization	Value and references of the study parameter reported	Sensitivity analysis reported
12	(Özmen et al., 2017b)	The number of women who were diagnosed with breast cancer, the stage-specific life expectancies, expected life-years differences	Primary data	Direct medical cost for diagnosis, treatment, follow-up, and surveillance of detected breast cancer patients and direct non-medical costs The indirect cost associated with the loss of working months due to cancer treatment	Social Security Administration	Yes	Yes (One-way and scenario-sensitivity analysis)
13	(Sun et al., 2018)	QALY	A previous study in China	Direct medical cost, direct non-medical cost, and indirect medical cost	Screening program, program working group, and cancer hospital	Yes	Yes (One-way and probabilistic sensitivity analysis)
14	(Nguyen & Adang, 2018)	Life-years gained	Literature	The direct cost of a screening test, laboratory test, and tumour biopsy	Ministry of Health	Yes	Yes (One-way and probabilistic sensitivity analysis)
15	(Okubo et al., 1991)	Life-years saved	Literature; expert opinion	The direct cost of the screening tests	The government fee schedule and literature	Yes	Yes (Multi-way sensitivity analysis)

Sensitivity analysis was conducted to handle uncertainty around the cost-effectiveness ratio. **Table 3. 1.** outlines the analytical methods used in the included studies to deal with such uncertainty. Fourteen studies performed a sensitivity analysis, seven of which involved a single method, either one-way sensitivity analysis (Hatam et al., 2016a; Kang et al., 2013; Lee et al., 2009), scenario analysis (Barfar et al., 2014; Ohnuki et al., 2006; Okonkwo et al., 2008; Okubo et al., 1991) or probabilistic sensitivity analysis (Wong et al., 2007). Six studies applied a combination of techniques. Three studies combined one-way sensitivity analysis with a probabilistic sensitivity analysis (Haghighat et al., 2016; Nguyen & Adang, 2018a; Sun, Legood, Dos-Santos-Silva, Gaiha, & Sadique, 2018), while three studies combined scenario analysis and multiway analysis (Özmen et al., 2017; Sato et al., 2014; Zehtab et al., 2016). One RCT study, which deployed the statistical analysis approach did not demonstrate the method for exploring any study uncertainty (Ishikawa et al., 2012).

The parameter values of breast cancer screening effectiveness were the results of screening trials conducted within the studies' country of origin or from other countries. Three studies from Japan (Okubo et al., 1991; Özmen et al., 2017; Sato et al., 2014), one from Korea (Lee. et al., 2009), and one from Iran (Zehtab et al., 2016) were referenced for the values of sensitivities and specificity of screening modalities from the reports of pilot studies and observational studies within the country. On the other hand, the study from Hong Kong, Vietnam, and India used references from studies in the United States, Japan, and the Netherlands, respectively (Nguyen & Adang, 2018; Okonkwo et al., 2008b; Wong et al., 2007). Only one study used expert opinion to justify the values of mammography sensitivity and specificity (Haghighat et al., 2016)

Parameters related to the relative risk of invasive breast cancer, stage distribution, and survival were obtained from the Surveillance, Epidemiology, and End Results program, randomized trials, and simulation studies (Haghighat, Akbari, Yavari, Javanbakht, & Ghaffari, 2016; Özmen et al., 2017; IWong, Kuntz, Cowling, Lam, & Leung, 2007)

A range of starting and terminating ages was used to *report the target population*, with 10 studies evaluating the starting and terminating age-specific cost-effectiveness measures. Nine of these studies simulated the model with a starting age range in the 40s, while four started at the younger age range (30–35 years old). The reported range of terminating ages reported was between 59 and 75. In one study in Iran, specific subgroups of the population were analyzed to improve accessibility to screening program*s* in rural areas and among low-socioeconomic women (Barfar et al., 2014).

3.6.3. Early-detection strategies

Table 3. 4 provides information on the different strategies of early detection intervention for reducing breast cancer incidence and mortality. The most common was two-yearly population-based screening program (Ishikawa et al., 2012b Lee et al., 2009; Ohnuki et al., 2006; Okonkwo et al., 2008b; Özmen et al., 2017; Sato et al., 2014; Wong et al., 2007); other strategies included deployment a reminder system to enhance screening rates within the non-adhering population (Ishikawa et al., 2012). The main screening modality used was mammography testing, while three studies included combined mammography and clinical breast examination (CBE) (Ohnuki et al., 2006; Okonkwo et al., 2008; Okubo et al., 1991).

Table 3. 4 Early-detection strategies and target population based on the different country settings of included studies

No.	Country	Year of Publication	National/Regional early-detection strategies	Target population	Authors
1	Japan	1991	Annual clinical breast-examination physical exam for all people screened, with further mammography or ultrasonography testing	Women 30 years of age or older	(Okubo et al., 1991)
2	Japan	2006	Biennial mammography and CBE	Women aged 45–49 years	(Ohnuki et al., 2006)
3	Hong Kong	2007	Biennial mammography screening program	Chinese women aged 40–69 years	(Wong et al., 2007)
4	India	2008	Biennial clinical breast examination;	Women aged 40 to 50 years; women aged 40–60 years; or women aged 50–70 years	(Okonkwo et al., 2008)
5	Korea	2009	Biennial mammography screening	Women aged 45–55 years; and younger than 45 or older than 55	(Lee. et al., 2009)
6	Japan	2012	Biennial mammography screening	Women aged 51–59 years	(Ishikawa et al., 2012)
7	Japan	2012	Biennial mammography screening	Women aged 50 years	(Sato et al., 2014)
8	Korea	2013	Biennial mammography screening	Women aged 40 years or older	(Kang et al., 2013)
9	Iran	2014	National mammography screening aimed at low-socioeconomic women — all the services were offered free of charge	Women aged 35 years and older; a low-socioeconomic subgroup	(Barfar et al., 2014)
10	Iran	2016	The triennially organized mammography screening program	Iranian women aged 40–70 years	(Haghighat et al., 2016)
11	Iran	2016	Organized mammography	Iranian women aged 35–69 years;	(Zehtab et al., 2016)

			screening program in rural Iran	a subgroup in rural areas	
12	Iran	2016	Adoption of an intensive follow-up strategy based on the guidelines of the National Comprehensive Cancer Network (NCCN)	Breast cancer patients with full treatment and at least five years of follow-ups	(Hatam et al., 2016)
13	Turkey	2017	Three rounds of a biennially population-based mammography screening program	Turkish women aged 40–69 years	(Özmen et al., 2017)
14	China	2018	A risk-based cancer screening program in Urban China	Women aged 40–69 years	(Sun, Legood, Sadique, et al., 2018)
15	Vietnam	2018	Opportunistic mammography screening	Vietnamese women aged 45–64 years	(Nguyen & Adang, 2018)

3.6.4. Study designs and key assumptions

Study designs are generally described in two categories: modelled and non-modelled cost-effectiveness studies. Ten studies were categorized as incorporating the model approach, seven of which adopted the Markov model (Haghighat et al., 2016; Hatam et al., 2016; Nguyen & Adang, 2018; Sato et al., 2014; Sun, Legood, Sadique, et al., 2018; Wong et al., 2007; Zehtab et al., 2016b), two applied a *mathematical model* (Ohnuki et al., 2006; Okubo et al., 1991) and one study adopted the Microsimulation Screening Analysis model. Given the data limitation various assumptions for the base case were created and validated by comparison with the results of randomized experiments and justified by the local context of the screening program (**Table 3. 4**)

Table 3. 5. Type of decision–analytical models and base-case assumptions underpinning the model of breast cancer early-detection strategies

Authors	Type of decision–analytic model	Base-case assumptions	Country
(Nguyen & Adang, 2018)	Decision-tree and Markov chain analysis	*Participation rate*: 100% of the target population would participate. A 23.6% participation rate was tested and referred to the National Breast Cancer Screening in Korea; *Adequacy of treatment*: all breast cancer patients underwent prompt and adequate treatment; *Stage distribution* in the screened group and the non-screened group were the same in each group; *Transition probability* between health states for the 60–64 age group was the same as that for the 50–59 age group; *Coverage of diagnostic test (biopsy and cytological testing*): Among women with an abnormal mammogram, 50% required biopsy and 50% required cytological testing.	Vietnam

Authors	Type of decision–analytic model	Base-case assumptions	Country
(Haghighat et al., 2016)	Decision-tree and Markov model	*Participation rate*: 80% of the target population would participate in the screening program; *Percentage of abnormal findings:* abnormal findings would be detected in 60% of attendance; *Coverage of further assessmen*t: from 60% of attendance almost 7% (3–10%) require further assessment; *Cancer interval*: the probability of developing breast cancer in the intervals between routine screening was assumed based on National Cancer Screening Program data and published articles; *Cancer detection rate:* cancer detection rate in the non-screen group was assumed to be constant during the second and third screening round; *The incidence rates:* the incidence rates in screened women were considered to be 0.001, 0.0007 and 0.0005 in the first, second and third round of screening, respectively; *Recall rate:* recall rates in the first, second and third round of screening was assumed as 7% (3–10%), 3.6% (3–7%) and 3.7% (3–7%), respectively; Interval cancer rates were assumed to be constant during three rounds of screening	Iran

Authors	Type of decision–analytic model	Base-case assumptions	Country
(Ohnuki et al., 2006)	Simulation model	*Participation in screening program:* each woman would participate in the program annually for the annual model or biennially for the biennial model unless breast cancer was detected or the woman died of causes other than breast cancer; *The life-years of survival* were estimated based on the 5-year survival rate for early-stage breast cancer or another stage; *The proportion of target population:* a proportion of women undergoing the early stage of breast cancers would be asymptomatic women who undergo breast cancer screening; *The effect of annual and biennial screening:* difference in the effect of annual and biennial screening emerged in the rate of false-positive; *Proportion of early breast cancer* among women with a false-negative screening result would be similar to those women who were not screened	Japan
(Sato et al., 2014)	Decision-tree and Markov model	*The re-screening rate* was 100%, however two years after the initial screening in the Markov model the actual rate is lower; according to the Miyagi Cancer Society: 50.3%, average rate between 2002 and 2006.	Japan

Authors	Type of decision–analytic model	Base-case assumptions	Country
(Kang et al., 2013)	Simulation	*The cost for specialty consultation fee:* half of the participants with false-positive screening results received specialty consultation and the remaining half received retesting from a general physician, with the cost for specialty consultation fee being multiplied by 50% under this assumption; *Productivity cost*: productivity cost corresponding to about half of an average day for women to participate in breast cancer screening	Korea
(Lee. et al., 2009)	Simulation	*The sojourn time* in the preclinical state might follow an exponential distribution according to age-specific mean sojourn time (MST); The *MST* in the preclinical state ranged from 2 years for women younger than 50 years of age, 3 years for women aged 50–59 years, and 4 years for women older than 60 years of age	Korea

Authors	Type of decision–analytic model	Base-case assumptions	Country
(Okonkwo et al., 2008)	Microsimulation and Markov model	*Epidemiology background:* a lower incidence and delayed presentation in case of symptoms would be the main differences in the natural history of breast cancer in India compared with more developed countries; *Attendance rate:* 100% attendance rate was used to show the maximum attainable health effect of any given screening program; however, the sensitivity analysis demonstrated that lowering the attendance rate had only a minor effect on the cost-effectiveness ratio; *Efficacy of clinical breast examination (CBE):* screening with CBE reduces breast cancer mortality (this will also be highlighted as a limitation of the study concerning the efficacy of CBE in reducing breast cancer mortality have not been verified in a randomized trial	India
(Özmen et al., 2017)	Simulation	*The total cost of screening* associated with the national breast cancer registry program was zero; The *proportion of stage 0 and stage I* cancer among all cancer was equal to the lower bounds of its quantities; *The proportion of stage II, III, and stage IV caner* were the same as those observed in the national breast cancer registry	Turkey

3.6.5. Evidence of the cost-effectiveness of early detection

The result of the cost-effectiveness of early detection was divided into two intervention approaches, screening and early diagnosis. The results of the economic evaluation of each study are summarized in **Table 3. 2.**

3.6.5.1. Screening

Fourteen studies had national or regional organized screening strategies in place, which was the rationale for conducting cost-effectiveness analysis. Two studies conducted in Japan reported the cost-effectiveness ratio of strategy options (Ohnuki et al., 2006; Okubo et al., 1991) and reporting four combinations of screening, together with the additional costs for physical examination (PE), mammography screening (SMG), and PE-SMG combined (relative to no screening). Applied to a cohort of 100 000 Japanese women, the cost was reported to be $89 552 for PE alone, $72 795 for PE followed by SMG for each additional life-year saved. In the study by Ohnuki et al., three screening modality strategies were combined with screening intervals. The authors reported that biennial clinical breast examination combined with mammography for women aged 30 to 79 years was the most cost-effective strategy, compared to that involving annual CBE and annual CBE-mammography combined for women in the same age group.

Evidence of the cost-effectiveness of computer-aided detection used in screening mammography was obtained by comparing effective cost with the expected cost and life expectancy of double reading. The reported incremental cost-effectiveness ratio reported was $3261 per life-year gained (Sato et al., 2014).

Mammography screening organized biennially was reported to be possibly not cost-effective among Hong Kong–based Chinese women based on an arbitrary threshold, which compared the results of mammography and no-screening strategy of women aged 40-69 years, or 50-79 years (Wong et al., 2007). A study in India reported that mortality reduction is estimated to be the greatest for programs targeting women between the ages of 40 and 60 years. CBE performed annually from ages 40-60 was predicted to be nearly as efficacious as biennial mammography screening for reducing mortality while incurring only half the net cost. The cost-effectiveness ratio increased to US$1 612 per life-year gained for every 5-year CBE, and to US$1 905 for biennial CBE for women aged 40-60 years.

There was also evidence that biennial mammography screening of Korean women aged at least 40 years was cost effective. The study by Lee et al. suggested that the starting age could change from 40 to 35 years, and also that combined 2 and 3 year of intervals screening would be considered a cost-effective alternative.
This conclusion was based on the comparably low incidence of breast cancer among Korean women, and peak incidence rate was reported among women in their 40s.

A study in Iran adopted the perspective of the insurance policymaker to investigate the cost-effectiveness of population-based mammography screening of women aged 35 to 69 residing in the rural area. The incremental cost-effectiveness ratio reported was US$6470.32 per DALY (Zehtab et al., 2016).

3.6.5.2. Early diagnosis

One study in Iran measured the cost-effectiveness of follow-up procedures for a patient with early breast cancer, based on the National Comprehensive Cancer guidelines. The results showed that per-unit increase of effectiveness would

produce US$156 931 increase in costs of intensive model compared to the standard model. This incremental cost-effectiveness ratio was considered above the threshold, and therefore, the intensive follow-up model was conclusively not cost-effective compared to the standard one (Hatam et al., 2016)

3.6.6. Study reporting appraisal

The quality of the reporting in the reviewed studies ranged from 45% to 98%., including nine high-graded studies, five medium-graded, and one low-graded. The low-graded study score tended to omit important elements of economic evaluation methodology; for example, no information was given on the year base and the costing perspective taken. In comparison, the articles graded as high provided more detailed information on both the rationale of the economic evaluation and the methods used in the reporting.

3.7. Literature review in context to current evidence and added value of this study

This literature review identified 15 publications on the economic evaluation of breast cancer early-detection strategies in Asian countries. The review has synthesized three general issues: 1) the type of early detection that was most likely to be introduced in national or regional programs; 2) the extent to which policy decisions on early-detection practical guidance were applied in the economic evaluation studies; and 3) how various methodologic elements of economic evaluation were used to produce cost and effectiveness evidence in the studies.

The literature review conducted for this thesis study indicates that organized mammography screening may be more economically attractive than no screening in selected countries in Asia. However, each study's analytical results were difficult to compare and generalise due to variation in the model structures use, assumptions, program, performance, screening coverage, epidemiological profiles, and local economic setting. These factors may affect the cost-effectiveness options and the health benefit of a particular strategy.

Early-detection strategies were mainly undertaken for population-based screening programs. However, relatively few studies have mentioned specific information on epidemiologic background, such as in the age group relating to the peak breast cancer incidence rate, or information on the availability of healthcare resources to support early-detection programs. This also highlights the lack of evidence on economic evaluation to investigate early-diagnosis strategy which generally increases the chances for successful treatment by focusing on detecting symptomatic patients as early as possible (WHO, 2007b). In addition to the early-diagnosis approach for a country with particularly limited health resources, raising awareness among women about the signs and symptoms of breast cancer as well as screening or clinical breast examination programs is more feasible in stemming the increasing burden of breast cancer (Benjamin O. Anderson et al., 2011; Dey, 2014). As such, approaches are also likely to be economy attractive (Zelle & Baltussen, 2013).

Most of the current knowledge on breast cancer has been generated from studies conducted in Western population which strongly recommends inviting women ages 50-69 to mammography screening every two years (Zielonke et al., 2021). Policy decisions on practical screening guidelines in the reviewed studies were most likely applicable at younger starting ages (35 or 40 years old, and the terminating age of 59–75 years). The rationale for this was that peak incidence occurred at young age (Okonkwo et al., 2008; Tsuchida, Nagahashi, Rashid, Takabe, & Wakai, 2015). The benefits and costs of screening have proved to be effective for women aged 50 to 69 years (Koning et al., 1991). The estimation of screening efficacy for women aged 40–49 years from the Canada trial revealed that several biologic phenomena, such as greater breast density, might explain the lower efficacy of screening and resulted

in lower sensitivity of mammography and lower detection rate by screening (Fletcher, Black, Harris, Rimer, & Shapiro, 1993).

Given the limitation of using data from randomized controlled trials, the model-based analysis provides relevant estimates of the cost-effectiveness of mammography or CBE screening programs. Considering the overestimated assumptions for countries with poorly resourced healthcare services, there needs to be caution in interpreting the results of economic evaluation results (Okonkwo et al., 2008). Furthermore, specific input parameters such as the sensitivity and specificity of mammography for specific age groups, indirect costs, stage-specific treatment costs, and probabilities, are likely to come from several sources (Nguyen & Adang, 2018; Wong et al., 2007). Therefore, the data process incorporated into the model should be transparent, well described, and referenced in sufficient detail (Philips, Bojke, Sculpher, Claxton, & Golder, 2006). Case that used expert views (Okubo et al., 1991) must described and justify the methods and sources (Philips et al., 2006). In addition to the methodologic aspect, sensitivity analysis is critical in addressing any uncertainties regarding modelling the natural history of breast cancer, as well as validation of the cost-effectiveness model (Schiller-Fruhwirth, Jahn, Arvandi, & Siebert, 2017).

3.8. Summary

This study has added values to providing evidence on the variation of starting age of breast cancer screening in selected Asian countries, the sensitivity and specificity of screening modalities, and the model structure and critical assumptions used in the existing model. This information will be essential to consider when populating model parameters of breast cancer screening strategies in Indonesia. Breast cancer policies in selected Asian countries also provide insights into guidelines for

systematic management of breast cancer screening programs and clear standards on patient pathways, such as follow-up services to access prompt and appropriate treatment.

The next chapter presents qualitative methods for approaching contextual domains in breast cancer early detection within the Indonesian healthcare system to inform a country-specific decision-analytic model.

Chapter 4: Methods: Contextualizing breast cancer early-detection decision-making and accessible data sources for the economic evaluation in Indonesia

4.1. Overview

The findings of the systematic review presented in **Chapter 3** suggest the limited amount of research on economic evaluation of breast cancer early detection strategies in Asia. In addition, published literature claims that lower income countries with limited research resources often apply methods or evidence from higher income countries without considering their relevance or transferability (Drummond et al., 2009a; Wong et al., 2007a). These findings suggest that researchers may encounter problems due to data limitations that potentially affect the quality, consistency and transparency of decision-making processes (Caro, Briggs, Siebert, & Kuntz, 2012; M. Drummond et al., 2009). Some researchers argue that more in-depth research is required before a health economic model can be developed to address relevant decision problems in the provision of healthcare in a given country (Chilcott et al., 2010; Inotai et al., 2018) and to make the results in the model more widely considered by decision-makers (Xie, Malik, Linthicum, & Bright, 2021).

In addition to model development, the country-specific context is necessary to allow a greater transferability of evidence (Hailu et al., 2021; Liu, Huffman, & Trieu, 2020). Furthermore, a clear understanding, description and explanation of context enables

judgments to be made about the transferability of any interventions (Skivington et al., 2021).

This chapter describes the methodological approach used in the decision-analytic model development. The aims of this chapter are threefold: 1) set clear boundaries in the model scope by contextualizing the decision problem from healthcare perspectives; 2) explore the availability of data sources for the program, related to breast cancer early detection; and 3) identify relevant parameters and justify the assumptions to inform the development of the decision–analytic model undertaken for this thesis.

To accomplish three aims above, four research questions are formulated: 1) What is the government's policy to address the early detection of breast cancer? 2) How is the national policy operationalized at national and sub-national levels in the context of input, activities, output, and outcome? 3) What are the policy options to strengthen the current breast cancer early-detection programs? 4) To what extent are the availability and quality of the existing screening data sufficient to inform the development of an economic evaluation model?

This chapter begins by outlining a working definition of context applied in this thesis. The second section explains in detail the research designs, including the framework of the WHO framework to the Indonesia context. The third section focuses on the method undertaken. Three consecutive methods of research undertaken are outlined separately: namely 1) document analysis; 2) semi-structured in-depth interviews; and 3) Working Group Discussions (WGDs).

4.2. A working definition of context

In this study, the term context refers to any features of the circumstances in which early-detection objectives of breast cancer programs in Indonesia are implemented to produce the desired health outcomes (Craig, Ruggiero, Frohlich, Mykhalovskiy, & White, 2018). As explained earlier, breast cancer opportunistic screening program in Indonesia is called SADANIS. The name SADANIS is the abbreviated *Pemeriksaan Payudara Klinis* or clinical breast examination, CBE. In the absence of a formal screening program in Indonesia, the SADANIS program is a national program designed to respond to a finding on clinical breast examination or concerns expressed by a woman during routine care or when she presents with symptoms.

4.3. Research design

This study used an explanatory sequential mixed method design(Creswell & Plano Clark, 2011) over two study phases. A systematic literature review was used in the first research phase to collect a large amount of quantitative data to understand the parameters populated in the cost-effective analysis model. The second phase of study involved discussing the findings from the literature review with SADANIS program stakeholders. This qualitative component also provided an opportunity to explore stakeholder perspectives on the policy, organisation and delivery of breast cancer screening. This second phase provided a more in-depth understanding of the contextual breast cancer screening program within the Indonesia healthcare setting as well as validating quantitative findings.

The *Rapid Situational Assessment* of *Data and Data Systems* framework was adapted to facilitate the identification of salient features of SADANIS across the implementation of a continuum of cancer care. Developed by the World Health

Organization in 2018, this approach was initially applied to plan, scale up, and improve cervical cancer screening and treatment services in low-resource settings (Drummond, Were, Arrossi, & Wools-Kaloustian, 2017; WHO, 2018). WHO designed this approach as a toolkit in programmatic contexts to assist the Ministry of Health and other stakeholders in improving data systems for decision-making (WHO, 2018). The modified framework of *Rapid Situational Assessment* o*f Data and Data Systems* was used in this study to guide a comprehensive assessment using two building blocks is presented in **Figure 4. 1** . The first building block consists of seven key domains to assess the landscape of existing breast cancer early-detection programs in Indonesia and the variable data to be captured. The obtained data within the Building Block I domains are expected to shape information in Building Block II by taking into account six context-relevant groups of information required for Health Technology Assessment (Downey et al., 2018; Hollingworth et al., 2020; Kaltenthaler, Tappenden, & Paisley, 2013).

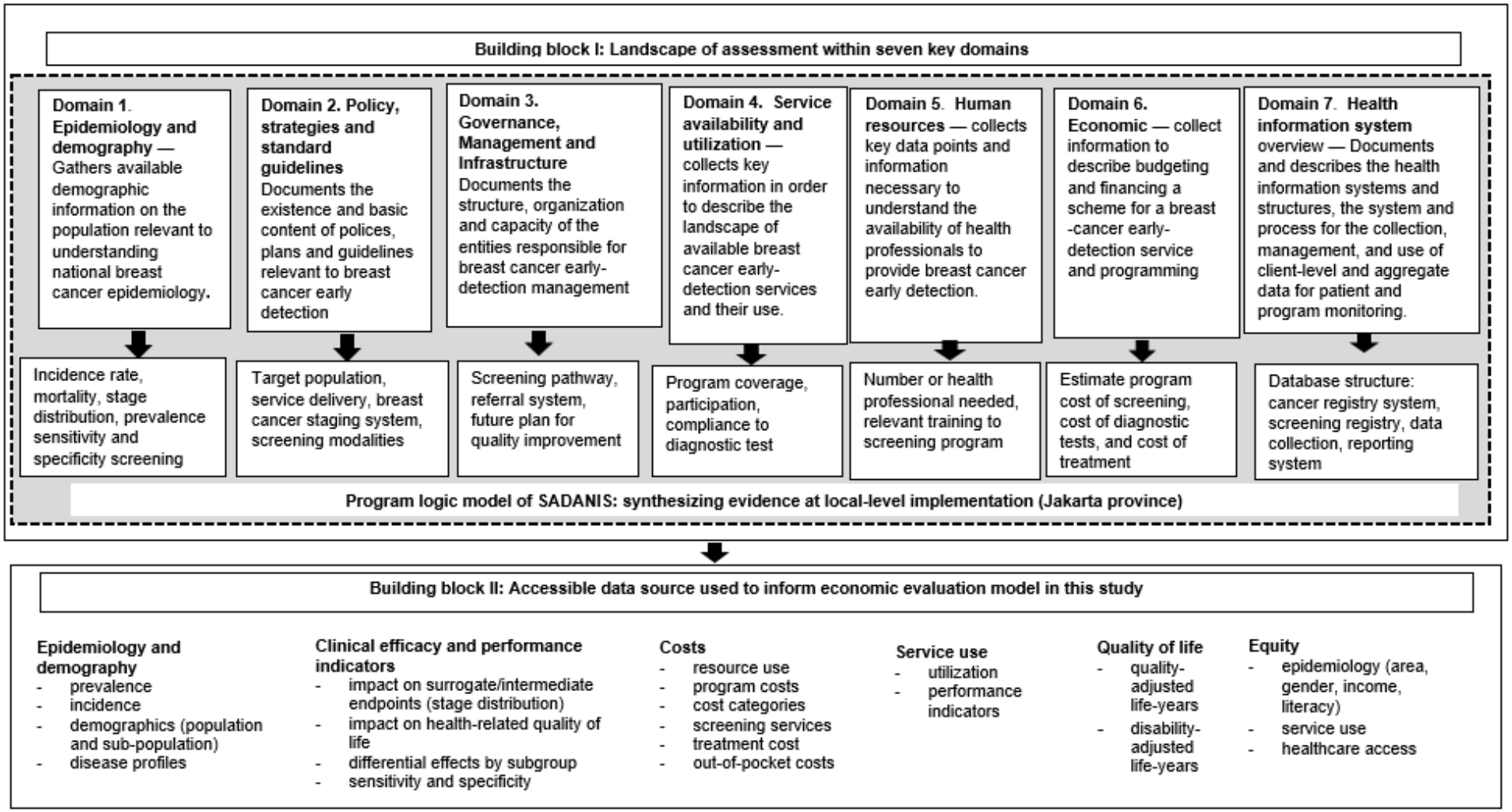

Figure 4. 1 The analytical framework for document analysis, semi-structured in-depth interview and focus-group discussion guideline

The research approach involved linking the domains in the analytical framework (**Figure 4. 1**) to research question in this thesis, **Table 4. 1** outlines the specific research questions posed against the contextual factors that contribute to the breast cancer early-detection program.

Table 4. 1 Domains and questions pertaining to contextual factors in the SADANIS program

Domain/sub domain	Specific questions to address considered contextual factors
▪ Epidemiology and demography: - incidence - prevalence - stage at diagnosis	How are the epidemiological/demographic features of the target population appropriate to the breast cancer early-detection program?
▪ Policy environment: - content - context - policy process to strengthen the existing intervention program ▪ Strategies ▪ Standard guideline	How does the position of the breast cancer early-detection program fit within the broader framework of Indonesia's health policy? - Is the SADANIS program required due to a government commitment to ensure equity of breast cancer early detection? - What are the stakeholders' expectations for SADANIS? - What are the plans for improvement? - How is the SADANIS program embedded with national cancer control strategies to achieve desired outcomes?
Governance, management and infrastructure	What are the barriers inherent in the health system, and program management, organizations, infrastructure, medical equipment and clinical capacity as they affect capacity to deliver timely health care?
Service availability and utilization	- Is the health service design feasible in the existing infrastructure in all of the provinces / regional health authorities? - What are the influencing factors prompting people to engage in help-seeking behaviours that draw on cancer knowledge, attitudes and beliefs, fears and their access to health care? - How will these program features affect their effectiveness?

Domain/sub domain	Specific questions to address considered contextual factors
Human resources	- Are there health human resource (HHR) gaps? - Does the province have the required number of appropriately trained and qualified practitioners to provide the service(s) in question? - Are there any staffing arrangements or training options that could fill these HHR gaps?
Economic	- What are the barriers to timely health care in terms of financing? - What are the barriers to timely presentation in terms of costs?
Health information systems	- Is the database of cancer registry, or the screening registry, generating and maintaining early-detection data to permit evaluation of screening performance (such as sensitivity, specificity and positive predictive values)? - Is the design of the cancer information system required to incorporate linkages to population-based cancer registry data or another source of pathology data to understand the full effect of breast cancer early detection on cancer outcomes? - Can the data on pathological or biological characteristics of tumours, together with patient demographic and risk factor information be linked to a population/hospital-based registry? - What are the sources of accessible data to support the model?

4.4 Research methods

The study component described in this chapter was conducted from November 2018 to July 2019. It employed exploratory qualitative methods to understand the experiences of relevant stakeholders and unpack some of the complex issues inherent in the Indonesian healthcare system and those relating to breast cancer screening Indonesia. As Patton and Fund (2002) suggest, qualitative research integrity can be strengthened by using several data collection methods. Therefore, this study engaged three interrelated methods of data collection: document analysis, semi-structured in-depth interviews, and working group discussion **(Figure 4. 2).** These methods were considered optimal for capturing the detailed landscape,

including the challenges in plans for improving the breast cancer screening program in Indonesia and identifying the availability of relevant data sources to support evidence-based decision-making.

Method I involved a document analysis to determine the predominant strategy and approach to the SADANIS program. Method II was a semi-structured in-depth interview to clarify operationalization of the technical aspect, eliciting stakeholder experiences and their perceptions about the goal of SADANIS and the factors that support or hinder goal achievement. In method III, the Dharmais Cancer Center working group convened with the researcher to collaborate on their research agenda for the early detection of breast cancer. There were three series of activities: two collaborative expert workshops and a web-based collaborative learning project hosted by the National Cancer Institute, the ECHO project, for comprehensive breast cancer control (Cira et al., 2020). The researcher nested these working group discussions together to gather relevant information for this study. The following sections describe the sequence of activities in each consecutive methodology.

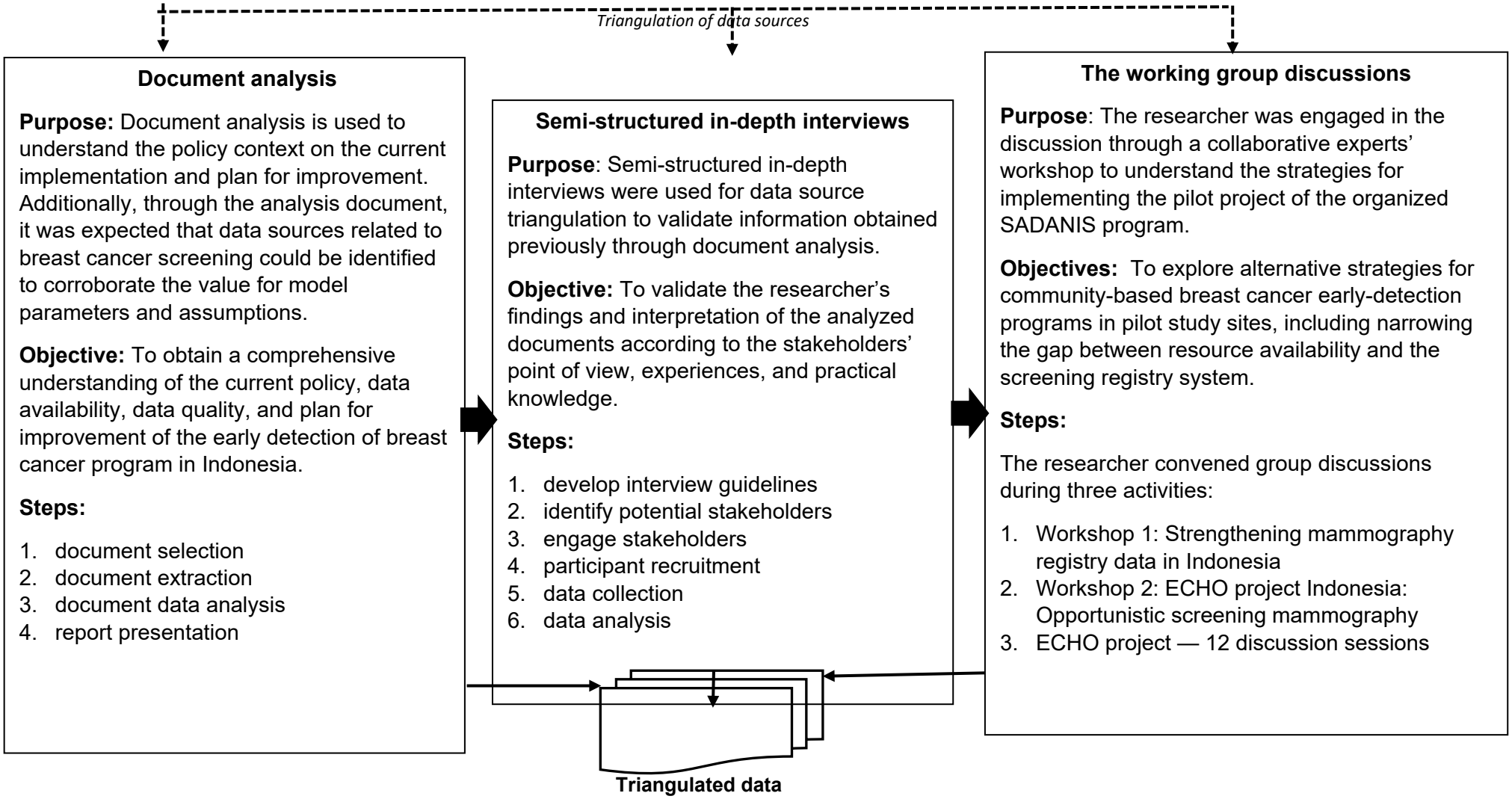

Figure 4. 2 Consecutive data collection methods applied in this research

4.4.1 Document analysis

The purpose of phase I was to aggregate data-describing policies, and the goals and the current implementation of the SADANIS program, along with determining program challenges and a program improvement plan. In addition, documents were also analyzed to gather information on the types of screening-related data that could be used to populate the screening model developed in this thesis. The availability of data sets at the primary healthcare and hospital level, including the cancer registry system, was also explored at this stage.

4.4.1.1 Document selection

At the outset, the nature and number of documents were determined based on document selection guideline (**Appendix C**) related to the domains presented in the research framework (**Figure 4. 1**). The researcher obtained the documents directly from the website of Indonesia's Ministry of Health, or from participants who provided relevant documentation to the researcher during the interview or working group discussion process. The researcher then expanded the search by identifying relevant scholarly documents on the early detection of breast cancer in Indonesia, which were referenced in electronic databases. The key terms used in the researcher's scholarly search were "breast cancer," "screening," "early detection," "early diagnosis," "Indonesia," and "SADANIS." In addition, she searched the website of the Institute for Health Metrics and Evaluation (IHME) for data related to breast cancer epidemiology.

4.4.1.2 Document data analysis

The data analysis entailed identifying, selecting, making sense of, coding, and narratively synthesizing data contained in the included documents (Bowen, 2009).

Figure 4.3 illustrates the four main stages of content analysis used in this study. Adapted from Bengtsson (2016), the researcher used this analysis framework was utilized to organize and elicit meaning from the document analysis's quantitative and qualitative findings and drew a realistic conclusion. The content analysis approach, applied to both qualitative and quantitative data, was engaged for making valid inferences from the text (or other meaningful matter) as to the context of their use (Bengtsson, 2016; Krippendorff, 2018). The researcher used NVivo (QSR International, 2021) software to extract and analyze the information.

At stage 1 – decontextualization, the researcher familiarized the text and quantitative data from all documents obtained, namely legal documents, official documents, scholarly work, implementation documents, working documents and data sets. After the data and information were familiarized, the researcher gained insight to answer questions relating to contextual factors in the SADANIS program. After obtaining the appropriate meaning units, the researcher performed stage 2 – the recontextualization to sort out substantive information and excluded inappropriate information.

At stage 3 - the categorization, the researcher used a combination of deductive and inductive coding approaches. In the first round of coding, top-down coding was applied. The domains were created as pre-defined vital themes of the coding template, while the information within each domain was pre-specified as sub-themes. The words or parts of the text unit were then identified, highlighted, copied and inserted to fit the coding template (Table 4. 1). Then, the inductive coding approach was carried out to shape the thematic contexts which emerged from the assigned excerpts in the study's deductive coding process. At the last step, stage four (the compilation), driven by the analytical framework, the researcher conducted manifest t

followed by latent analysis to find the essence of the phenomenon related to the implementation of SADANIS (Burnard, 1995).

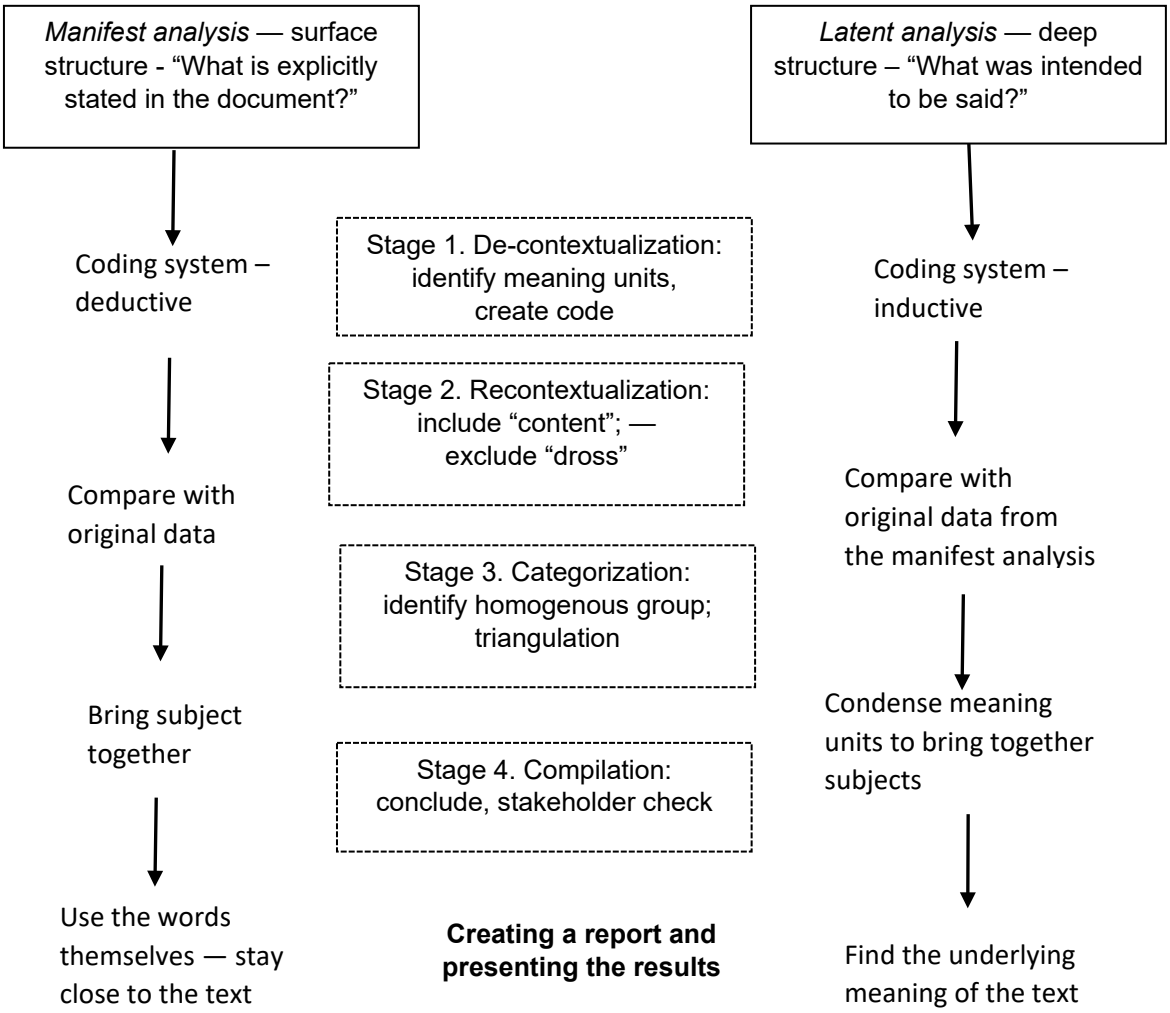

Figure 4. 3 The process of document data analysis

Table 4. 2. Deductive domain codes, definitions, and dimensions that interact to inform model development

ID codes	Domain codes (Building block 1)	Description	The relevance and importance of dimensions within the domain for model development (Building block 2)
1a	Epidemiology of breast cancer	Epidemiological information includes the frequency of new cases of breast cancer, vital statistics, late-stage shifting, the total number of breast cancer cases, all-cause mortality, breast cancer mortality	Measures of population effect used in decision models of prevention intervention (Alberg, Lam, & Helzlsouer, 1999; Haddix, Teutsch, & Corso, 2003)
1b	Demography	Refers to quantifiable characteristics of the eligible population (age distribution, geographic area, life expectancy)	Factor (characteristics of the target population) that might impact the risk of breast cancer
2a	Policy and strategies	The existence of policy content, context and process, related to breast cancer early-detection program	- Current intervention strategies - Comparative/alternative strategies - The degree to which SADANIS reaches the intended target population (the penetrance)
2b	Standard guideline	The SADANIS services pathway, including a referral system for those diagnosed with a breast abnormality	Model structure based on standard - clinical guidelines - algorithm to evaluate palpable breast masses - algorithm of the diagnostic chain
3	Governance, management, and infrastructure	Organization of program, recruitment of target population, the capacity of entities responsible for the SADANIS program, availability of screening equipment	A real-world setting that potentially affects intervention effectiveness, such as adherence to attending the screening, compliance with a diagnostic test, timely follow-up
4a	Service availability	Availability of breast cancer early-detection services	Plan for improvement of intervention
4b	Service utilization	Refers to the percentage of women who use early SADANIS services over the eligible population in a period	- Access of care - Current use of early detection modalities - Knowledge, attitude, and practice to utilize early detection services
5	Human resources	Availability and competency standards of health professionals to provide breast cancer early detection	The cost associated with multiple strategies to improve the performance of early detection

ID codes	Domain codes (Building block 1)	Description	The relevance and importance of dimensions within the domain for model development (Building block 2)
6	Financing, budgeting, costing	Budgeting and financing scheme for SADANIS: - program costs - cost categories - screening services - treatment cost - out-of-pocket costs	- Cost inventory - Cost to the resources
7	Health information system	The structures, system, and process for the collection, management and use of client-level and aggregate data for patient and program monitoring, including cancer registry and screening registry (if available)	The sources of accessible data

4.4.2 Semi-structure in-depth interview

The main objective of phase I was to assess the given policies and evidence throughout the implementation. The purpose of phase II was to extend this by inclusion of a verification process involving semi-structured interviews with participants to clarify and confirm the accuracy of the researcher's interpretation. Besides capturing the key stakeholders' or implementers' perceptions about SADANIS goals and goal attainment for the program, this phase sought to identify the factors that support or hinder goal achievement.

4.4.2.1 Participants and setting

The term 'stakeholder' has numerous definitions, many of which are linked to its context (Kuhlmann & Burau, 2018). In this phase, stakeholder refers to a person or group interested, involved, or invested in a breast cancer control program.
High quality or trustworthy qualitative research has a dimension of factors, including credibility (Creswell & Poth, 2016). To strengthen the credibility of research, Creswell and Poth (2016) suggest selecting participants based on their knowledge

and experience of a topic. Following this approach, the researcher therefore chose participants based on their expertise in the clinical area of breast cancer, and specifically their program implementation experience or history of involvement with the cancer registry. Patton and Fund (2002) highlight that purposive sampling focuses on choosing information-rich cases to learn more about the central issues being investigated in a study. In addition, interviewing participants from a wide range of sectors allows researchers to capture and explore a variety of perspectives and examine the underlying issues (Creswell & Poth, 2016).

Potential participants were found and identified from records of the authorized national institutions for breast cancer early-detection programs.
The first step was compiling lists of possible institutions with a potential roles in implementing the intervention of breast cancer prevention in Indonesia. The lists included a diverse set of representatives and experts from different groups, such as breast cancer program staff at the Jakarta Provincial Health Office and District Health Offices, health service administrators, professional organizations, researchers in health economics, and non-government organizations. The diversity of shortlisted organizations was likely to have captured a broad range of perspectives on community-based implementation of the SADANIS breast cancer early-detection program. **Table 4. 3.** provides the list of relevant key stakeholders, their role and area of expertise within the breast cancer early-detection program.

Table 4. 3. Stakeholder mapping for the SADANIS breast cancer early-detection program

Stakeholder	Rational for engagement	Role	Competency
Ministry of Health — cancer control program at: - central level - provincial level - district level	Government at all levels has responsibility for disease prevention and health protection at societal and community levels	- Ensure that the policy framework in which primary, secondary and tertiary health services operate includes the breast cancer continuum of care - Create an environment that proactively promotes early detection of breast cancer - Create opportunities for capacity-building for health workers	- Develop health-related public health policy - Responsible for public health and safety - Responsible to the constituency for health and wellbeing - Provides capacity-building and training on relevant topics
Ministry of Health — the National Institute of Health Research and Development (NHRD)	Research is central to progress in global health and identifies how NHRD can work with partners to harness science and broader knowledge to produce research evidence and tools for improving health outcomes	- Measure the magnitude and distribution of the health problem - Understand the diverse causes or determinants of breast cancer, either biological, behavioural, social or environmental factors	- Develop a solution or intervention that will help prevent or mitigate the problem - Implement or deliver solutions through policies and programs
Professional organization (oncologist, radiologist)	Support the development of evidence-based practice and the articulation of standards for the profession, and knowledge transfer for medical-related procedures	- Provide technical expertise in developing policies, acts, standards, project implementation procedures and negotiations - Upgrade and maintain the professional and technical competence of members of the professional association	- Develop the guideline and procedure - Develop and issue a code of conduct for organization members
Non-government organizations (NGOs) (such as the Indonesian Breast Cancer Foundation)	Advocacy NGOs promote breast cancer awareness, encourage acceptance, and increase knowledge of breast cancer early detection through activist events.	- Provide services and health advocacy (such as the combination of individual and social actions designed to gain political commitment, policy support, social acceptance, and system support.	- Devise and carry out programs in a faster fashion than the government organization because NGOs are smaller units with a more flexible administrative system and less cumbersome bureaucracies

After reviewing all institutions on the list, the second step was to meet with them to identify one suitable key informant to represent each institution. The researcher contacted the identified individuals using an introductory personal message sent via email or WhatsApp, aiming to introduce herself and outline her research, and invite them for an interview. Attached in the private message were relevant documents for the study, including the official permits from the institutions, the research proposal, and an informant consent form. Once securing agreement and consent for the interview, the researcher arranged a suitable date and time was arranged via email or WhatsApp.

4.4.2.2 Interview schedules

The purpose of the interview was to triangulate the findings from document analysis and gain a comprehensive, empirical knowledge. This understanding emphasized how the interview subjects understood the way the SADANIS program was operationalized in their institution and how they viewed any implementation gaps at the institution as they related to program management. The framework of assessment domains and information categories for framing an economic evaluation (**Figure 4. 1** was used as the basis to formulate an interview schedule. The interview guidelines used in this interview were adapted from the original question items listed in the *Rapid Situational Assessment* o*f Data and Data Systems*.
The question structure used was identical for all participants, with slight adjustments to maintain relevance with the role of the interviewees' institutions. In addition, the questions were elaborated upon with previous insights gained from the analyzed documents to develop a good grasp of the substance of the research (Kallio, Pietilä, Johnson, & Kangasniemi, 2016). A full copy of the interview guidelines are provided in **Appendix B.**

All interviews took place at the participant's workplace, a space which they perceived as the most natural setting to feel most comfortable and which facilitates the development of rapport (Byrne, 2001; Green & Thorogood, 2013). The interviews lasted for about 45 minutes on average. All respondents requested that the discussion be documented manually using handwritten notes instead of verbatim recording. DeWalt (2011) suggested that handwritten records should also be transcribed into electronic files. Therefore, the researcher compiled handwritten notes during all interviews and then transcribed them into a text file saved in a Word document format. A total of 13 interviews were undertaken with stakeholders from various backgrounds. **Table 4. 4** shows the basic characteristics of these stakeholders.

Table 4. 4. Interview participants characteristics

ID	Gender	Age	Nature of work	Length of work (year)	Location of work
I1	Female	58	Radiologist / Mobile mammography team	14	National Cancer Centre (Dharmais Hospital)
I2	Female	46	Pathologist / head of the national cancer registry unit	9	National Cancer Centre (Dharmais Hospital)
I3	Female	43	Epidemiologist / head of the research and development unit	6	National Cancer Centre (Dharmais Hospital)
I4	Female	31	Data custodian of the national cancer registry	5	National Cancer Centre (Dharmais Hospital)
I5	Male	56	Oncologist / former head of early detection unit	12	National Cancer Centre (Dharmais Hospital)
I6	Male	42	Head of primary health service unit	7	Health Social Security Agency

ID	Gender	Age	Nature of work	Length of work (year)	Location of work
I7	Female	29	Data custodian	5	Health Social Security Agency
I8	Female	44	Head of sub-unit cancer control program	6	Ministry of Health at central-level non-communicable disease sub-directorate — subunit cancer control program
I9	Female	34	Data custodian	4	Ministry of Health at central-level non-communicable disease sub-directorate — subunit cancer control program
I10	Male	45	Medical doctor / program manager of clinical breast examination	3	Jakarta Provincial Health Office, the non-communicable disease unit — subunit of the cancer control program
I11	Female	32	Medical doctor / data custodian of SADANIS program	6	Jakarta Provincial Health Office, the non-communicable disease unit — subunit of the cancer control program
I12	Female	43	Public health specialist / centre for health resources and health service	8	Ministry of Health — the National Institute of Health Research and Development
I13	Female	40	Medical doctor / centre for health resources and health service	5	Ministry of Health — NHRD

4.4.3 Working group discussions

The objective of working group discussion was to elicit a view from stakeholders about the accuracy of the researcher's interpretation of the findings. As described earlier in section 4.4, in this phase theresearcher was involved formally in the Dharmais National Cancer Center team to conduct two consecutive collaborative expert workshops and be part of the twelve-sessions workshop of Project ECHO for Knowledge Summaries for Comprehensive Breast Cancer Control workshops of which there were twelve sessions. In her capacity as a lecturer and academic researcher who co-researched breast cancer early detection, together with other team members, the researcher took up the role of preparing a list of discussion questions and/or topics used, while acting as the sessions' moderator and facilitator during the discussion process.

The following sections describe the setting of activities and participants who attended the two workshops and the ECHO project sessions.

4.4.3.1 Setting and participants

Participants

The participants in the first collaborative expert workshop 1 were stakeholders who played a significant role in the implementation of SADANIS program, especially in Jakarta Province. Participants who attended the workshop represented 15 institutions of healthcare system providers, academics, non-government organizations, research institutions, funding agencies and professional organizations. Regarding the recruitment process for participants, researchers did not conduct recruitment directly, but followed the procedure determined by the

Dharmais Cancer Hospital early detection team. As previously explained, in carrying out the qualitative study process for this research, researchers did not independently arrange the process but nested it with the early detection team at Dharmhais Hospital.

Collaborative expert workshop I

The first multi-stakeholder workshop on Mammography Registry Data for Reducing Breast Cancer Incidence in Indonesia was held in Bandung, 2 November 2018. The general aim was to build systematic collaborative strategies and a communicative form of planning with government and private stakeholders. The expected output of the activities was ensuring the successful coordination of services for early diagnosis and mammography screening pathways, management of clinical and image-detected cases, operating a referral system, and structuring the program's screening registry system. This workshop brought together experts in health sectors (such as program implementers, clinicians, data custodians, radiologists, breast cancer activists and public health specialists) to strengthen community-based breast cancer early-detection programs. The working group were then asked to translate the formulated strategies into pilot sites in Jakarta province.

The discussion sessions held during the workshop provided an opportunity for the researcher to share preliminary findings from document review with program implementers and stimulate dialogue about the policy planning in improving the service delivery of the SADANIS program. Regarding data validation, the results of the discussions also informed aspects of sustainability and plans for scaling up the intervention program. Experiences shared by the program implementers in operationalizing breast cancer early-detection policies at the community level prompted discussion by the participants around policy implementation and policy

options for breast cancer early-detection programs in Jakarta Province.

The discussion helped ascertain if any policy option(s) were planned in particular contexts with a goal of achieving program improvement.

Collaborative expert workshop II

The second stakeholder workshop was conducted on 11 January 2019 at Dharmais Hospital Jakarta and was as follow-up meeting to the first workshop. The participants recruited for the second working group discussion were those who had attended the first one. However, only some representatives of the institutions participated in both meetings. **Table 4. 5.** outlines the list of attending participants in both working group discussions.

Table 4. 5. Participant attendance in sequential multi-stakeholder meetings

Participants	**Institution**	**Workshop series**	
Pilot project team	NCC — Dharmais Hospital	√	√
Healthcare system provider (central level)	Directorate of non-communicable disease — Ministry of Health	√	√
Healthcare system provider	Cancer control program — Ministry of Health	√	√
Healthcare system provider	Jakarta Provincial Health Office	√	√
Healthcare system provider	North Jakarta District Health Office	√	——
Healthcare system provider — referral system	NCC — Dharmais Hospital		——
Healthcare system provider — referral system	Secondary referral hospital	√	——
Research institution	Institute of health research and resources development — Ministry of Health	√	——
Academic	School of Public Health Universitas Indonesia	√	√
Academic	School of Mathematics and Science Universitas Indonesia	√	√
Non-government organization	The Indonesian Breast Cancer Foundation	√	√
Non-government institution	The Nuclear Energy Regulatory Agency	√	——
Funding agency	The national health financing agency	-	√

Participants	Institution	Workshop series	
Professional organization	Association of oncology specialists	√	√
Professional organization	Association of radiology specialists	√	√

Working group discussions through the ECHO project collaborative learning

The ECHO-KSBC project is a web-based telementoring service facilitated by the National Cancer Institute's Centre for Global Health (NCI-CGH) designed to share knowledge summaries on breast cancer. This approach has supported the development and implementation of locally relevant and resource-appropriate cancer control policies and programs in low-resource settings through mentorship and the use of the Knowledge Summaries for Comprehensive Breast Cancer Control program (Cira et al., 2020; Zujewski et al., 2018). The methods used by the ECHO-KSBC project are described in more detail in a series of publications by the National Cancer Institute for Global Health, the University of Washington, and the Fred Hutchinson Cancer Research Centre (Brew et al., 2018; Cira et al., 2020; Zujewski et al., 2018). Expert group discussions were carried out systematically through 12 thematic sessions to prepare a program planning document for higher level of decision-maker.

The output target for participating in this ECHO project was to formulate an official plan to implement the pilot project. The ECHO-KSCB Indonesia team was chaired by a radiology specialist from Dharmais Hospital (Informant I1 in **Table 4. 2**).
The members of the Indonesia team were mainly staff from Dharmais Hospital and clinicians from Gadjah Mada University who previously implemented a pilot mammography screening program in the Yogyakarta region. In addition, program managers from the Ministry of Health and Jakarta Provincial Health Office were recruited as the team's mentors.

The researcher joined the Indonesia ECHO team in 12 interactive sessions of ECHO-KSCB held from 13 January 2019 through to 11 July 2019. A copy of the statement of collaboration is provided in **Appendix D**. The researcher was involved in the group discussions and contributed to providing information to facilitate completion of the worksheets based on the information obtained from document analysis and semi-structured in-depth interviews to be further verified by the chairperson and other members. The completed working worksheets are provided in **Appendix E**.

4.4.3.2 Discussion guide

In the first and second collaborative expert workshops a discussion guide was designed by the Indonesia ECHO team from the Rapid Situational Assessment of Data and Data system (WHO, 2018). The aim of the guide was to stimulate an informal discussion with participants, allowing them to share their experiences and understand their perceptions, concerns, questions and information needs in relation to implementing the SADANIS program. In addition, inquiries about recommendations and alternative strategies for strengthening community-based screening strategies were made of each participant based on their institution's role.

The discussion guidelines for the twelve ECHO working group were developed by the ECHO project facilitators (such as the National Cancer Institute, Washington). The aim of the discussion guidelines was to direct working group discussion and capture in a worksheet. Each session had a specific topic **Table 4. 6**. The ECHO discussion guidelines included questions focussed on the pre-planning and planning phases, strategic and technical knowledge, and to elicit a deeper understanding of the related policy approaches for breast cancer prevention (**Figure 4. 4.**) (Cira et al.,

2020; Zujewski et al., 2018). The researcher used the information from the workshops to enrich and validate the findings previously obtained from document analysis and interviews.

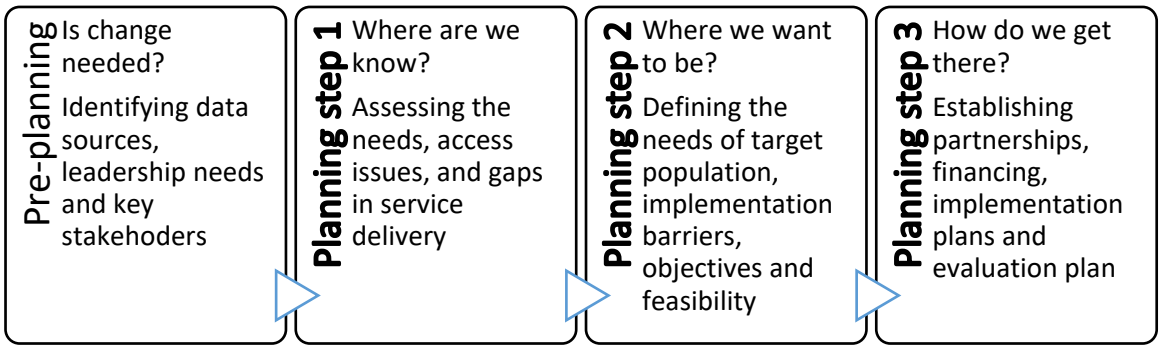

Figure 4. 4 The discussion guideline of the ECHO-KSBC framework

Table 4. 5. presents the topic sessions of ECHO-KSBC and a list of questions that were to be completed in the working sheet for each ECHO session. **Table 4. 6** details the ECHO-KSBC topic sessions and lists of questions.

Table 4. 6. ECHO-KSBC topic session and list of questions

Session and topic	**Session objective**	**Questions *(completed by the team using the given worksheet)***
Session 1 Introductory	To allow participants an opportunity to present their projects and pose planning questions	
Session 2 Preplanning	1. To recognize when a change is needed (policy/program is outdated or not evidence-based 2. To recognize how to identify data needs/sources 3. To identify key leadership personnel and stakeholders	1. Is your proposed program/project needed, and based on what criteria? 2. What data sources have you identified in support of your project? 3. What assessments have been conducted previously on this issue? 4. Name three key stakeholders/leaders to support your project

Session and topic	Session objective	Questions *(completed by the team using the given worksheet)*
Session 3 **Planning step 1: Assessing needs and the current service**	1. To know how to assess local disease burden 2. To map current services, stakeholders and partnerships	1. What is the current level of need or burden of disease in your community? 2. What current services exist, and by whom are they led? 3. How have previous assessments been conducted (who was involved), and what can be learned from this?
Session 4 **Planning step 1: Assessing access and barriers**	1. To know how to assess barriers to access (structural, sociocultural, personal and financial) 2. To know how to identify bottlenecks and gaps in service delivery	1. What barriers to accessing breast health services exist in your community? 2. What services exist to facilitate access to breast health services in your community? 3. How have previously identified barriers to access (via assessment if available) been addressed? What can be learned from that experience?
Session 5 **Planning step 1: Assessing health system capacity**	1. To know how to assess health system capacity to accurately/efficiently to detect/diagnose/treat/manage breast cancer (including human resource capacity, knowledge) 2. To know how to assess the availability/ affordability/ acceptability of services.	1. To what extent is the health system capable of providing accurate/effective breast cancer services? 2. To what extent are these services accessible/ affordable/acceptable? 3. What bottlenecks and gaps in service delivery exist in your community?
Session 6 **Planning step 2: Defining the target population and partnerships**	1. To know how to define the appropriate target population 2. To know how to engage stakeholders and key decision-makers, and build community and health system partnerships	1. What is the target population for your project? 2. How will you engage key stakeholders and decision-makers? 3. How will you build community and health system partnerships to support your project
Session 7 **Planning step 2: Defining the target population and partnerships**	1. To know how to identify barriers to program implementation	1. What are service delivery gaps and barriers to the implementation of your proposed program? 2. How will you communicate the need for action?
Session 8 **Planning step 2: Defining the target population and partnerships**	1. To know how to set achievable objectives 2. To know how to assess the feasibility of proposed interventions 3. To know how to establish process metrics for evaluation	1. To what extent are your project objectives achievable? 2. To what extent are your proposed interventions feasible? 3. What process metrics have you included in your project?

Session and topic	Session objective	Questions *(completed by the team using the given worksheet)*
<u>Session 9</u> **Planning step 3: Establishing partnerships, financing**	1. To know how to engage decision-makers and staff 2. To know how to establish financial support and partnerships 3. To know how to match investments to resource-appropriate interventions	1. How will you engage decision-makers and staff? 2. How will you establish financial support and partnerships? 3. Do your proposed investments match with resource-appropriate interventions?
<u>Session 10</u> **Planning step 3: Disseminating and implementing**	To understand best practices for coordination, implementation, and dissemination of the project and project outcomes	1. How do you plan to coordinate, implement and disseminate the outcomes of your project? 2. What are your messaging and communication strategies?
<u>Session 11</u> **Planning step 3: Monitoring and Evaluating**	1. To understand how to implement quality assurance measures in project design 2. To understand key concepts in monitoring and evaluation	1. What indicators will you use to assess quality and impact? 2. What process did you use to identify these indicators? 3. How do you plan to implement and collect data on the quality assurance measures for your project? 4. What are your monitoring and evaluation plans?
<u>Session 12</u> **Closing session: Report on the overall assignment**		Prepare a finalized project plan and/or policy brief that addresses: 1. the need 2. current service barriers 3. current capacity 4. The target population 5. partners 6. potential barriers to implementation 7. feasible objectives 8. the model for financing and partnership 9. plans for dissemination, implementation and evaluation

4.5 Triangulation of findings and data analysis for semi-structured in-depth interviews and Working Group Discussion

Triangulation of three consecutive methodologies applied in this study required a convergence triangulation to ensure data validation. It was achieved using the logic model to align and validate the research output **(Figure 4. 5.)**.

The interview and discussion transcripts were incorporated and coded into pre-defined distinct domain areas using NVivo software (Miles et al., 2014; Pope, Ziebland, & Mays, 2000; Sutton & Austin, 2015). In addition, to better understand interrelation between components in terms of program implementation, the researcher used the logic model framework to scrutinize the program's input, activities and outcomes. This framework provides a useful template to pictorially represent the information in systematic and comprehensive formats (Cooksy, Gill, & Kelly, 2001). Besides profiling the main elements, processes and goals, this framework provides a practical structure for depicting the actual program component (Dwyer & Makin, 1997; McCawley, 2001).

The researcher and stakeholders co-established the SADANIS logic model.
A backcasting approach adapted from Wilson, Tansey, and LeRoy (2006) was used to present the identified outcomes before working backward to identify the activities and inputs that were used to achieve these outcomes**.** This model enabled the researcher and stakeholders to glance at the main features of the SADANIS program and how they were operationalized in Indonesia, particularly at the provincial level**.**
Figure 4. 5. presents the steps taken in structuring the logic model of SADANIS using backcasting. The SADANIS logic model provided a useful template to

assemble findings derived from document analysis, interviews and discussions in this study. An elaborated logic model was deemed to facilitate the analysis of the considered contextual factors that may influence the effectiveness of the SADANIS program. **Figure 4. 6** depicts the elaborated SADANIS logic model template.

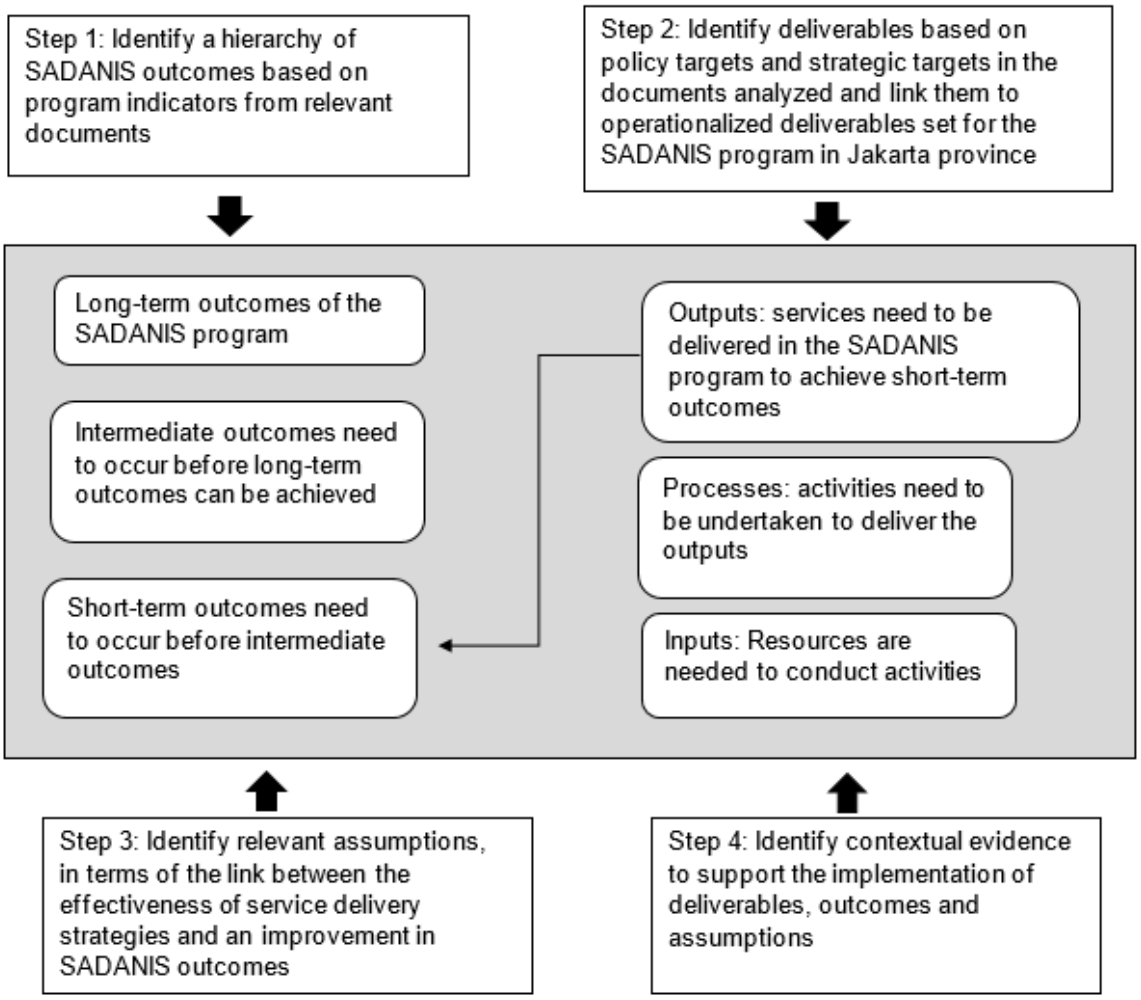

Figure 4. 5 Steps in constructing the SADANIS logic model using the backcasting approach

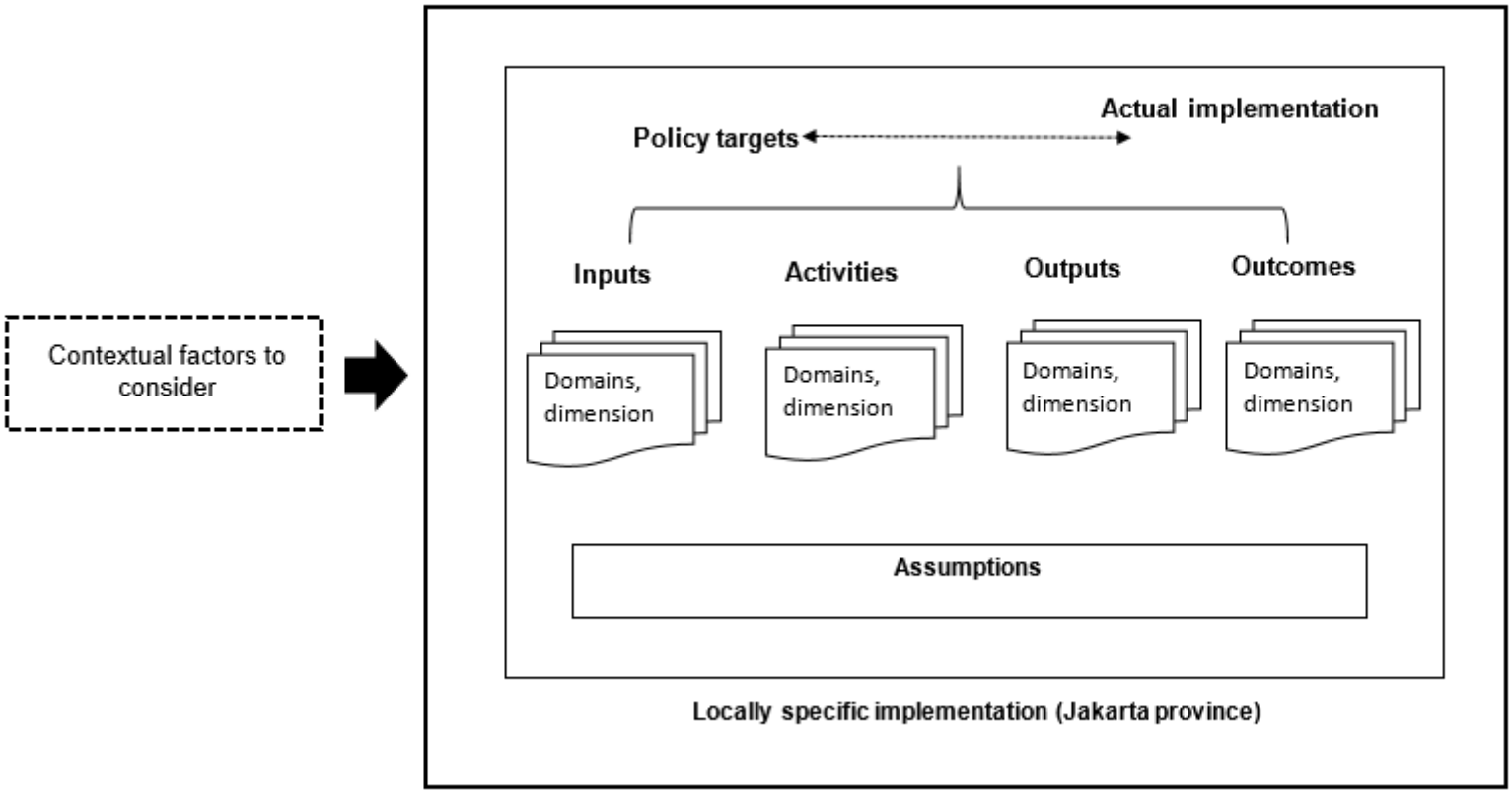

Figure 4. 6 The SADANIS logic model assembles findings

The inputs are the identified resources for the SADANIS program. *The policy target* is related to the inputs incorporated in the SADANIS program, including government regulation, healthcare system capacity, service-availability standard guidelines, infrastructure, service availability, financing and cancer registry system. *An actual implementation* is the knowledge of empirical evidence on policy target performance concerning the inputs of the early-detection program of breast cancer encountered by participants.

Activities are the processes or events undertaken by the SADANIS program or its partners to produce the desired outcome. *Policy target* is the formally stated attempted strategies to achieve an effective SADANIS program.
Actual implementation (related to activities) is the knowledge about empirical evidence gained from the experience of implementing the perspectives of stakeholders and organizations.

Outputs are the direct results of strategies applied — measured by defined indicators related to the availability of standard guidelines, referral hospital networks and human resources.

Outcomes are the desired short-term, intermediate and long-term results of the SADANIS program to decrease late-stage breast cancer presentation and breast cancer incidence, and breast cancer mortality.

Assumptions are the theories used to develop strategies for improving breast cancer detection and diagnosis (Herdman & Norton, 2005). There are three assumptions: 1) Early detection is a process, not a test; 2) The capacity of organizing care to improve early-detection outcomes matters, so there is a need to organize transitions

between continuums of care; and 3) Focusing only on improving the composition of the continuum care, rather than on how women are transitioning from one step to another, will not result in improved breast cancer screening.

Contextual factors to consider are the relevant characteristics and circumstances that are relevant in early-detection programs geared toward reducing the incidence of breast cancer in Indonesia, and are categorized based on domains in the relevant analytical frameworks.

4.6 Summary

This chapter has provided an overview of the explanatory sequential mixed method used to generate a country-specific contextualization for cost-effectiveness model development in this study. It has detailed a research design and three consecutive methods used which engaged key stakeholders to make sure contextual knowledge synthesis was a priority concern for health system decision-makers. The next chapter will outline a report of the research's synthesized evidence.

Chapter 5: Result: Contextualizing breast cancer early detection decision-making and accessible data source for the economic evaluation in Indonesia

5.1. Overview

This chapter presents the results of the contextualization of breast cancer early-detection program in Indonesia within the method outlined in **Chapter 4**. By analysing analysis of the qualitative research found in the seven domains (**Figure 4. 2**), the researcher explored the unique context of breast cancer early-detection programs operating in Indonesia, which potentially influenced the applicability and relevance of the model developed in this study. The main findings of the study are presented using a logic model framework to help readers develop a clear understanding of the richness of evidence available in this study. The findings can also help the readers to understand the policy processes relevant for making improvements to implementation of early-detection programs. The following manuscript was submitted to BMC Health Services Research on 16 July 2022, and it is currently under quality check.

Popy Yuniar, Kardinah, Dian Sinulingga, Anggi Kartikawati, Lady M.F. Sirait, Budi Utomo, Suzanne Robinson, Rachael Moorin, Richard Normal, Marshall Makate. **Contextualizing policy implementation, challenges and plans for improvement of breast cancer early-detection programs in Indonesia.** The abstract of the manuscript is included as **Appendix G**: Abstract of manuscript.

5.2. Data reporting

Figure 5. 1 depicts the logic model used to convey the elements of Indonesia's early-detection breast cancer programs.

The findings of this chapter consist of two main parts. Firstly, they describe the lists of documents that were available and the relevant datasets that were associated with legal aspects, along with guidelines, implementation reports, and relevant datasets available on breast cancer early-detection programs (which are referred collectively as the SADANIS program for the rest of this chapter). Secondly, the contextual themes are presented within the frame of a SADANIS logic model (showing aspects such as inputs, program activities and outputs, and outcomes). In addition to the context, two themes are described separately in the chapter: the source of accessible data to inform the economic evaluation model, and the policy process adopted in a stakeholder's implementation or response to the SADANIS program, used to strengthen the program.

The researcher used different descriptions for data excerpts obtained from interview transcripts, documents analysis, and working group discussions. Text excerpts from interview transcripts were coded with *"interview/stakeholder meeting, participant (I) ##".* The participant's number referred to the list of participants presented in **Table 4. 4**. Any extracts of document analysis were coded with *"ID doc number (##)".* The numbers referred to the list of analyzed documents are shown in **Table 5. 1 ,** while the excerpts from working group discussions were coded with *"Group Discussion, worksheet number (##),"* to refer to a relevant discussion topic in the completed working sheets in Table 4. 5. .

An example of tables and diagrams that helped the researcher organize and visualize extracted data are presented in **Appendix F** to give the reader an understanding of data analysis process that was applied in this thesis.

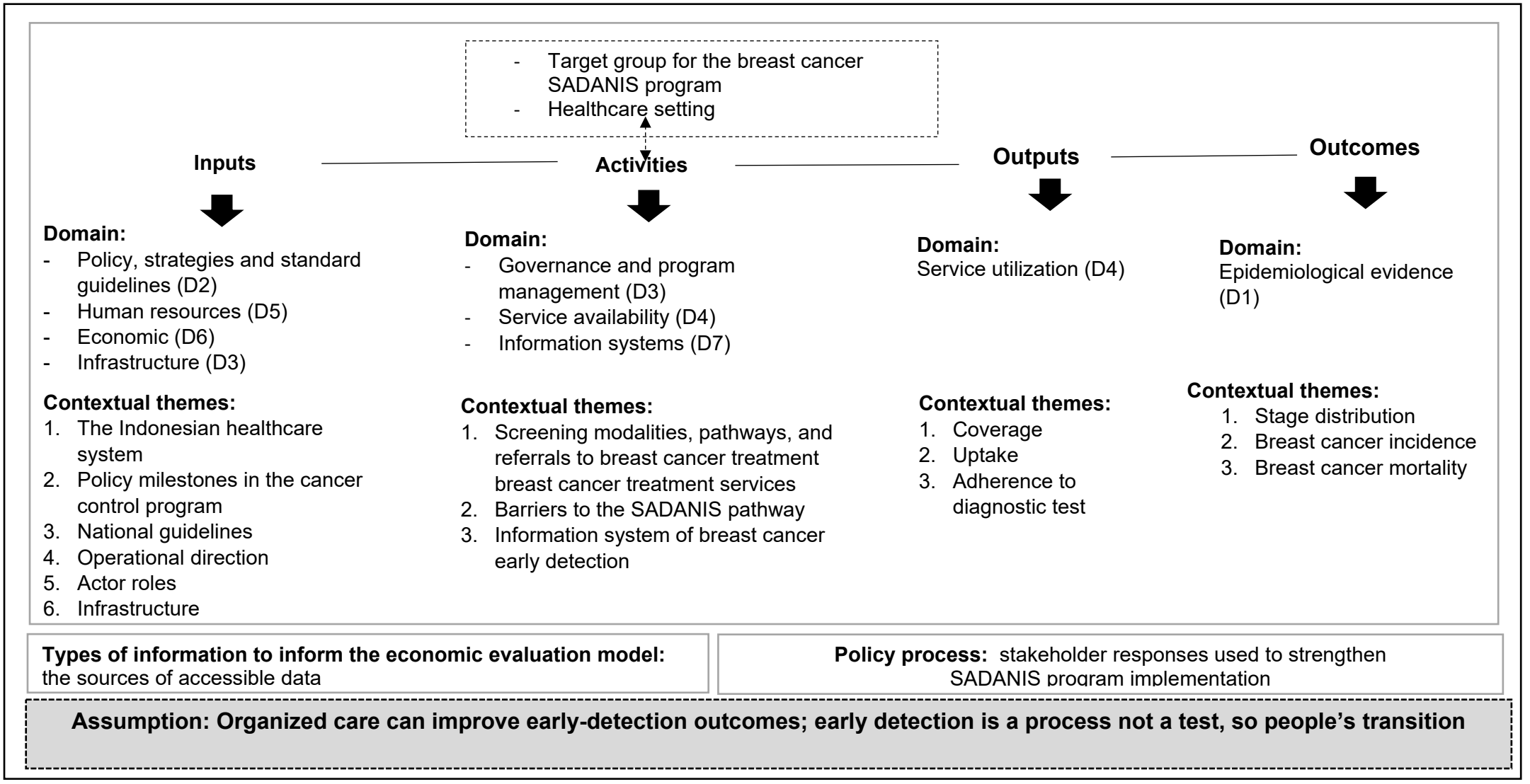

Figure 5. 1 An expanded SADANIS program logic model and its various contexts

5.3. Document analysis

Forty-three documents were analyzed and put into five categories: legal documents, official documents, scholarly works, implementation documents, and working documents. Additionally, six relevant datasets were obtained from the hospital-based cancer registry (HBCR), the Jakarta Provincial Health Office reporting system, and the website of the Institute for Health Metrics and Evaluation Institute, IHME **(Table 5. 1).** The majority of the documents were scholarly works, including studies conducted at the national, provincial, or district levels. Six legal documents consisted of five regulations and decrees issued by the Ministry of Health and one document published by the Provincial Government of DKI Jakarta. Four official documents were technical guidelines, policy directives, and official declarations released by the Ministry of Health and the National Committee of Cancer Control Program (NCCP).

There were eight working documents produced in two formats. First, six presentation slides were collected from a stakeholders' workshop presented by the Ministry of Health, Dharmais Cancer Hospital, Jakarta Provincial Health Officer, and the Indonesian Breast Cancer Foundation, entitled 1) The Indonesian Cancer Control Program 2010–2014, 2) Breast malignancy — hospital-based data, 3) Results of mammography screening in West Jakarta, 4) mammography registry data, 5) historical evidence from mobile mammography, and 6) implementation of the population-based cancer control program in Jakarta Province. Second, two working documents consulted were the terms of reference for the pilot project of mammography screening in Jakarta. An implementation document reports breast-

tumour prevalence, obtained from the Non-communicable Disease Directorate, in the Cancer Control Program Sub-directorate, Ministry of Health.

The researcher collected five patient-level datasets. An authorized data custodian at Dharmais Cancer Centre (DCC) facilitated the data collection on breast cancer stage at diagnosis and treatment cost. The women's screening history and diagnosis status of breast cancer were derived from the database of the early-detection unit linked with the HBCR database. One SADANIS dataset at patient level was obtained from the data custodian at the Jakarta Provincial Health Office. Finally, one dataset of the epidemiological features of breast cancer in Indonesia (such as incidence, prevalence, all-cause mortality, and breast cancer death) was downloaded from the Institute for Health Metrics and Evaluation, IHME.

Table 5. 1 The documents analysed listed by document types

Doc ID	Type and category of document	Name of document	Year	Source
Legal documents (LD)				
1	Decree	Ministry of Health decree No 796 on technical guidelines for the breast and cervical cancer control program	2010	https://peraturan.go.id
2	Regulations	Ministry of Health regulation No. 34 on the breast cancer and cervical cancer control program	2015	
3	Regulations	Ministry of Health regulation No. 29 on the breast cancer and cervical cancer control program	2017	
4	Regulations	Ministry of Health regulation No. 14 on the National Committee of Cancer Control Program	2017	
5	Regulations	Governor DKI Jakarta instruction No. 116 on supporting policy for breast cancer early detection in DKI Jakarta Province	2018	
6	Regulations	The national guideline on breast cancer standard medical procedure	2018	
Official documents (OD)				
7	World Health Organization – fact sheet cancer country profile 2014	Indonesian burden of cancer	2014	https://www.who.int/cancer/country-profiles/idn_en.pdf

Doc ID	Type and category of document	Name of document	Year	Source
8	Policy directives	A community intervention model on prevention and control of non-communicable diseases in Indonesia	2017	The Ministry of Health, Non-Communicable Prevention and Control Directorate
9	Health System Review	The Republic of Indonesia Health System Review	2017	(Mahendradhata et al., 2017)
10	Recommendation screening policy	Breast cancer screening age range and interval: Pilot Indonesia	2019	The LRCB-Dutch expert centre for screening proposal to Dharmais Hospital
11	World Health Organization - Fact sheet cancer country profile 2020	Indonesia burden of cancer	2020	https://www.who.int/cancer/country-profiles/IDN_2020.pdf?ua=1
Scholarly works (SW)				
12	Epidemiology profile	Cancer in Indonesia, Present and Future	2002	(Tjindarbumi & Mangunkusumo, 2002)
13	Breast self-examination	Breast self-examination in Indonesia according to the national socio-economic survey 1998 and national household health survey 2004	2006	(Suhardi, Pradono, Hapsari, & Isfandari, 2006)
14	A comparative study	Comparison of breast cancer in Indonesia and Malaysia — a clinic pathological study between Dharmais Cancer Center Jakarta and University Malaya Medical Center, Kuala Lumpur	2011	(Ng et al., 2011)
15	Determinant of early detection	Factors associated with follow-up for early detection of breast cancer in screened positive women at the early detection unit, Dharmais Hospital	2012	(Kartikawati, 2018)
16	Population-based cancer registry	Population-based cancer registration in Indonesia	2012	(Wahidin et al., 2012)
17	Pilot implementation	Evaluation of a 5-year Cervical and Breast Cancer Prevention (CECAP) project	2013	(Kim et al., 2013)

Doc ID	Type and category of document	Name of document	Year	Source
18	Economic burden	The total economic burden of breast cancer in Makassar South Sulawesi, Indonesia	2013	(Palu, Maidin, Sudirman, & Nurdin, 2013)
19	Pilot implementation	Short report: Limited effectiveness of screening mammography in addition to clinical breast examination by a trained nurse	2014	(Kardinah, Anderson, Duggan, Ali, & Thomas, 2014)
20	Cancer registry	CanReg5 networks for Indonesia	2015	(Pardamean, Suparyanto, & Fadilah, 2015)
21	International cancer control event	Supporting evidence-based national cancer control planning: The Asia-Pacific Phase II Leadership Forum	2017	(Singh, Pearlman, & Kostelecky, 2017)
22	Policy review	The dynamic of non-communicable disease control policy in Indonesia	2017	(Christiani, Dugdale, Tavener, & Byles, 2017)
23	Systematic review and meta-analysis of non-communicable disease	How is Indonesia coping with its epidemic of chronic non-communicable disease? A systematic review with meta-analysis	2017	(Schroders et al., 2017)
24	Breast cancer awareness	Breast cancer awareness among Indonesian women at moderate-to-high risk	2017	(Mardela, Maneewat, & Sangchan, 2017)
25	Development of EQ-5D value set	The Indonesian EQ-5D-5L value set	2017	(Purba et al., 2017)
26	Breast cancer awareness and participation	Determinants of cancer-screening awareness and participation among Indonesian women	2018	(Anwar et al., 2018)
27	Quality of life	Quality of life and health status of Indonesian women with breast cancer symptoms before the definitive diagnosis: A comparison with Indonesian women in general	2018	(Setyowibowo et al., 2018)
28	Health system equity	An evaluation of health system equity in Indonesia: study protocol	2018	(Wiseman et al., 2018)
29	Hospital-based cancer registry data source	Increase coverage of the cancer registry by strengthening and improving the reporting of the breast cancer screening program in Jakarta		(Sinulingga et al., 2018)
30	Breast cancer awareness	Awareness level about breast cancer risk factors, barriers, attitudes, and breast cancer screening among Indonesian women	2019	(Solikhah, Promthet, & Hurst, 2019)

Doc ID	Type and category of document	Name of document	Year	Source
31	Hospital-based cancer registry	The challenge of the implementation and evaluation of a hospital-based cancer registry in Indonesia's national referral hospital	2020	(Gondhowiardjo Ekaputra, E. ,. Randi, A. ,. &. Jayalie, V. F., 2020)
32	Hospital-based breast cancer management	Multicenter Management of Breast Cancer in Indonesia: Ten Years of Experience	2020	(Gondhowiardjo Ekaputra, E. ,. Randi, A. ,. &. Jayalie, V. F., 2020)
33	Determinant of early breast cancer presentation	Determinants of early breast cancer presentation: a qualitative exploration among female survivors in Indonesia	2020	(Dewi, Massar, Ardi, & Ruiter, 2020)
34	Hospital-based cancer registry	Five-year cancer epidemiology at the national referral hospital: hospital-based cancer registry data in Indonesia	2020	(Soehartati Gondhowiardjo et al., 2021)
Implementation documents (ID)				
35	Implementation documents	Survey report: Non-Communicable Disease Research: Breast Tumour (SADANIS-positive) Prevalence and Precancerous Cervical Lesion	2016	(National Institute of Health Research and Development Ministry of Health Republic of Indonesia, 2016)
Working documents (WD) — PowerPoint presentations				
36	The working plan of the cancer control program	Indonesian Cancer Control Programs 2010–2014	2010	The Ministry of Health, Non-Communicable Prevention and Control Directorate
37	Hospital-based data on breast malignancy	Breast malignancy	2019	Cancer registry unit — National Cancer Center
38	Overview on mammography registry data	Mammography registry data to support intervention of late-stage breast cancer in Indonesia	2019	Dharmais Hospital
39	Preliminary report	Preliminary results of mobile mammography screening in West Jakarta district	2019	Dharmais hospital in collaboration with the Indonesia Breast Cancer Foundation and Jakarta Provincial Health Office)
40	Overview of the breast cancer control program in Jakarta Province	Population-based cancer control program: Jakarta experience and challenges	2019	Jakarta Provincial Health Office
41	The role and experience of advocates in implementing early detection	The role of the Indonesian Breast Cancer Foundation in implementing screening and early detection	2019	The Indonesian Breast Cancer Foundation

Doc ID	Type and category of document	Name of document	Year	Source
42	Proposal for pilot project	Policy proposal on breast cancer early detection	2019	Dharmais Hospital
43	Proposal for pilot project	Model design on screening registry system	2019	Dharmais Hospital
Dataset (DS)				
1	Breast cancer stage at diagnosis	Patient-level data: breast cancer stage at diagnosis based on patient admission from early detection unit — Dharmais Hospital	2010–2012	Cancer registry Dharmais Cancer Centre
2	Cost of breast cancer treatment	Patient-level data: treatment cost of breast cancer patients based on clinical staging	2012–2013	Hospital information system — Dharmais Hospital
3	Mobile mammography	Indonesia Demographic and Health Survey	2017	Dharmais Cancer Center
4	Routine reporting data on the CBE program	Patient-level data: program reporting of CBE in five districts of Jakarta Province	2017	DKI Jakarta Provincial Health Office — sub-directorate of cancer prevention
5	Epidemiology data on breast cancer	Global Burden of Disease study (GDB 2019): Breast cancer prevalence, breast cancer death	2019	Institute for Health Metrics and Evaluation http://ghdx.healthdata.org/gbd-results-tool

After collecting the documents, the researcher extracted and analyzed text references relevant to the information covering the seven domains.

Table 5. 2 shows the identified text references within the analysis documents.

Table 5. 2 The coding matrices reference a number of document and text references

No	Domain	Number of documents	Text references
1	Demography and epidemiology	22	76
2	Policies plans, strategies and clinical guidelines	26	140
3	Governance, management and infrastructure	17	65
4	Service availability and utilization	14	54
5	Human resources	2	5
6	Financing, budgeting and costing	5	20
7	Health information systems	11	49

Most of the 43 documents were sources that related to policy plans, strategies and clinical guidelines on breast cancer early detection. Meanwhile, data related to the demography and epidemiology of breast cancer in Indonesia were identified in 76 reference texts, most of which were found in the scholarly document and cancer country profile published by the World Health Organization. Forty-nine text references found in the health information system domain were mostly related to the nation's cancer registry, the screening database, variable data and recommendations for implementing data integration strategy. Information that related to human resources was limited — with only five references obtained from one legal document and one from scholarly work.

Furthermore, through deductive coding of the text references in **Table 5. 2** , the contextual themes were generated and categorized within the logic model

components. **Table 5. 3.** presents the contextual themes grouped by input, activities, and the outputs and outcomes of the SADANIS program.

Table 5. 3. Contextual themes by SADANIS logic model components

Logic model component	Context	Domain
INPUTS	- The Indonesian healthcare system	2
	- Policy milestone in cancer control	3
	- National guidelines on the community-based program of breast cancer early detection	2
	- Operational direction to SADANIS program	2
	- Actors	5
	- Infrastructure	3
	- Cost components	6
ACTIVITIES	- Screening modalities, detection pathways, and breast cancer treatment services	4
	- Barriers to SADANIS pathways	4
	- Information system of breast cancer early detection	7
OUTPUTS	- Coverage	4
	- Uptake	4
	- Compliance with diagnostic test regime	4
OUTCOMES	- Stage distribution	1
	- Breast cancer incidence	1
	- Breast cancer mortality	1

*Domains: **1** = demography and epidemiology; **2** = Policies plans, strategies and clinical guidelines; **3** = Governance, management and infrastructure; **4** = Service availability and utilization; **5**= Human resources; **6** = Financing, budgeting, and costing; **7** = Health information systems.*

The following sections describe in detail the substance of each contextual element in the implementation of the SADANIS program as a community-based breast cancer early detection program in Indonesia.

5.4. Inputs

5.4.1. The Indonesian healthcare system

The findings highlighted several keywords related to the decentralized system of health services in Indonesia in the context of the pattern of administrative power executed in managing early-detection programs as part of community-based preventive interventions. The country's decentralization reform in 1999 resulted in an increased in political power, financial resources, planning and the management of service delivery at the district and municipal level, and therefore bypassing the nation's central government and provincial bureaucracy (Holzhacker, Wittek, & Woltjer, 2016). The power transferred included responsibilities for determining and managing health services throughout a decentralized government system. However, according to the health of cancer control program, the Ministry of Health still holds overall responsibility for organizing and developing public health services in Indonesia, particularly for disease surveillance and preventive activities:

"Early detection is one of four prevention programs which are mandatory as basic health services [The Minister of Health Regulation No 43/2016] in central, provincial and district/municipal health sector."

(I8, interview)

The Indonesian health system is supported jointly by public and private providers (Mahendradhata et al., 2017). While the country's public system is run in parallel to administration with the nation's decentralized government, responsibility for service delivery is shared between provincial and district health authorities, and provided at the local level through specialized programs and individual health facilities, including the primary health centres and their networks.

As stated by the head of the cancer program at the Ministry of Health and Provincial Health Office (PHO):

"According to government regulation (number 8/2003 on the organization of regional structure), the MoH is responsible for organizing and developing public health in Indonesia, [particularly] for disease surveillance and preventive activities. Delivery of services is shared with local governments [provincial/district/municipal] through specialized programs and health facilities including PHC."

(I8, interview)

The coordinator of the SADANIS program also emphasized the responsibility of local government and central government for the delivery of essential health services:

"Local government is responsible for the delivery of basic health services, including early detection as part of preventive services, while the central government defines the expected standards for the provision of services…the transfer of authority from the central government to the governor as the representative of the central government."

(I10, interview)

Interestingly, despite the seemingly coordinated platform of basic health services provided across the central, province and district levels, the data custodian from PHO perceived that the communication systems were weak at the national level due to multiple disconnected reporting systems.

"Different formats of the recording system affect the communication between the national health information system that links to provincial and district-level and district health information systems."

(***I9 interview)***

5.4.2. Policy milestone in the cancer control program

The following section presents information relating to how national breast cancer control plans were developed in response to the burden of breast cancer. The researcher found evidence in the analyzed documents that the political commitment of the designated responsible government for the cancer control program had been

carried out since 1970 (Kim et al., 2013; Pardamean et al., 2015; Tjindarbumi & Mangunkusumo, 2002). Through the Ministry of Health, the government has also established a partnership with all relevant stakeholders to achieve sustainability to accelerate action in the cancer control program (Singh et al., 2017). **Table 5. 4.** outlines Indonesia's national approach to the early detection of breast cancer.

Table 5. 4. Policy milestone in the cancer control program in Indonesia

Year	Development
1970	The first cancer registry in Central Java was established
1987	Pathology-based cancer registration for 13 areas, involving 64 branches of the Indonesian Clinical Pathology Laboratory located in several different provinces, was implemented
2007	Expansion from a hospital-based cancer registry to a population-based cancer registry in a pilot study in Jakarta province
2007	Cancer control regulation through the Ministry of Health decree No.430 was enacted
2007	The Cervical and Breast Cancer Prevention, CECAP pilot project was launched, in partnership with JHPIEGO and the Ford Foundation
2008	Ministry of Health decree on National Cancer Registry No. 1068/ Menkes/SK/XI/2008 was enacted
2008	Ministry decree on team development and determination of pilot locations for Indonesian cancer registration was enacted
2009	Ministry decree on the working group for breast and cervical cancer was enacted
2010	Technical guidelines for breast and cervical cancer control were launched
2015	Ministry decree on breast cancer– and cervical cancer–control program was enacted
2017	Ministry decree on breast cancer– and cervical cancer–control program was amended
2017	Ministry decree on National Committee for Cancer Control (NCCC) formation was enacted
2018	Ministry decree on National Clinical Guideline for Breast Cancer was enacted

Focusing on primary detection methods and the limited levels of detection methods in operation, the Ministry of Health introduced the Cervical and Breast Cancer Prevention Project in 2007 in partnership with JHPIEGO and the Ford Foundation. The goal of this five-year project was to develop a national model for cervical cancer prevention and breast cancer awareness (Kim et al., 2013). The authors highlight lessons learned to improve the effectiveness, quality, and sustainability of these prevention services as the pilot project scaled up throughout Indonesia.

"Points to improve service delivery: 1) intensifying community mobilization and expanding the role of static service delivery sites to increase screening coverage; 2) Incorporating continuous quality improvement to strengthen provider's skills; 3) Collecting and utilizing data to strengthen strategic planning and program management."

(**Document analysis — ID doc: ID17)**

The government recognized the vital function of the cancer registry as the first attempt to develop the first pilot site in Semarang, Central Java in 1970 (Wahidin et al., 2012). Since then, many cancer registries, such as hospital-based and, pathological-based units were developed until 2004 (Pardamean et al., 2015). Unfortunately, the implementation was discontinued due to lack of human resources and no national body or unit was responsible for developing policy and implementation (Wahidin et al., 2012).

In 2008, the national cancer registry was established and the pilot location was in DKI Jakarta. The desired output was to contribute the registry's collected data to a team estimating cancer incidence in five continents for the International Agency for Research on Cancer. However, the data put forward were rejected because of their alleged poor quality (Soehartati Gondhowiardjo et al., 2020). In addition to IARC data, the data custodian from Dharmais hospital explained that Dharmais hospital

has currently re-submitted data for the period 2013-2017 and still waited for the review

"IARC rejected our cancer data for a period of data collection in 2008-2012 due to the low quality…currently we re-submit data for period 2013-2017"

(I4, interview)

The attention given to breast cancer early detection is increasing at the global and national levels through partnerships, technical assistance, and collaborative research (Singh et al., 2017). Nevertheless, there were insufficient political interests in the issue of non-communicable disease control in Indonesia because infectious diseases remained the predominant problem in public health (Christiani et al., 2017; Mahendradhata et al., 2017),

"*For global partnerships, we [the NCC] are an active member of the Union for International Cancer Control — UICC. We also have been assisted by the International Atomic Energy Agency IAEA) to expand access to radiotherapy in the northern and eastern part of the country."*

(I1, interview)

In 2014, Indonesia participated in the Asia-Pacific Leadership Forum and presented two national cancer priority-action plans: 1) Implement a population-based cancer registry pilot program, starting with Jakarta and Yogyakarta provinces; 2) Improve the implementation of comprehensive cancer service guidelines. The leadership forum event raised national awareness and a nation's capacity to develop and implement a national cancer control plan, and encouraged people to embark on experiences that help them to learn how other countries are managing their cancer prevention and control activities, and advancing evidence-based policymaking (Singh et al., 2017).

In 2015, a community-based program for clinical breast examination was designated as a national program in Indonesia. The program sought to reduce the diagnosis of late-stage breast cancer at first diagnosis, to increase the probability of survival.

In 2021, a collaborative research plan was created to set up an integrated pilot project for a mammography screening system in Jakarta province as the follow-up project to the output of the ECHO-KSBC project:

> *"[We] have proposed our pilot project plan to the Ministry of Health as the follow-up of [our] ECHO project. On 22 October 2021, we [Dharmais Hospital and Jakarta Provincial Health Office] have signed the memorandum of understanding with the Dutch National Expert and Training Centre for Breast Cancer Screening (LRCB) to have the government-to-government pilot project agreement."*
>
> ***(I1, interview)***

5.4.3. National guidelines on the community-based program of breast cancer early detection.

There is global recognition that developing NCCPs is critical to effectively addressing and coordinating the continuum of cancer care (Romero et al., 2018). Accordingly, the researcher contextualised the relevant evidence, setting out governance arrangements made to provide breast cancer early-detection strategy guidelines in the Indonesian healthcare setting.

The researcher obtained most of the information related to this context from one of the participants who was at that time a member of the national cancer control committee team, and the team leader of the ECHO-KSBC project.

The Ministry of Health adopted the resource-stratified strategies introduced by the Breast Health Global Initiative (BHGI) that underscore the determination of a realistic pathway of comprehensive breast cancer program management in a country with limited resources. In addition to elaborating on the BHGI strategies,**Table 5. 5.** describes the scope related to each strategy's resource level, detection methods and evaluation indicators. Based on the information provided, Indonesia's national policy on breast cancer early detection currently focuses on the basic and limited level, adjusting to the available resources.

"For the national policies framework, we referred to the global initiative from WHO [for] resolution of cancer control programs, [it was published in 2005 and updated in 2017], and the guidelines from Breast Health Global Initiative [BHGI] on early detection strategies based on four-tier of country-specific resources."

(I1, interview)

Table 5. 5. The Breast Health Global Initiative on early detection and access to care based on the level of resources

Level of resources	Detection method(s)	Evaluation goal
Basic	Breast health awareness (education, ± self-examination); clinical breast examination (clinical education)	Baseline assessment and repeated surveying
Limited	Targeted outreach/education encouraging CBE for the at-risk group; diagnostic ultrasound ± diagnostic mammography	Down-staging of symptomatic disease
Enhanced	Diagnostic mammography; opportunistic mammographic screening	Opportunistic screening of asymptomatic patients
Maximal	Population-based mammographic screening; other imaging technologies as appropriate (e.g. high-risk groups, people posing unique imaging challenges)	Population-based screening of asymptomatic patients

Source: (Yip & Anderson, 2007)

As BHGI's strategy became the cornerstone of Indonesia's breast cancer control plan, the SADANIS program was promoted in 2015 to the national breast cancer early-detection program implemented in Indonesia. SADANIS encompasses early diagnosis for symptomatic patients and comprises an awareness campaign to encourage prompt help-seeking for possible breast cancer symptoms. However, the unsystematic process adopted in SADANIS identifies and addresses barriers to diagnostic and treatment services at the population and service-provider levels. The priorities are to build service capacity and quality, and establish referral pathways for women diagnosed with abnormalities, as described by the SADANIS program coordinator:

"SADANIS is a national program of breast cancer early detection in Indonesia, where its implementation is regulated by Ministry of Health regulation No.34/2015, and amended by Regulation No.29/2017 … The aim is to downstage breast cancer rather than [introduce a comprehensive] screening program. However, we have piloted the mammography screening in Jakarta province, which is considered adequate in terms of infrastructure and commitments."

(I8, interview)

The current SADANIS strategies to downstage women's symptomatic breast abnormalities are considered an essential preparatory step before starting a screening program at the enhanced or maximal level of resources (WHO, 2007a). Meanwhile, the ability to perform mammography screening is being piloted at the sub-national level with adequate resources.

5.4.4. Operational direction of the SADANIS program

The operational direction specifies how the SADANIS program should be organised to achieve the desired outcome. In the absence of an organized screening program, the SADANIS program used both opportunistic screenings conducted to detect breast cancer in asymptomatic women and diagnostic examination of women at the primary health centre (Puskesmas) to evaluate breast complaints. Opportunistic screening is a term describing the non-systematic mechanism that involves fewer formal decisions regarding whether to screen, who to screen, and at what interval screening should be performed, as explained by the program coordinator:

"[Puskesmas has a] target population based on [its] working area, but because SADANIS is an opportunistic program we are not sending a personal invitation to the target group. Through [the] health promotion program [in Puskesmas or the hospital, members of the group] were encouraged to [regularly] perform breast self-examination and clinical breast examination by [the] health provider."

(I8, interview)

In practice, the breast cancer detection intervention begins at the community level, facilitated by community health promoters who aim to educate women about breast cancer awareness and the need for performing breast self-examination and undergoing clinical breast examination conducted by trained providers.
A recommendation to perform regular BSE and CBE is highlighted in the SADANIS standard guideline, as follows:

> *"BSE should be done every time after menstruation (day 10, starting from the first menstruation). The initial CBE should be performed when a woman is between 20 and 30 years of age, as part of the routine physical examination every three years, and continued annually [once] the woman is 40 years old."*
>
> (**Document analysis — ID doc: LD2)**

The regular frequency of CBE written in the protocol is every three years for women aged 20 to 30 years, then once a year for women aged 40 years and older.

"The initial CBE should be a routine physical examination every three years when women [are] aged 20–30 years and annually when they reach 40 years old."

(**Document analysis — ID doc: LD2)**

Meanwhile, case management for patients with palpable masses began at the primary level of care with physical examination, including clinical breast examination (CBE) followed by diagnostic imaging and tissue sampling at secondary-level care; and referral to a tertiary-level care facility to ensure appropriate and timely treatment. In addition to mammography screening, static services were available at secondary and tertiary hospitals.

5.4.5. Stakeholders' roles — who does what in the SADANIS program

Early detection of breast cancer is a multi-professional responsibility which is comprised of a quality-assured, multidisciplinary combination of clinical breast

examination, diagnostic imaging, interventional diagnostic procedures, and patho-morphological tissue evaluation (Albert et al., 2009; WHO, 2007a). The researcher mainly explored SADANIS program information related to stakeholders and their responsibilities in excerpts from regulation documents. The researcher obtained additional information about the institutions from the participants she liaised with as their representatives. The lists and characteristics of actors involved in the SADANIS program are presented in **Table 5. 5.**

Table 5. 6. The mapping actors of breast cancer early-detection program

Stakeholder	**Characteristics**	
	Interest in secondary prevention of breast cancer	**Classification of stakeholder**
Women at risk (symptomatic or asymptomatic)	Continuum of early-detection care services	Beneficiaries
Community groups	Community groups have a strong influence on program implementation considering the common health risk, cultural setting and language	Beneficiaries / opinion leader
Central government	Provides overarching guidance by formulating standards, regulating policy, providing resources, monitoring performance, and evaluating program implementation	Decision-makers
Local governments	The program coordinator that supports infrastructure collects and analyzes data to monitor and evaluate the program	Decision-makers / program operators
Specialist doctors	Trainer who also performs technical supervision and receives referrals	Decision-makers / program operators
General practitioners	Performs CBE at primary healthcare facility or private health services location	Decision-makers / program operators

Stakeholder	Characteristics	
	Interest in secondary prevention of breast cancer	**Classification of stakeholder**
Midwives	Perform CBE at primary healthcare facilities	Decision-makers / program operators
Professional organizations	Undertake training, deliver services, and engage in coaching and reporting	Decision-makers / program operators
The Social Security Management Corporation for the Health Sector (BPJS)	Facilitates payment for clinical breast examination by agreeing to a schedule of fees found in a capitated contract	Decision-maker/funder
The National Cancer Committee	Formulates the National Cancer Action Plan, conduct a Health Technology Assessment for the cancer control program	Decision-maker/program operator
Non-government organization — The Indonesian Breast Cancer Foundation	Engage in health promotion, education and ongoing dialogue with the central government and local governments, provides mobile mammography services (in Jakarta province)	Program operator for mobile mammography
Lay health workers	Provide education and CBE service delivery in primary health centre (PHC) settings	Program operator / supporter

5.4.6. Infrastructure

The main discussion around the infrastructure highlighted the context of the cancer registry system and the need for an adequate information system to document screening data and evaluate the impact of early detection of breast cancer — reducing breast cancer mortality and detecting cancer at an advanced stage.

In Ministry of Health Regulation No 35/2015, the guideline for recording and reporting the SADANIS program is embedded within the Non-Communicable Disease program. The program officer at a primary health centre should collect demographic information on breast cancer risk factors and incorporate them into an

electronic surveillance system application. However, the PHC cannot link the recorded data to other referral hospitals to provide diagnostic and further treatment information.

At the national level, there is no standard platform designed to comprehensively document the breast cancer screening process and integrate it with the cancer registry database. Data regarding the eligible SADANIS population, the screening test of clinical breast examination performance recorded in the primary health centres were not able to link diagnostic workup, treatment and aftercare to patient surveillance function. In contrast, the development of an early-detection information systems solely focuses on the standalone platform used in the PHC or hospital, as described by the data custodian from Jakarta Provincial Health Office and Dharmais Cancer Center:

> *"At the national level, an integrated cancer screening registry platform has not yet been developed; the recording system is part of primary health centre or hospital information system."*
>
> ***(I4, stakeholder meeting 1)***

Given the performance of the recording and reporting system of the screening program, the head of the research and development unit at Dharmais Cancer Center emphasized the need to improve coverage of the population-based cancer registry by providing additional investment so a screening registry system could be established:

"Currently the data coverage in the population-based cancer registry is still less than 50%, we are still working together with five referral hospitals to increase the data coverage … Screening is a complex process, and it takes effort to build an integrated screening registry system."

(I12, stakeholder meeting 1)

5.4.7. The cost components

In current practice, the cost component of the SADANIS program is mainly consisted of programmatic costs that cover budgetary allocations for health promotion and education (printing, counselling materials, media, transportation to community visits, incentives for cadre (if possible), training (fee for facilitators, transport, room rent, administrative support), screening (materials and equipment, and reporting and recording). Meanwhile, from the patient's perspective, the cost of performing CBE at the primary health centres is covered by the person's national health insurance coverage, based on capitation financing. Other target populations, particularly if any private insurance does not cover them, may be liable for extensive OOP payments.

5.5. Activities: a showcase of SADANIS implementation in Jakarta Province

5.5.1. Health care setting and target population

Since activities for the early detection of breast cancer were introduced in 2007, Jakarta province has been identified as the main area for pilot testing of mammography screening in addition to clinical breast examination and the operation of a community-based cancer registry (Kardinah et al., 2014; Pardamean et al., 2015; Wahidin et al., 2012). In 2018, as a part of ensuring the implementation of the SADANIS program, government decree No 116/2018 was enacted to regulate the role and responsibilities of key stakeholders related to the implementation of SADANIS. The enactment of this government decree has had a positive impact on accelerating program implementation in Jakarta. According to the program coordinator, the SADANIS program has been implemented in 44 community health centres (collectively, PUSKESMAS) across five districts in Jakarta. The delivery of SADANIS services was integrated into the province's existing family planning program. In addition, due to fiscal decentralization, the provincial government took responsibility for allocating the SADANIS program budget for Jakarta, as stated in the governor's decree:

"All financing related to the SADANIS program in Jakarta will be allocated from Jakarta Provincial Health Office budget, regional apparatus budget, and other budget resources according to the provisions apply."

(The governor's decree, 2010)

The primary health centre focused on women aged 30-to-50 years old in its catchment area to promote breast cancer early diagnosis and breast cancer screening through the SADANIS program. **Table 5. 6.** presents the distribution of the target population of SADANIS in Jakarta province

Table 5. 7. The total target population of the SADANIS program in Jakarta Province, 2017

District	Eligible population (Women aged 30–50)
South Jakarta	374 061
East Jakarta	476 013
North Jakarta	285 807
West Jakarta	398 548
Central Jakarta	148 240
Kepulauan Seribu	3 643
Total	**1 686 312**

Source: Jakarta Provincial Office, cancer control sub-directorate, 2017

However, because SADANIS is not a formal screening program, the age group here does not refer to the lower and upper age limit for screening but the eligible age of the target group. Due to the nature of opportunistic screening, the program coordinators could not mobilize the target population to access the services through personal invitation, as emphasized by the program coordinator:

"SADANIS as screening is offered over opportunistic mechanism, and we do not send a personal invitation. Women at eligible age attending the primary health care [Puskesmas] will be offered a clinical breast examination."

(I8, interview)

5.5.2. Service availability: screening modalities, pathways, and referral to breast cancer treatment

The clinical breast examination is the primary detection modality in primary health care to downstage clinically detectable breast disease, and self-detected or clinician-detected masses. CBE is a standardized procedure whereby a healthcare provider examines a woman's breast, chest wall and axillae (B. O. Anderson et al., 2003). Similar to the role of CBE in limited resource countries (B. O. Anderson et al., 2003), CBE in the SADANIS program is delivered as either a screening test or a diagnostic test, depending on the clinical setting in which it is applied. CBE is a screening test when it is used by a healthcare provider to detect cancer in a woman who is not aware of any abnormalities in her breast. CBE is a diagnostic test when it is used by a healthcare provider to identify whether symptoms and changes in a breast found by a woman who examines herself are likely to be cancer.

Figure 5. 2.illustrates the SADANIS service delivery pathway and associated management services for detecting, diagnosing and treating breast cancer. As the SADANIS is a program based at PUSKESMAS, the pathway to early detection begins with a health promotion program to raise awareness of breast cancer and education for breast self-examination and clinical breast examination. Women with suspected masses were referred to the district-level hospital for evaluation, including with diagnostic mammography.

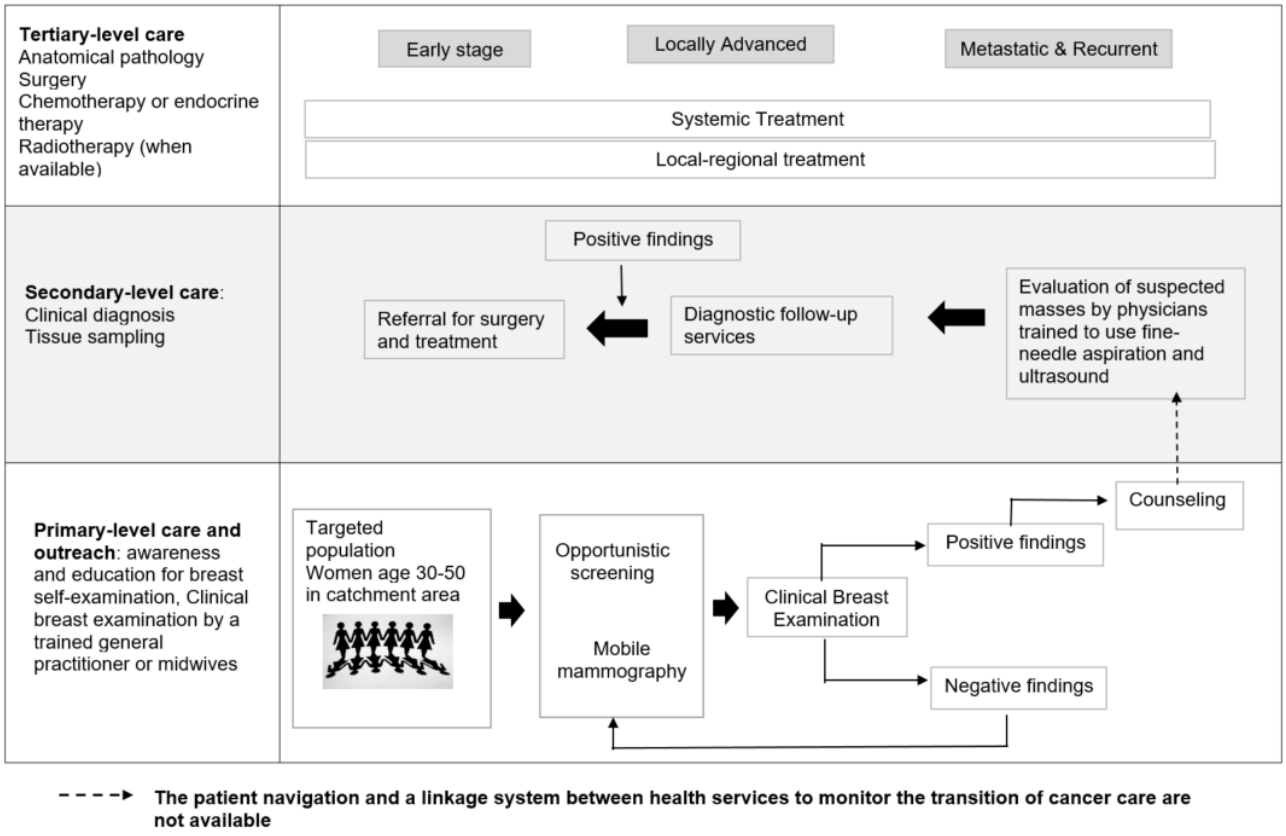

Figure 5. 2 The SADANIS pathways and associated management services for patient triage in early detection, diagnosis and treatment of breast cancer

The treatment services a patient receives at the tertiary level of the healthcare system includes early distinguished tumour staging, determination of locally advanced stages and metastatic cases, as well as treatment planning:

"Breast cancer staging is determined according to the 2010 American Joint Committee on Cancer (AJCC) TNM Classification System, 7th Edition for Breast Cancer. Management of breast cancer patients consists of surgery, systemic therapy, hormonal therapy, target therapy, and radiotherapy. Breast cancer treatment."

(**Document analysis — ID doc: LD6)**

In Jakarta, currently, there are 32 government hospitals throughout five regions (http://eis.dinkes.jakarta.go.id/dashboard.php). Based on their capacity to provide secondary-level of cancer care, these hospitals are categorized into three-tiers, as explained by the ECHO team leader:

"*The services available in a first-tier hospital are breast ultrasound, basic pathology and mastectomy. Second-tier hospital services include breast ultrasound and mammography, molecular pathology (not in every hospital), mastectomy, chemotherapy and radiation therapy (not in every hospital). The tertiary level hospitals perform diagnostic and treatment [services] according to the guidelines (staging conventional/PET-CT staging, molecular pathology, surgery with reconstruction, radiotherapy, chemotherapy, targeted therapy).*"

(Working group discussion, worksheet 5 — health system capacity)

Following the standard procedure, CBE at the primary level is performed by trained general practitioners and midwives. Training includes coaching in providing information on breast cancer risk factors, breast anatomy and disease, visual inspection, palpation techniques and interpretation of medical professionals' reporting of findings (Kardinah et al., 2014).

In addition to conducting outreach screening, the annual mobile mammography service was carried out collaboratively by the Dharmais Cancer Center, the provincial health office, and the Indonesian Breast Cancer Foundation. Over a decade, mobile mammography successfully reached 11 170 women in selected areas (Indonesian Breast Cancer Association, 2017). Unfortunately, the mobile mammography data available could not be integrated with the PHC or the referring hospital, which makes it difficult to ensure compliance with the diagnostic test.

"The results of mammography examination through the mobile mammography unit from 2014 to August 2017: 8286 women were examined, 1060 were suspected of having a benign tumour, and 123 were suspected of being malignant and required further examination."

(**Document analysis — ID doc: WD43)**

“We don’t have an integrated system to get the data from mobile mammography, the mobile mammography team sends the data manually through the data custodian from Dharmais hospital and we input it into our system.”

(I4, interview)

5.5.3. Barriers to SADANIS pathways

The critical components of a successful screening program are high coverage of the target population, quality-assured screening tests, and of a screen-positive person with the diagnostic investigation, treatment and follow-up care (Sankaranarayanan, 2014). Barriers to these essential factors, which if not implemented would impede the effectiveness of SADANIS are most likely influenced by the absence of an organized program resulting in non-optimal participation, and inadequate recruitment and limited access to tests. The failure to test people during the expected follow-up of abnormalities is more likely due to the unavailability of a notification system and patient navigation of the system, as discussed and summarized in the ECHO working sheet:

"*The main problem with program effectiveness is the absence of an organized system. The unorganized or spontaneous screening program made it difficult to mobilize the target population to access the services. [Therefore] we don't have a mechanism such as a reminder system, patient navigation for systematic recall, investigations and follow-up care of women with abnormalities on screening."*

(WGD, worksheet 2 — implementation gap)

However, as people’s responses have overcome barriers to the early-detection pathways, the Jakarta Provincial Health Office has begun canvassing people door-to-door to increase breast cancer awareness and participation in SADANIS services.

Another measure to increase the effectiveness of the screening program is to partner with private and government institutions for active mobile mammography outreach that is held in conjunction with special events, such as Breast Cancer Awareness Day, the celebration of Indonesia's Independence Day, and International Women's Day activities:

"For outreach, the Jakarta Provincial Health Office carried out a program known as 'know on the door, serve with the heart', wherein community health workers visited every household to provide information related to breast cancer awareness and early-detection efforts through the SADANIS program".

(**Document analysis — ID doc: WD 42)**

5.5.4. Information systems for breast cancer early detection

Alongside implementing SADANIS as the national, community breast cancer early-detection program, Indonesia's Ministry of Health standardized the reporting and recording forms people use, and the platform of electronic application tools regulated through Ministry of Health Decree 34/2015. Based on the information explained in the decree and additional information from the data custodian and program coordinator, the researcher illustrated the data flow and database structure to manage SADANIS pathways in **Figure 5. 3**

Two stand-alone information systems are used in the primary healthcare setting. The risk factor surveillance and patient recording systems are attached to the non-communicable module in the primary-health-centre information system. The first-tier information system in the PHC consists of three databases: 1) patient data, 2) breast cancer risk factors, and 3) clinical breast examination results. The patient database contains details on variables of the eligible population, such as name, date of birth, address, contact information, education, occupation, weight, height and marital

status. In addition to the target population, the PHC is able to retrieve the data of eligible women from the health insurance membership database for each catchment area of the PHC. The risk factors of breast cancer database records are related to family history, reproductive factors and lifestyle.

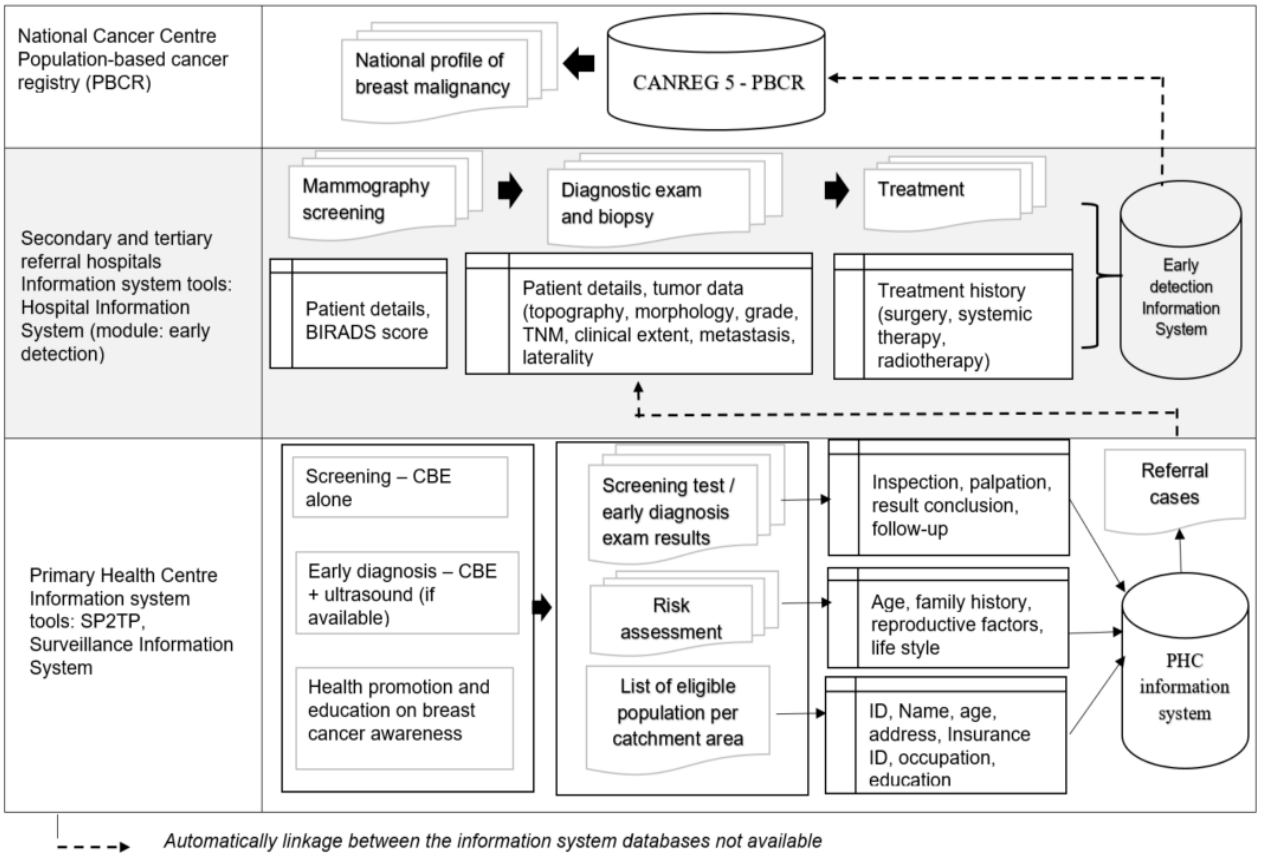

Figure 5. 3 A three-tiered breast cancer early-detection information system

The CBE screening or early-diagnosis information systems capture, organize and make available data about the results of the three standardized CBE procedures: 1) visual inspection of the underlying masses evidence (such as inspection of breast symmetry, and the skin of the breasts, areola and nipple for enema, puckering, dimpling or ulceration), 2) palpation of the axillae and supraclavicular fossae to

assess symmetry and nodularity, and 3) palpation of the breast for asymmetric masses, thickenings or densities (Anderson et al., 2003).

The second tier of tools represent the information system structure for the early-detection program activities conducted at secondary health services and illustrate the design at Dharmais Cancer Center. There are two categories of patients based on their admission type. First, positive-detected patients are referred from the PHC or mobile mammography services, as shown with the dashed line in **Figure 5. 3**, and second, patients who opportunistically attend the hospital for mammography screening. The databases generated through this process included patient details, tumour data, and breast cancer treatments. The recorded variables were name, age, the Breast Imaging Reporting and Data System (BIRADS) score, tumour grade, tumour morphology, tumour size, breast cancer TNM staging and treatment history (such as surgery, systemic therapy and radiotherapy).

The third tier represents the national population-based cancer registry is known as SRIKANDI (abbreviated from the Bahasa Indonesian name ***S**istem **R**egistrasi **Kan**ker In**d**one**s**i**a,*** Indonesia's cancer registry system) and is designed for the collection, management, storage and analysis of data on individuals diagnosed with various cancers. The national database of the PBCR is currently managed by Dharmais Cancer Center using the CanReg5 software platform adopted from the International Agency for Research on Cancer, IARC (Pardamean et al., 2015). However, there is no interconnection or data linkage within the structure of the PBCR with the databases used in each level of the various services provided (such as early detection, diagnostic and treatment). In addition, the absence of a screening registry to provide the documentation of services makes it difficult to assess the effectiveness and cost-effectiveness of the early-detection program.

5.6. Outputs

5.6.1. Participation and patient adherence to diagnostic test

Two participation measures were adopted for assessing the SADANIS program's effectiveness, coverage and uptake. Coverage is reported as the percentage of women who had opportunistic clinical breast examinations within a defined period (WHO, 2020). The researcher's data source for coverage was the Management Information System of Puskesmas which is a facility-based reporting system that provides estimates of the proportion of women who have attended SADANIS on an opportunistic basis at the primary health centres. **Table 5. 8.** shows the coverage rate of women aged 30 to 50 years of age in five regions of Jakarta province, averaged over one reporting year.

Table 5. 8. Target population and SADANIS program coverage rate in Jakarta province, 2017

District	N	Eligible population (Women aged 30–50)	Coverage (%)
South Jakarta	8 377	374 061	2.2
East Jakarta	1 954	476 013	0.4
North Jakarta	4 728	285 807	1.7
West Jakarta	4 751	398 548	1.2
Central Jakarta	1 905	148 240	1.3
Kepulauan Seribu	177	3 643	4.9
Total	**21 892**	**1 686 312**	**1.2**

The coverage rate under the opportunistic SADANIS program has remained below 5%. Meanwhile, the Ministry of Health has forecast the program's coverage rate will reach 50% for 2018 and 80% in 2024 at the district or provincial level (The Ministry of Health Republic of Indonesia, 2020). The Indonesia Health Profile reported that in 2017 the average cumulative coverage of SADANIS tests within thirty-four provinces in Indonesia was only 2.98%.

An uptake measure does not apply to SADANIS as an opportunistic strategy, because there was no personal invitation for the target population to attend the screening program, hence no denominator. However, in a community survey setting, where at personal invitation was applied, the uptake of a total of 38 of 749 eligible respondents was found to be more than 50%. Information on the characteristics of the eligible population of the SADANIS program was obtained from two different research settings. Firstly, Kardinah *et al*. (2014) reported the demographic characteristics of respondents in the pilot study of SADANIS and the mammography screening conducted in five districts in Jakarta:

> *"The average age of women participating was under 50 years old, and the majority are premenopausal, housewives, non-smokers, completed high school and have heterogeneously dense or extremely dense [breasts] on a mammogram."*
>
> (**Document analysis — ID doc: SW19)**

Secondly, a scholarly work using the Indonesian Family Health Survey reported that the predisposing determinant of mammography awareness was higher in women living in an urban area, women with high household expenditure, women who graduated from high school, women who have insurance, while women's location as living further health services was inversely associated with a predisposing determinant of increased awareness of mammography – meaning women living farther from health services were less likely to be aware of mammography (Anwar et al., 2018).

"[We found] higher odds of being aware of mammography in women living in urban areas (OR 4.51, 95% CI: 3.36-6.06), women who had graduated high school (OR 7.70, 95% CI: 6.19-9.58), women with higher household expenditure (OR 2.28, 95% CI: 1.88-2.76), women who have insurance (OR 2.01, 95% CI: 1.65-2.44). Living further from health services and being postmenopausal were inversely associated

with being aware of mammography in the model."

(**Document analysis — ID doc: SW26)**

In addition, 36.6% of women who were most likely to follow up after early detection through mobile mammography were those who were married, individuals living in Jakarta and urban settlements, aged less than or equal to 35 years, had graduated from college or higher level study, barely had health insurance, and had five risk factors (Kartikawati, 2018). The main inhibitor factors for low attendance of breast cancer screening are due to lack of knowledge, fear, anxiety, and discomfort when they are diagnosed with breast cancer (Solikhah et al., 2019).

After being diagnosed as cancer-positive at early detection, patient adherence to follow-up diagnostic tests significantly affects effective treatment (Martin, Williams, Haskard, & Dimatteo, 2005). Information about SADANIS patient adherence is not readily available because service providers have no integrated data accessible with the databases available at secondary health services that provide further diagnostic assessment. Therefore, the researcher identified the relevant information based on the prevalence of breast tumour survey reports. The survey evidence showed that from 3 121 patients referred to a diagnostic test, only 758 (24.3%) underwent mammography a mammography or breast ultrasonography.

5.7. Outcomes

The downstaging of breast cancer is the most common means of judging outcome measures in low- to middle-income countries that implement breast cancer early-detection strategies similar to the SADANIS program (Devi, Tang, & Corbex, 2007; Gutnik et al., 2016; Miller, 2008). Meanwhile, in developed countries with formal population-based screening programs, the effects are reported in terms of reduction

in mortality from cancer relative to mortality without screening or based on pragmatic objectives of public health policy for screening programs (Collette, Collette, Fracheboud, Slotboom, & de Waard, 1992; Hakama, Pukkala, Soderman, & Day, 1999). Data on breast cancer early-detection practices should link to data from the population-based cancer register and provide an impact evaluation for cancer early detection (Ballard-Barbash et al., 1997).

The absence of an integrated information system between datasets for early-detection programs and the cancer registry renders it impossible to measure the full effect of the SADANIS program implementation as a public health policy. Noting this limitation, the researcher sought to determine outcome indicators by exploring the incidence, prevalence and stage distribution of breast cancer to represent the magnitude of the public health problem in Indonesia.

5.7.1. Breast cancer prevalence and incidence

At the end of 2020, there were 201 143 females diagnosed with breast cancer in Indonesia which, according to the International Agency for Research on Cancer (2020), represents a total five-year prevalence (all ages) of breast cancer, of 148.11 women per 100 000 (IARC, 2020). At the national level, according to the Indonesia Basic Health Survey in 2007, the estimated prevalence was 4.3 women per 1000 population (Wahidin et al., 2012).

The burden of breast cancer is significant in Indonesia. According to the World Health Organization, in the period 2012–2020, the number of cases in Indonesia increased and was estimated to follow an upward trend in the next few decades. A total of 65 858 new breast cancer cases were diagnosed in 2020, indicating about 180 females a day were diagnosed with breast cancer in 2020.

"In 2018, the total number of cancer cases was 348,809 where breast cancer is the most common cancer case, with an incidence proportion of 16.7%. The estimated past and future trends in total cases per year in 2012, 2018 and 2020 were 48,998, 58,256 and 65 858, respectively. In the meantime, the estimated future trends of total cases per year in 2040 will be … 89,512."

(**Document analysis — ID doc: OD11)**

Two national referral hospitals reported that breast cancer accounted for 16.7% of all reported cancer in Indonesia:

"Based on the HBCR data from Dharmais hospital in 2015, breast cancer is the most common cancer among women in Indonesia, accounting for 39.51% of all cancer cases in women."

(Interview I4; WGD: working sheet 2)

"Based on a five-year HBCR study (using data from 2008–2012) in Cipto Mangunkusumo Hospital, breast cancer is the second-most commonly diagnosed cancer."

(**Document analysis — ID doc: SW 34)**

Using a dataset of breast cancer incidence from 1990 to 2017, downloaded from the Institute of Health Metrics Evaluation IHME website, the researcher found an increasing incidence starting from 2007, which may be due to the introduction of breast cancer early-detection activities at the national scale **(Figure 5. 4.)**

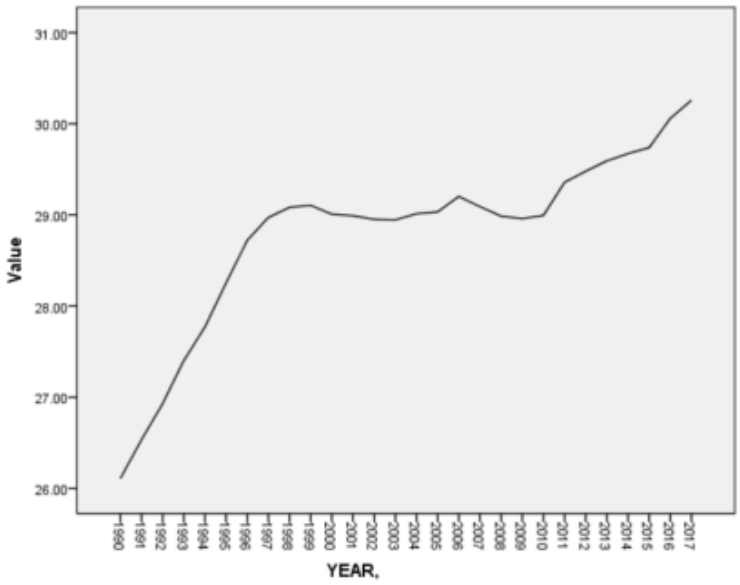

Figure 5. 4 The trend of age-standardized breast cancer incidence(per 100 000) in Indonesia 1990–2017

(source of data set: http://ghdx.healthdata.org/gbd-results-tool)

Data from GLOBOCAN on the indirect estimation of age-specific breast cancer incidence in Indonesia indicates an increase between the years 2012, 2018 and 2020. In addition to indirect measures of age-standardized incidence, GLOBOCAN 2018 used data from two neighbouring countries, Malaysia and Brunei Darussalam.

> *"In 2012, the age-standardized incidence rate of breast cancer was 40 per 100,000; 42.1 per 100,000 population in 2018 in 2020; and in 2020 the number of new cases was 65,858 [44.1 per 100 000]."*
>
> (**Document analysis — ID doc: WD 36, OD 7, OD 11)**

> *"For Indonesia, GLOBOCAN estimates were derived by incorporating weighted average from Malaysia (2008–2010) and Brunei Darussalam (2010–2012) applied to 2018 for incidence, with all-site estimates from neighbouring country partitioned using national frequency data from national cancer registry at Dharmais National Cancer Center."*
>
> (**Document analysis — ID doc: SW 34)**

The official document number ten in **Table 5. 1** regarding age range recommendations for pilot screening in Indonesia, it is stated that *"the lower average age at breast cancer diagnosis- compared to, for example, the Netherlands – may be explained by a difference in the age distribution of the overall female populations",* as presented in **Table 5. 9**

Table 5. 9 Age distribution in female population in Indonesia and in the Netherland (2020)

Age group	Indonesia		The Netherland	
	N	%	N	%
0-4	11,565,560	8.5	418,520	4.9
5-9	11,886,870	8.8	434,970	5.1
10-14	11,174,785	8.2	455,971	5.3
15-19	11,310,294	8.3	494,411	5.8
20-24	11,027,508	8.1	498,403	5.8
25-29	10,278,030	7.6	528,262	6.1
30-34	10,018,019	7.4	531,580	6.2
35-39	10,603,161	7.8	505,223	5.9
40-44	9,787,218	7.2	501,135	5.8
45-49	8,996,891	6.6	573,974	6.7
50-54	7,947,047	5.9	634,060	7.4
55-59	6,659,928	4.9	619,723	7.2
60-64	5,245,489	3.9	562,550	6.5
65-69	3,575,894	2.6	509,900	5.9
70-74	2,525,488	1.9	488,293	5.7
75-79	1,658,010	1.2	337,169	3.9
80-84	1,002,256	0.7	245,836	2.9
85-89	384,796	0.3	161,076	1.9
90-94	113,431	0.1	73,454	0.9
95-99	16,989	0.0	20,726	0.2
100+	1,189	0.0	2,492	0.0
Total	135,805,760		8,597,728	

Source: *Population Division of the Department of Economic and Social Affairs of the United Nations, World Population Prospects 2019, https://population.un.org/wpp/Download/Standard/Population/*

5.7.2. Stage distribution and survival of females with breast cancer

The characteristics of breast cancer patients were obtained from five scholarly documents. Two research settings were in referral hospitals at the national level (Gondhowiardjo Ekaputra, E. ,. Randi, A. ,. &. Jayalie, V. F., 2020; Ng et al., 2011), one setting at the sub-national level (Palu et al., 2013), and one at the pilot site in five areas of Jakarta (Kardinah et al., 2014). All these research documents reported that most breast cancer patients were diagnosed before 50 years old, which can be relevant to the highlights related to country-specific age distribution mentioned above. Based on an excerpt from a participant's data, the national non-communicable survey in the urban area reported that 32.1% of the female population aged 25-to-64 years living in urban areas in 34 provinces and having been diagnosed with breast cancer were in the age group of 25-to-34 years:

> *"[We have] the data from a community survey on the prevalence of breast tumours in an urban area in 2016 that the highest distribution of the female population who had been diagnosed with breast cancer in urban areas was in the 25–34 years age group (32.1%) and the lowest was in the 55–64 years age group (8.6%)."*
>
> ***(I8, interview)***

Data derived from the Dharmais Cancer Center showed a higher proportion of women present with late-stage disease that may require intensive and expensive treatment, which is associated with significantly worsened outcomes (Verdial, Etzioni, Duggan, & Anderson, 2017). A hospital-based dataset between 1993 and 2013 for the national cancer centre shows that the cumulative proportion of breast cancer stages was 3.6%, 17.84%, 22.09% and 20.83% for stages I, II, III and IV respectively, while the information on cancer stage for the rest of the 27.1% was not available.

Similarly, a comparative pathological study by Ng et al. (2012), using data from breast cancer patients at Dharmais Cancer Center and the University Malaya Medical Centre, showed that almost 80% of breast cancer patients present in the late stage:

"Less than 20% of breast cancer patients are presenting with stage I/II … Patients in Dharmais Cancer Center were highly likely to present with metastatic breast cancer compared to patients in University Malaya Medical Centre OR: 3.01; 95% CI: 2.02–4.48."

(**Document analysis — ID doc: SW14)**

5.7.3. Breast cancer mortality

While mortality from breast cancer in 2018 was 11% of total cancer death, breast cancer became the first most common cause of cancer death of females, with 22 430 females dying from the disease in 2020 in Indonesia. The age-standardized mortality rate for breast cancer was 15.3 women per 100,000.

"*In 2020, the standardized mortality rate of breast cancer is 15.3 per 100,000, which is lower than estimated data in 2012 (20 per 100,000)."*

(Document analysis — ID doc: OD 7, OD 11)

The observed survival by stage at diagnosis examined at the hospital level provides insight into how survival outcomes differ depending on the extent of cancer spread at diagnosis:

> *"The five-year survival on stages I, II, III and IV were 96%, 81.4%, 51.8% and 28%, respectively. Patients' 10-year survival was lower for stage I-IV at 92.3%, 70.4% and 17.5%, respectively."*

(Document analysis — ID doc: SW32)

5.8. The sources of accessible data to inform the economic evaluation model

The model input for ex-ante evaluation in this study primarily used locally relevant information. In this section, the researcher analyzed and elaborated excerpts related to the accessibility and availability of data sources to inform the model development. As illustrated in **Figure 4. 1 ,** the building blocks of information included demographics and epidemiology, clinical efficacy and performance indicators, cost, service use, quality of life and equity. Most of the evidence related to the data sources was triangulated to the participants from the National Institute of Health Research and Development, the Ministry of Health, data custodians from Dharmais Cancer Center, and the Jakarta Provincial Office. The reason for using institute information is that the facility has a leading role in providing national health data.

5.8.1. Demographics and epidemiology

The published data from the Central Bureau of Statistics (CBS) is the primary source to obtain demographic data. The CBS is the leading authority for the collection of demographic data regarding vital statistics (such as births and deaths) in Indonesia through a registration system, population censuses and surveys. (Siagian, Wandasari, Sahputra, & Kusumaningrum, 2019). The CBS has regularly published registration results containing the total population by district, sex, citizenship and age (the distinction between children and adults only). Unfortunately, the vital statistics resulting from the registration are grossly under-registered (Pratiwi & Kosen, 2013).

According to Indonesia's census law, the population census, No.6, 1960, is carried out once every 10 years, ending with 0 (zero), with the most recent being in 2020. In addition, a series of surveys are carried out regularly by the CBS, namely 1) the

Intercensal Population Survey (SUPAS) conducted every ten years in the year ending with five, 2) the National Socio-Economic Survey (SUSENAS) conducted annually to collect data on socio-economic characteristics of the population such as consumption, health and so on, 3) the Demographic and Health Survey which gathers fertility, mortality, health and family planning data.

Information on the prevalence and incidence of a disease is necessary when developing economic evaluations, (Hollingworth et al., 2020). The researcher obtained prevalence data for breast cancer from published literature (Wahidin et al., 2012) which was referenced in the Basic Health Research Survey (BHRS) in 2007. Unfortunately, in the recent BHRS in 2018, the prevalence of site-specific cancer was not reported. The prevalence of breast cancer data was also found in the published report prevalence survey of breast tumours in 2016 by the Ministry of Health. The data were obtained by asking respondents aged 26-to-64 years living in urban areas about their history of diagnosis with breast cancer.

The researcher found limited information on the availability of valid and reliable national representative data on breast cancer incidence due to lack of population-based cohort studies to follow the occurrence of new cases in the population, and insufficient coverage of the population-based cancer registry (Soehartati Gondhowiardjo et al., 2020). Alternatively, one participants from the Ministry of Health suggested the researcher mines data from the official website of the International Agency for Research on Cancer (https://gco.iarc.fr/today/home) and the Institute for Health Metrics and Evaluation (https://vizhub.healthdata.org/gbd-compare) about the country profile for incidence, prevalence and breast cancer death:

“Data on prevalence, incidence, and breast cancer death can be accessed from the website of the Institute for Health Metrics and Evaluation; Indonesia is participating country to supply data for counting the national global burden of disease”

(I12, interview)

The characteristics of breast cancer patients were obtained from four scholarly documents (Ng et al., 2011; Soehartati Gondhowiardjo et al., 2020; Kardinah et al., 2014; Palu, Maidin, Sudirman, & Nurdin, 2013) which reported that most breast cancer patients were diagnosed before the age of 50.

> *“[We have] the data from a community survey on the prevalence of breast tumour in urban areas in 2016 that the highest distribution of the female population who had been diagnosed with breast cancer in urban areas was in the 25–34 year age group (32.1%) and the lowest was in the 55–64 years age group (8.6%).”*

(I8, interview)

5.8.2. Clinical efficacy

Although government regulation mandated using an information system to collect and report the process of implementing the SADANIS program, providing clinical efficacy of early detection endpoints (such as reducing disease incidence and breast cancer mortality) becomes very challenging in Indonesia due to the absence of a formally organized screening program. The main barriers have been underdeveloped standards and inadequate information system structures to support systematic data collection across the continuum of care for early detection, diagnosis, treatment and follow-up.

“We don’t have a standard platform for integrating data between service providers. We are unable to trace whether the patient referred performed a diagnostic test or accessed the information on the diagnostic data.”

(I4, interview)

Information on clinical efficacy through randomized controlled trials is necessary to understand whether a given intervention achieves its primary goal and performs well

compared to all reasonable comparators (Downey et al., 2018; Wilkinson et al., 2016). However, RCT studies to evaluate the impact of early-detection programs have been virtually non-existent in Indonesia, as conveyed by the team coordinator of mobile mammography in her capacity as a member for national cancer control. In addition to the data source of the cancer stage distribution, the difference proportion for each stage of cancer between intervention and non-intervention groups in the setting of developing countries was reported in the published articles (Groot, Baltussen, Uyl-de Groot, Anderson, & Hortobagyi, 2006; Miller, 2008).

"As far as I know, there has been no pilot study designed with an RCT method to assess the comparative outcome of early-detection intervention."

(I1, interview)

Assisted by a data custodian, the researcher explored the distribution of cancer staging based on the patient's early-detection status at Dharmais Cancer Center to obtain indirect intermediate endpoints as a proxy for clinical efficacy parameters based on the available health services data. The data were obtained by matching the patient's unique identification number from two databases — the early detection information and the cancer registry from 2011 to 2013. However, the process encountered several problems due to incomplete cancer staging data and early detection history.

5.8.3. Costs

The context of cost data reflected the perspective of health services that provide the SADANIS program. As outlined in Ministry of Health Decree No 34, 2015, the costs of the SADANIS include health promotion and education (printing and counseling media), transportation to visit the community, incentives for cadre (if possible), training, screening (materials and equipment, and reporting and recording).

Indonesia's national health insurance covers the cost of performing clinical breast examination at the primary health centres, based on capitation financing. Other target populations, particularly those not covered by any private insurance, may be liable for extensive out-of-pocket payments. For the case study in Jakarta province, the unit costs/prices for opportunistic CBE and mammography services were obtained from DKI Jakarta Governor Decree No 141 / 2018 on the standard tariff of regional hospitals class C and class D.

The estimated cost data of breast cancer treatment were obtained through the Hospital Information System which was linked to the outpatient registry, the medical record and billing systems of Dharmais Cancer Center. The extracted data period is from January to December 2013, which is validated, according to the data custodian.

5.8.4. Service use and performance indicators

The information related to health service utilization is essential for economic evaluation to estimate the population affected by an intervention or service (Downey et al., 2018; Hollingworth et al., 2020). The feature of the SADANIS service is available through routine and non-routine data sources. **Table 5. 6.** presents data sources that provide relevant information on the use of the SADANIS service, along with the type of service delivered, screening modalities and total eligible target group.

The community-based prevalence survey is a non-routine data source that provides information on the attendance rate of a respondent using the SADANIS service. The inclusion criteria of the respondents are women aged 26-to-64 years old who signed the consent form, and who were not pregnant or in the first six months of any breastfeeding periods.

Table 5. 10 Type of screening service, modality and target population

Data source	Type of service delivered	Screening modality	Target group	Target population
Report on the community-based prevalence survey on breast tumours (National Institute of Health Research and Development Ministry of Health Republic of Indonesia, 2016)	Organized	Clinical breast examination	26–64	43 948
Routine data of CBE (SADANIS) program from Jakarta Provincial Health Office, 2017 — Patient-level data	Opportunistic	CBE	30–50	1 686 312
• North Jakarta				476 013
• Central Jakarta				398 548
• South Jakarta				374 061
• West Jakarta				285 807
• East Jakarta				148 240
• Kepulauan Seribu				3 643
The Indonesian Family Life Survey (IFLS) wave-5 (2014/2015)	Opportunistic	Mammography	≥ 40	5 397 (Anwar et al., 2018)

The monthly data at district/provincial level provides the total number of SADANIS clients, which is regularly reported based on a routine reporting system from the primary health centres to the district health office. The Centre of Health Data and Information, at the Ministry of Health, reported this aggregate information in the annual Indonesia Health Profile at the national level.

The fifth wave of the Indonesian Family Life Survey (IFLS) contained variables on SADANIS and mammography services for early detection of breast cancer. IFLS makes longitudinal panels data available to the public at https://www.rand.org/well-being/social-and-behavioral-policy/data/FLS/IFLS.html, including specific questions on SADANIS and mammography practice in the outpatient section of the questionnaire (coded for RJ 24–26). However, although the sample-design of IFLS

allows for longitudinal data analysis (Anwar et al., 2018), there are no further questions to address the endpoint of early detection (screened-detected cancer).

Information on performance indicators is needed to optimize the use of resources and ensure the quality of detection tests performed and interpreted (Charaka et al., 2016). The indicators include screen-detection rates, small-tumour detection rates, follow-up rates, sensitivity, specificity, positive predictive value and interval cancer. and rates can be measured by matching screening data with invasive breast cancer cases in the cancer registry (Loy, Molinar, Chow, & Fock, 2015).

The insufficient infrastructure of the current information systems used means the program implementer of SADANIS is unable to measure these complex performance indicators. For instance, matching women's data with abnormal reading test results and breast cancer diagnosis is still done manually, as described by the person in charge of mobile mammography:

"It takes several weeks to match the data between the results of mobile mammography and the results of the diagnostic test until a patient gets the final results. We don't have an automatic system to capture those data, so the process is done manually."

(I3, stakeholder meeting 1)

Evaluating early-stage shifting to reflect the effectiveness of SADANIS program implementation is also challenging due to limited data on the baseline and post-intervention scenarios. Therefore, to obtain model parameters related to the performance of the screening program, the researcher mainly used data from a systematic literature review reported in this thesis in **Chapter 3** (Yuniar, Robinson, Moorin, & Norman, 2020).

5.8.5. Quality of life

Disability-adjusted life years based on the GBD studies are widely used, especially in the low-income and middle-income countries (LMIC) setting (Groot, Baltussen, Uyl-de Groot, Anderson, & Hortobagyi, 2006; Hollingworth et al., 2020). A GBD study in Indonesia conducted by Mboi et al. (2018) is potentially useful as the data source to inform the study's economic evaluation. The alternative health outcome measures generally used by researchers in Indonesia are life-years saved and quality-adjusted life years (QALYs) (Machlaurin, Dolk, Setiawan, van der Werf, & Postma, 2020; Suwantika, Supadmi, Ali, & Abdulah, 2021). Life-years saved is an estimate of the average expected survival for a cohort receiving a prevention strategy compared to a baseline strategy.

Natural units such as life-years saved, averted DALY or QALY gained are considered more useful in economic evaluation rather than a change in clinical measures (Drummond et al., 2008), as they allow comparison across conditions and populations. Conversely, economic evaluations that only consider clinical measures are limited in their usefulness because the relative value of the intervention can only be ascertained within the scope of that health outcome (Hollingworth et al., 2020; Wilkinson et al., 2016).

QALYs represent average survival combined with expected utility. The EuroQoL with five dimensions and either three or five levels of severity (EQ-5D-3L and EQ-5D-5L) is one of the most frequently used measurement tools to assess country-specific patient's health stages and estimates of utilities to calculate QALYs (Gerlinger et al., 2019). Two published papers were identified related to the Indonesian EQ-5D-5L value set (Purba et al., 2017). They evaluated health-related

quality of life depicted in studies encompassing Indonesian women who had breast cancer symptoms before a definite diagnosis (Setyowibowo et al., 2018). However, the researcher cannot identify local studies addressing the utility value of the breast cancer stages.

Since local data sources for utility weight are limited, researchers consider accessing the cost-effectiveness analysis registry instead (https://cevr.tuftsmedicalcenter.org/databases/cea-registry). This CEA registry contains utility weight records for specific stages of breast cancer used in some studies of breast cancer in both developed and developing country settings, and the focus here was on utility weights generated in the developing setting to better reflect the Indonesian context.

5.8.6. Equity

Equity in the context of cancer is concerned with creating equal health opportunities in terms of access and provision of support on the cancer care continuum to vulnerable populations (Deandrea et al., 2016) and bringing health differentials down to the lowest level possible (Whitehead, 1992). It is also essential in priority-setting decisions and needs to be incorporated in the development of health economic evaluation (Hollingworth et al., 2020; Panteli, Kreis, & Busse, 2015).

Indonesia faces challenges such as exacerbating inequalities across the cancer continuum of care due to geographic barriers, lack of oncologist distribution and low numbers of cancer centres on islands outside of Java (Kardinah et al., 2014). Moreover, the existence of opportunistic early detection has been causally linked to less equity in access in comparison with organized programs (Palència et al., 2010; Peisl, Zimmermann, Camey, Betticher, & Bouchardy, 2019).

The researcher found limited information about equity-related data on the early detection of breast cancer. There are only two relevant sources to address the equity questions on early detection of breast cancer in Indonesia. First, the Indonesian Family Life Survey dataset provides variables on mammography service use and the SADANIS program. The sample design of IFLS provides an estimated proportion of women who practice breast-self-examination, clinical breast examination and mammography, disaggregated by the urban-versus-rural area and socioeconomic status. Second, the breast-tumour prevalence survey is conducted in urban areas in 36 provinces. This data source also explores the equity of access to SADANIS services. Wealth quintiles are available for households in the dataset (National Institute of Health Research and Development Ministry of Health Republic of Indonesia, 2016).

5.9. Stakeholders' responses to strengthen the SADANIS program

In this section, the researcher examines the policy process to gain insights into stakeholders' plans for strengthening breast cancer detection in Indonesia.
The process embraces the approach of stakeholder-driven efforts to coalesce Dharmais National Cancer Center and program implementers from the Jakarta Provincial Health office in formulating a plan for the pilot study of mammography screening. The following elements are featured during the policy process and in a joint statement on priority action for collaborative mammography screening:

5.9.1. Harmonizing perceptions of the SADANIS program

To ensure that the stakeholders share a common understanding of the scope of breast cancer early-detection, the topic of components of early detection (such as

early diagnosis and screening) and the characteristics of both services were presented by a participant from Dharmais Cancer Center at the first working group discussion:

"[I will refer to the definition of early detection according to WHO]… an early-detection program is the organized and systematic implementation of interventions that comprise early diagnosis and screening — early diagnosis is the recognition of symptomatic cancer at early stage, while screening is the identification of asymptomatic disease in the target population of apparently healthy individuals."

(I1, stakeholder meeting 1)

Despite two distinct definitions of related strategies in early detection, there was lack of shared understanding about the ultimate goal of the current program. Participants relayed a sense of confusion about the priority of existing practice and raised a question of whether both activities were managed under existing programs (such as the SADANIS program). One participant reflected:

> *"Just referring to things and understanding the given definition, so what is the main focus of early-detection strategy in the SADANIS program?"*

(I12, stakeholder meeting 1)

I1 explained that the current implementation of strategy is a downstaging strategy encompassing early-diagnosis programs for symptomatic patients. In addition, according to resource-stratification strategies, which are recommended by the Breast Health Global Initiative (BHGI), this strategy is appropriate for the resource-constrained setting because the number of patients with clinical symptoms requiring diagnostic evaluation is more manageable than for example, the number of women from the symptomatic screened population requiring screening and additional diagnostic imaging:

"The SADANIS program is more to the concept of early diagnosis or what we referred as down-staging, and represent the concept of awareness [by the health professional] of early signs and symptoms of breast cancer, this strategy is appropriate for limited-resource countries."

(I1, stakeholder meeting 1)

"SADANIS as screening is offered over opportunistic mechanism, we do not send a personal invitation. Women at eligible age attending the primary health care [Puskesmas] will be offered a clinical breast examination."

(I8, interview)

5.9.2. Leadership and coalition building

The National Cancer Hospital has been the leader in Indonesia in the formulation of policy that plans to strengthen the continuum of screening care, especially the referral system, and the monitoring and evaluation of the breast cancer early-detection program:

"The team proposal [ECHO] was accepted, this is a very good opportunity to make an improvement plan for the breast cancer early-detection program."

(I1, interview)

There were several stakeholder engagement meetings attended by program managers, referral hospital representatives, organizations' professionals, non-government organizations and board members of the national health insurance scheme that led to the establishment of joint statements to support the pilot project of integrated breast cancer screening in Jakarta province. Coalition and networks consisting of both internal stakeholders and international organizations were formed to influence a higher level of decision-maker, share resources and combine efforts to plan the implementation of the future pilot project more efficiently:

"Currently I am joining the rapid-diagnosis working group at the WHO Global Breast Cancer Initiative. Hopefully through international coalition and networks we can improve the referral system for CBE [SADANIS] or mammography positives."

(I1, interview)

"We have received approval from three people at the decision-maker level to become mentors in the ECHO project. They are the program manager of the cancer control program in the provincial health office Jakarta, head-of-cancer sub-directorate of cancer, and head-of-referral-service in the Ministry of Health."

(I1, interview)

5.9.3. Guided practice and advocacy to higher government levels

As ECHO project used an approach for knowledge-sharing and technical assistance, the discussion sessions were facilitated by the National Cancer Institute using thematic working sheets. This guided practice approach provides an insight to the Indonesian team on how a systematic policy planning phase is constructed and what lesson can be learned from other countries' experiences.

As the final output, a SMART (specific, measurable, attainable, relevant, time-bound) objective of the pilot project plan was completed and disseminated to the Ministry of Health.

5.9.4. Framing the policy option

Having an opportunistic screening approach has identified deficiencies in preventive health strategies, such as by adopting encounter-based not population-based screening. The situational context of an encounter is a limiting factor, while partial adherence is more likely than complete adherence, and more complex situations (such as follow-up, greater individual risk and so on) are less likely to be properly addressed (Chamot, Charvet, & Perneger, 2007; Herdman & Norton, 2005).

Therefore, the issue of adopting a systematic approach to strengthen the integrated services of detection, diagnosis and treatment of breast cancer was considered a cross-cutting issue to improve outcomes of breast health. Strategies to have the

various high-level decision-makers adopt this policy process were translated into two outputs. Firstly, a joint statement was developed among stakeholders to support the pilot project goal of integrating breast cancer screening in Jakarta province and, secondly, a SMART objective policy plan was produced as the output of ECHO project**.** The following elements are the priority action points listed in the stakeholder's joint statement:

Priority actions to strengthen the SADANIS program

1. Public awareness of early signs and symptoms of breast cancer is augmented through training primary healthcare staff.
2. Clinical breast examination will be the initial screening modality used to check breast abnormalities. It will be carried out by trained health workers, starting at the primary health service level.
3. The eligible population is women aged between 40 and 65 years old.
4. To avoid delays in diagnostic assessment, the national referral hospital will receive patients from primary health care facilities and district hospitals for further investigation.
5. The Breast Imaging Reporting and Data System (BIRADS 5th edition) will serve as the standard reporting methodology for ultrasonography and mammography diagnostic reports.
6. All related activities of SADANIS must be reported to the district/provincial health office.

Recommendation on mammography screening in Indonesia

1. Mammography screening age starts at the age of 40 and continues with screening at two-year screening intervals.

2. Mammography screening data will be standardized and used as the basis for the population-based cancer registry system.
3. All related activities of mammography screening must be reported to the district/provincial health office.
4. Organisational professionals, along with the Indonesian Breast Cancer Foundation, will advocate for the policymakers to support the implementation of the pilot screening program.
5. Coordination and collaborative care among multiple providers in the interdisciplinary team are needed to support timely access to diagnostic services and early treatment.

In addition, some supporting explanations related to the design plan for the pilot project were presented at the stakeholder meeting.

Instead of prioritizing early diagnosis, I1 presented the feasibility of implementing parallel systematic CBE combined with mammography for asymptomatic women (such as screening) to scale up a high-quality early detection:

> *"Screening implementation to identify breast cancer in a presumably asymptomatic population at regular interval is also needed to advance high-quality breast care … or the model can be based in the systematic management of clinically detectable (palpable) breast disease as a prerequisite to population-based screening in the future."*
>
> ***(I1, stakeholder meeting 1)***
>
> *"The screening can be implemented sequentially after all systems are ready or in an overlapping fashion on the scale of pilot sites."*
>
> ***(I3, stakeholder meeting 1)***

Although opportunistic testing may seem an appropriate strategy in the absence of population-based screening, I1 shared her perspective on the important advantages of having systematic population screening over opportunistic testing:

“Oftentimes, the opportunistic testing is of poor coverage; while some individuals have too many or too often, others have too few. The fragmented service in this type of test reflects inequity and a waste of valuable resources.”

(I1, stakeholder meeting 1)

Having agreed with this statement, another participant mentioned that it is important to first consider evaluating the current service delivery before establishing any screening program, including addressing the barriers and the availability of the adequate supporting system.

“Once high-quality, accessible services are in place to diagnose and treat clinically apparent disease, early detection in the form of screening programs can then be considered in addition to continuing to [achieve] effective early diagnosis for all women.”

(I10, stakeholder meeting 1)

A clear referral system guideline is perceived to be the main product that will be improved and tested within the pilot project. More specifically the need for an integrated referral system for the patient with positive CBE or mammography results is vital considering the problematic hierarchical tier of the referral procedures from primary healthcare settings to secondary and tertiary health facilities.

5.10. Summary

This chapter summaries the contextual domains and relevant data from local jurisdictions and highlights the relevance of incorporating a qualitative approach to establishing a decision-analytic model. The iterative data collection methods frame the cost-effectiveness analysis of breast cancer’s early detection in Indonesia’s healthcare setting. The document analysis provides the current government policy and standard guidelines of the program, and, from the perspective of healthcare providers, the researcher identified the implementation gaps, policy processes for program improvement and accessible data sources to populate the model. The next

chapter will focus on the method used to construct the model development and result.

Chapter 6: The structure of the model

6.1. Overview

This chapter describes the structural development of an *ex-ante* cost-effectiveness analysis model of organized screening within Indonesia's healthcare setting. The researcher's decision premise for the model is influenced by a policy plan of engaged stakeholders to implement a systematic screening strategy. The study's model development addressed two research questions to inform healthcare policy: 1) Should the program implement systematic/organized screening that has successfully been proven to cover a more prominent target population and, therefore, has greater effectiveness at the population level than opportunistic screening? and 2) Under what circumstances may systematic/organized screening be economically more attractive than opportunistic screening? Model structure development began with a brief outline of the analytic overview which underpinned the economic evaluation of breast cancer screening, then followed by a description of the components that framed this study. The information that frames the model structure, such as the location setting, and eligible population should be described as methodological context. However, the researcher believes that the information presented here improves the flow and ease of read the thesis.

6.2. Analytic overview

In breast cancer screening, the events to be modelled include the administration of screening, diagnostic tests, disease progression and survival (Moore, Shenoy, Fanucchi, Tumeh, & Flowers, 2009). For an economic evaluation, a screening model needs to consider the costs incurred, the utility values, and the duration of

each health state arising from an event of the diseases (Jonathan Karnon & Brown, 1998). The cancer stage distribution could also be included based on the screening strategies (Groot et al., 2006; Schiller-Fruehwirth et al., 2017). Moreover, cancer stage distribution has been used as the primary measure of clinical benefit because organized and opportunistic screening have different possible distributions on the prognostic profile (Bihrmann et al., 2008; Schiller-Fruehwirth et al., 2017). This intermediate outcome (Zapka, Taplin, Solberg, & Manos, 2003) is associated with different prognoses and outcomes such as complications, quality of life, pain, disease or death (Langlands & Kerr, 1978; Moons, Royston, Vergouwe, Grobbee, & Altman, 2009).

6.3. Screening modalities and practice of the usual care

The current primary breast screening modality mostly used in Indonesia is the clinical breast examination (CBE) which is commonly known in Indonesia's public health program as SADANIS *(PerikSA payuDAra Secara KliNIS),* followed by confirmatory diagnostic testing via mammography or breast ultrasound (B-US) (Ministry of Health Decree number 34/2015). The CBE is delivered opportunistically, which means health centre does not send an individual invitation to members of the eligible population to attend the screening nor monitor the patients in follow-up programs after screening.

Existing evidence suggests that careful and competent CBE appears to be a promising means of averting some deaths from breast cancer and clinicians may be able to identify lesions early enough in the natural history of breast cancer for the effective use of interventions (Weiss, 2003). In addition to the efficacy and effectiveness of CBE, a study conducted in five districts in Jakarta concluded that CBE was nearly as effective as single-view mammography in detecting prevalent

breast cancer in the unscreened population (Kardinah et al., 2014). Henceforth, the term opportunistic CBE will be used to represent SADANIS as the usual care of the screening program.

6.4. Location setting

The location of this *ex-ante* evaluation was Jakarta Province and was selected based on the showcasing site explored in the qualitative phase. Therefore, it represents the urban setting where an opportunistic clinical breast examination program is performed in over 30 primary centres in five regions, while follow-up confirmatory diagnostic testing is provided at the secondary health care facilities (hospitals), and an alternative strategy of organized screening is piloted in some areas (Kardinah et al., 2014; Pardamean et al., 2015; Wahidin et al., 2012). As Jakarta province is often used as the pilot area in initiating policies related to breast cancer early detection, it is assumed that program implementers have the required capacity to meet the criteria of organized screening that, according to Duggan et al. (2020), include geographical distribution of healthcare providers, referral networks that decentralize cancer care, and the involvement of stakeholders in the integration of cancer care into existing health service in a sustainable, resource-appropriate manner.

6.5. Characteristics of policy options

The economic analysis assessed the incremental cost-effectiveness of organized clinical breast examination undertaken during community-based screening compared to opportunistic CBE screening. The characteristics of organized screening as an alternative policy option include the following criteria: the invitation is issued to women in a defined target population; a mechanism is implemented to guarantee

high coverage and attendance (for example, a personal letter of invitation); there are adequate facilities for performing screening tests and diagnosis, including a referral system and appropriate treatment of confirmed abnormalities (Madlensky, Goel, Polzer, & Ashbury, 2003). Additionally, patient navigation for diagnosed patients that potentially increases compliance to diagnostic confirmatory tests is incorporated. It is evident that compared to cancers diagnosed clinically, cancers detected by organized screening were more likely to be diagnosed at an early stage, were smaller and more frequently did not feature nodal involvement (Vanier et al., 2013).

In contrast, opportunistic screening depends on requests from individual members of the community or the recommendation of their health advisors to do the screening (Anderson et al., 2008). It is different from an organized strategy in that few opportunities exist to monitor people with follow-up of diagnosed patients for confirmatory tests (Miles et al., 2004). Consequently, the opportunistic screening approach may cause a delay in people taking appropriate clinical care pathways (Ho et al., 2020).

6.6. Eligible population

The eligible population in the model included asymptomatic women with no history of ductal carcinoma in situ (DCIS) and breast cancer, and no breast radiation before the screening. The proportion of women with breast cancer symptoms is assumed to be determined at the baseline by prevalence data. The starting age of the target population when entering the models (both organized and opportunistic) was 40 years old, which is in line with the recommendation of the starting age for pilot mammography screening in Indonesia (Kardinah et al., 2014; Waal, Broeders, & Pijnappel, 2018).

6.7. Perspective, time-horizon, and discounting

This study used a health service perspective and considered the point of view of alternative strategy raised from engaged stakeholders who primarily represent healthcare providers of breast cancer early-detection services, thus shaping the aim of economic evaluation to assess the plan of organized screening. Besides, the setting of this *ex-ante* assessment meant there was likely to be considerable uncertainty around the information needed to extend the perspective to a social one, including productivity and out-of-pocket expenses (Bock et al., 2015). A lifetime horizon was included to capture all meaningful differences in costs and effects over the lifetime of the cohorts modelled (O'Mahony, Newall, & van Rosmalen, 2015). Following the Indonesian Health Technology Assessment Guideline on cost-effectiveness in health and medicine, a 3% discount rate was applied to cost and health outcomes (Ministry of Health Republic of Indonesia, 2017).

6.8. Outcomes

The model outcomes are the lifetime costs and quality-adjusted life-years (thus allowing a cost-utility analysis). It assumed that the objective of decision makers and engaged stakeholders planning to scale up opportunistic screening into organized screening is to maximize health improvement through early stage cancer detection in resource-constrained countries. The use of QALYs further assumes that health benefits can be measured or valued based on the amount of time spent in various health states (Weinstein, Torrance, & McGuire, 2009). QALYs incorporate the impact on both the quantity and quality of life which are calculated by multiplying the time spent in a health state by the health-related quality of life (HRQoL) weight (often termed a utility score or utility weight) assigned to this health state. To generate

QALYs, health utilities needed to value the health states, based on preference or desirability for the different health states (Weinstein et al., 2009). By convention, the absence of life is worth 0 QALYs while the upper end of the scale is defined as perfect health, with a value of 1. The more desirable (more preferred) health states will receive greater weight and will, therefore, be favoured in the analysis (Drummond et al., 2005).

Commonly, there are two methods to determine the quality weight — direct and indirect approaches. The direct methods include the visual analogue scale (VAS), the time trade-off (TTO), and the standard gamble (SG). The indirect method involves the use of the pre-scored generic preference-based measure in which health states are described using standardized generic utility questionnaires (Kim, Jo, Ock, Lee, & Lee, 2017; Siegel et al., 1996). These generic preference-based measures includes the widely-used EQ-5D Group five-dimension questionnaire (Brooks, Rabin, & Charro, 2003). Several health-state utility values (HSUVs) studies have evaluated a range of health states in various breast cancer states, for example the screening-related state (Bromley et al., 2019), and surgery for newly diagnosed breast cancer, locally recurrent cancer, chemotherapy treatment and metastatic breast cancer (Mokhatri-Hesari & Montazeri, 2020; Peasgood, Ward, & Brazier, 2010; Yang, Yu, & Zhang, 2020). The utility value used in this study was elicited from studies based on health status in the model structure (**Figure 6. 4**).
See **Chapter 7** section 7.6 — Utility estimation of health states for a detailed explanation of how the HSUVs are derived for the model.

6.9. Model structure

The model in this study consists of two parts: the breast cancer screening decision-tree, and the second part is the Markov breast cancer progression model. In the first part, the decision-tree was built based on the screening pathways to describe screening attendance, screening test findings and diagnostic test results. Then, at the end of each screening pathway are Markov progression models that track breast cancer–related events and mortality from the point of receiving a test result (or not if the test is not completed) to the point of death. The structure of the Markov model was informed by a range of published cost-effectiveness breast cancer screening model in the breast cancer models (Nguyen & Adang, 2018b; Sun, Legood, Dos-Santos-Silva, Gaiha, & Sadique, 2018; Wong et al., 2007). In addition, the researcher determined the descriptive validity of the model through correspondence with two oncologists based in Australia and Indonesia to review how the model structure incorporates the assumption about the allowable transition of progression-or-regression of breast cancer into a simplified design.

Assuming that screening is offered once in a lifetime, the model simulates the risk of breast cancer, screening care pathways and progression-of-the-disease estimates to long-term cost and outcome, given that breast cancer involves risk overtime and relapse (Feng et al., 2018; Sonnenberg & Beck, 1993). The models were run using TreeAge Pro Healthcare 2020 software (TreeAge Software, Inc., Williamstown, Massachusetts). **Figure 6. 1** shows a schematic screening management pathway of the cohorts. The screening model was intended to mimic the procedure of the national breast cancer screening program in Indonesia (the Ministry of Health Decree number 34/2015).

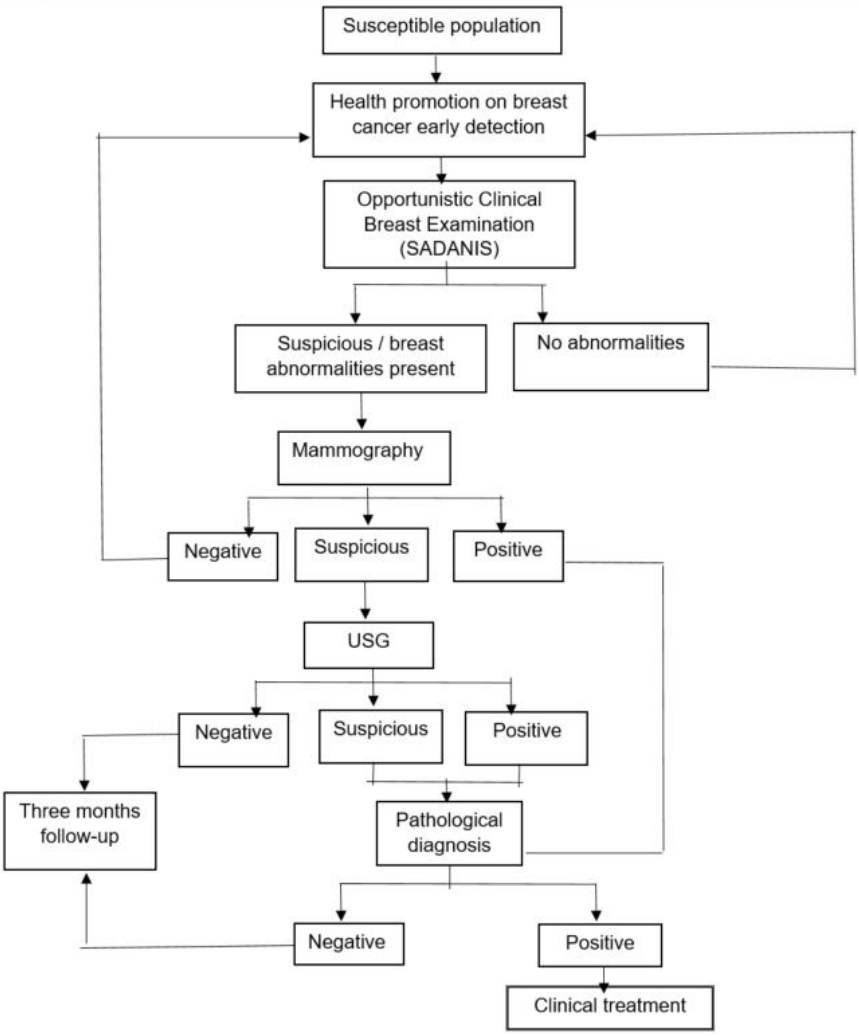

Figure 6. 1 The schematic model of combined breast cancer screening pathways and breast cancer progression model

Figure 6. 2 illustrates the decision-tree used to compare an organized screening strategy with the current practice (opportunistic screening). The decision tree describes screening attendance, screening test findings, and diagnostic test results.

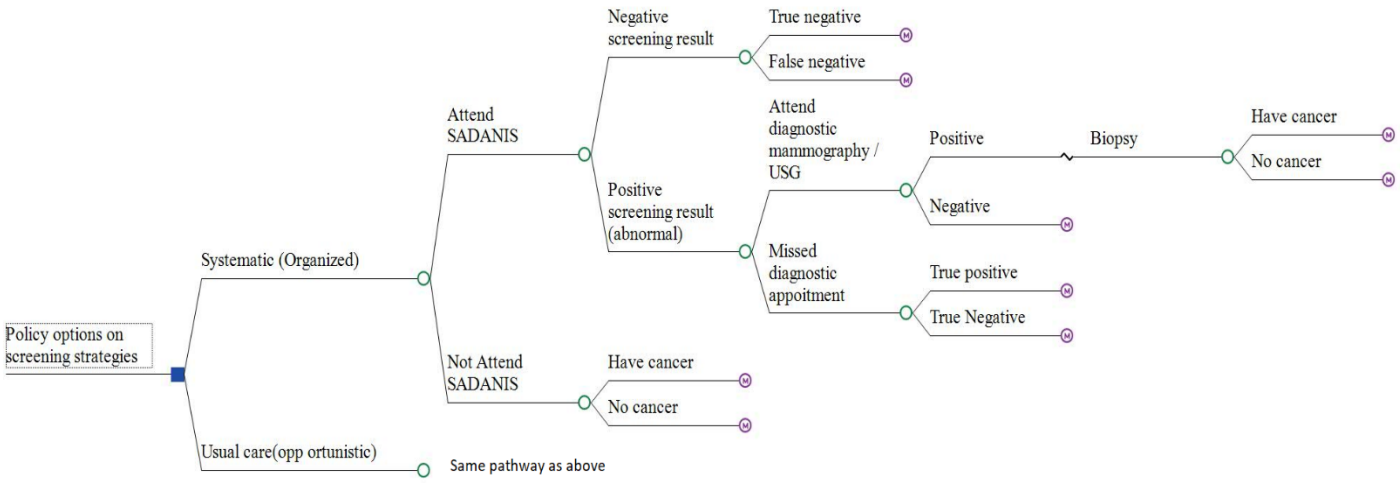

Figure 6. 2 The simplified subtree of screening pathways

A cohort of eligible women is channelled through different branches of the decision-tree's screening pathways. Details on the probabilities used for each pathway of the subtree are presented in **Chapter 7.**

In the **organized arm,** a screening test was offered systematically to eligible women. The midwives at primary health centres initially invited these women by letter to attend screening events at the local facilities (Kardinah et al., 2014). The branches emerging from the organized chance nodes represent the probabilities related to women who attended and did not attend the screening. The branches emerging from attended SADANIS screening events represent the probability of having positive or negative clinical breast examination results. Women who tested positive were assumed to have immediate notification of their result, within seven to ten minutes. If abnormality was detected during CBE, the women would be able to access mammography and biopsy provided at district-level hospitals on an appointed date. The branches issuing negative CBE represent the probability of women without breast cancer receiving a normal CBE result (true-negative) and

women with breast cancer receiving a negative result after screening or a normal CBE report is normal (false-negative).

Women with positive or abnormal CBE results would be referred for a subsequent diagnostic mammogram. The recall system would call positives back, and the case management would be performed according to the Breast Imaging–Reporting and Data System. According to the BIRADS category hierarchy, the assessment and management are as follows (D'Orsi & Acr, 2014):

- **Category 0: Incomplete** — This may take the form of additional mammographic views and ultrasound or other procedures for comparison.
- **Category 1: Negative** — Nothing to comment on. If there are clinical findings, a statement indicating that this finding should be dealt with independently of the negative mammogram should be added (essentially a 0% likelihood of malignancy).
- **Category 2: Benign findings** — Also negative, but the interpreting physician may wish to describe a typical benign finding: for example, calcified fibroadenoma (essentially a 0% likelihood of malignancy).
- **Category 3: Probably benign findings** — Short interval follow-up (six months) suggested (>0% but ≥2% likelihood of malignancy)
- **Category 4: Suspicious findings** — Biopsy should be considered. A finding without the characteristic morphology of breast cancer but has a definite probability of being malignant (>2% but <95%)
- **Category 5: Highly suggestive of malignancy** — Appropriate action should be taken. These findings have a high probability of being cancer (≥95% likelihood of malignancy).

Mammograms assessed as negative, benign or probably benign with no recommendation for biopsy or surgical consultation are considered negative (Balleyguier et al., 2007). Meanwhile, mammograms that are assessed as highly suggestive of malignancy, suspicious or in need of additional evaluation or a recommendation for biopsy or surgical consultation are considered positive or abnormal. The branches from diagnostic mammograms represent the probability of a negative or positive diagnostic result. Those who have a positive mammogram result will have the biopsy and go to the next chance node to represent the probability of being diagnosed with breast cancer and having no breast cancer. It is assumed that the biopsy test has a 100 percent sensitivity and 100 percent specificity; therefore, the biopsy result is considered a definitive diagnosis. Women with positive CBE results who do not see a doctor for diagnostic tests move on to the chance node of true-positive or true-negative.

In the opportunistic branch, a screening test is offered opportunistically to a woman when she attends medical services for a different reason (Hobbs et al., 2005) or the healthcare professional takes the opportunity to screen a woman during a routine consultation (Hill et al., 2020). Women may have their breast cancer diagnosed as part of routine care or if they experience breast cancer symptoms (lump in the breast, thickening or swelling of part of the breast, irritation or dimpling of breast skin), they will undertake mammography diagnostic tests to determine the presence of breast cancer. Therefore, the branches from opportunistic screening represent the probability of women who may or may not experience CBE practice as routine care. Diagnosis of breast cancer was then either identified through routine care (true-positive or true-negative) or a background incidental identification in the absence of applied screening.

6.9.1. Markov modelling

The multistate Markov models were applied to capture expected lifetime costs and benefits associated with breast cancer progression and mortality. An overview of the Markov flow diagram is presented in **Figure 6. 3.** The stages of breast cancer progression according to the natural history of the disease are constructed (these stages are no cancer, ductal carcinoma in situ and stages I, II, III and IV cancer). After treatment, the state will indicate whether the patient's cancer is progressing or in a state of zero evidence of cancer (remission) or cancer return after a period of remission (recurrent) in the vicinity of the original tumour (local recurrent) or in distant organs (distant recurrent). The progression of breast cancer was incorporated into the screening model only when the women were confirmed histologically as DCIS or stage I, II, III or IV cancer. Furthermore, as a confirmation, the diagnostic test confirmed non-invasive (DCIS) or invasive cancer, and the management of the practitioners' intervention was assumed to follow the standard treatment guideline of DCIS (Barrio & Van Zee, 2017) and invasive breast cancer treatment (Gradishar et al., 2020). After clinical treatment, the state indicates whether patients go into remission, or have locally recurrent or distant recurrent cancer. Women with a false-negative result will progress through the disease stages, but those who are negative and false-positive have the chance of being cancer-free or acquiring breast cancer and progressing through the disease states.

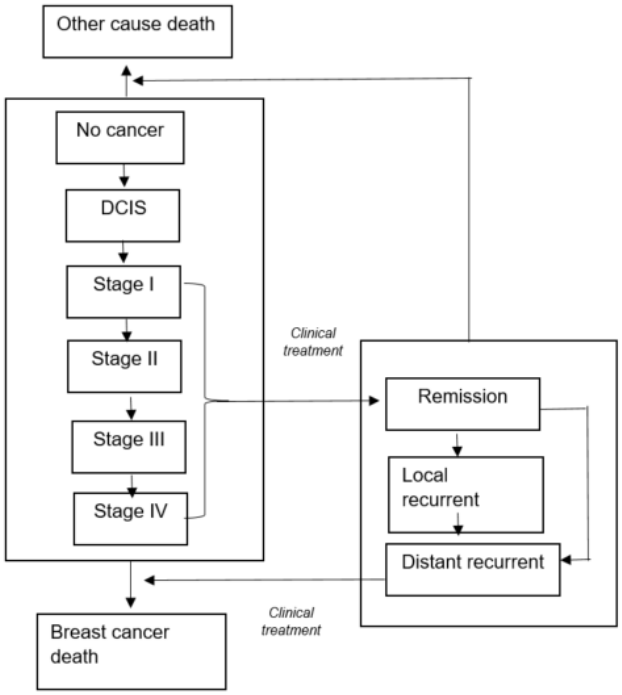

Figure 6. 3 The Markov model flow diagram

Sonneberg and Beck (1993) describe the Markov modelling for healthcare as analytical structures that represent the key elements of a disease and are commonly used in economic evaluation (Duffy, Day, Tabar, Chen, & Smith, 1997; Eichler, Kong, Gerth, Mavros, & Jönsson, 2004; Koning et al., 1991; van Oortmarssen, Boer, & Habbema, 1995). The models have particular use when researchers are evaluating the progression of chronic diseases such as cancer (van Oortmarssen et al., 1995), where input data such as transition probabilities costs or utilities change over time, because events are modelled as the transition from one health state to another (Cong & P.Tsokos, 2009; Tan et al., 2013).

The following steps were taken to build and analyze a Markov model in this study (Briggs & Sculpher, 1998; Sonnenberg & Beck, 1993).

6.9.1.1. Breast cancer progression — states and allowable transition

The states of disease and allowable transition were first specified to reflect the relevant natural history of breast cancer progression over time. Since sufficient empirical evidence on breast cancer screening in Indonesia to construct a suitably realistic model is non-existent, the structural feature of the natural history of the disease was built according to clinical experts' accounts as well as published articles (Feng et al., 2018; van Oortmarssen et al., 1995).

Figure 6. 4 depicts 11 mutually exclusive Markov states and possible transitions defined in the natural history progression of breast cancer. Tumor development was modelled as a process whereby a person goes through the various consecutive invasive breast cancer stages according to the American Joint Committee on Cancer (Amin et al., 2017), stages I, II, III and IV breast cancer, and death from the cancer. The model follows the work of Briggs and Sculpher which emphasized that the states must represent a clinically and economically important event in the disease process to be modelled; therefore the model in this study has included the interventions not only at the initial disease treatment but also captured the possibility that patients could experience a relapse or progression after their initial diagnosis (Bartelink et al., 2001; Rocca et al., 2008; Voogd et al., 2001). It was assumed that cancer progressed at a constant rate over the time-horizon at all ages (Engel et al., 2003; Gocgun et al., 2015).

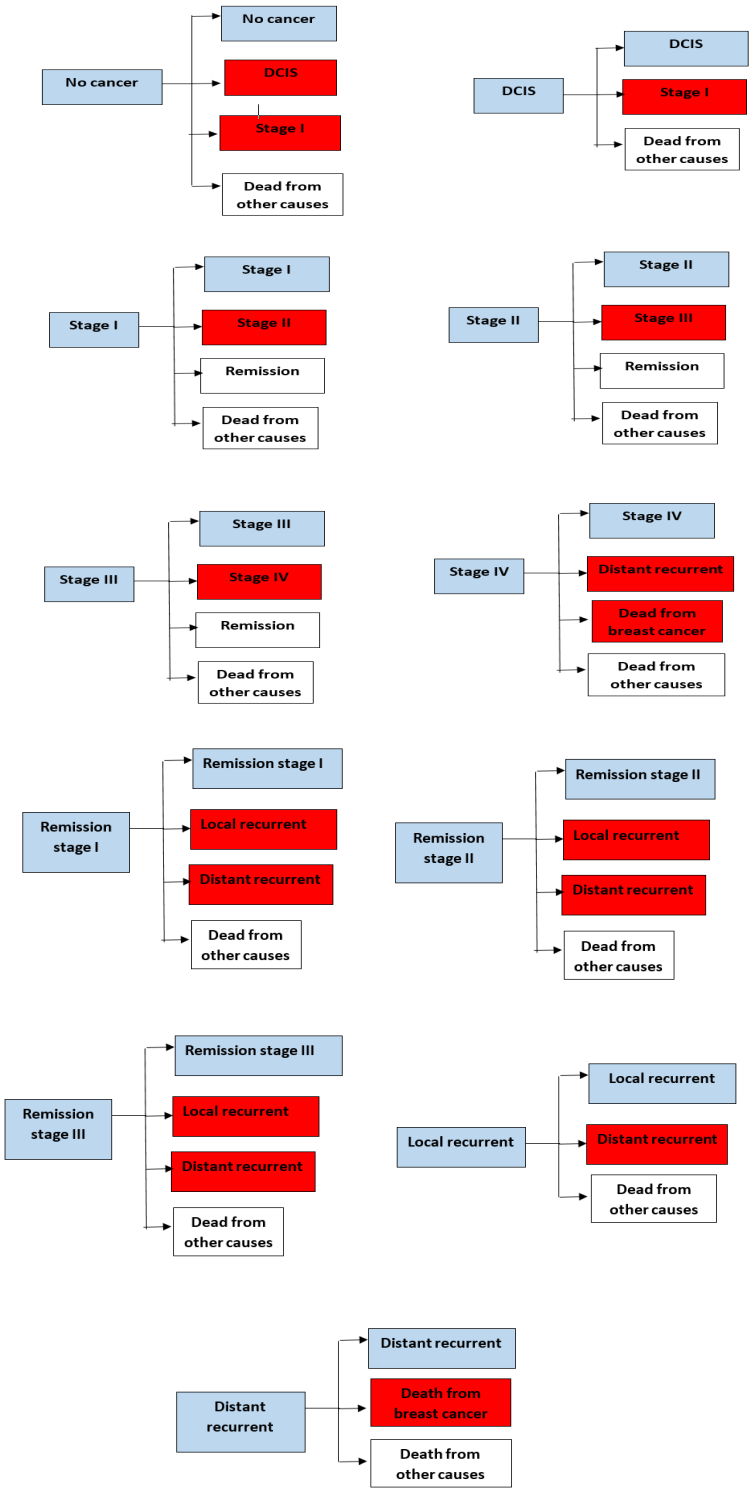

Figure 6. 4 The natural breast cancer progression structure and possible transitional states

The block on the left represents the health states defined in the model structure, and all blocks on the right represent the possible transition in each year. Blue blocks represented sustaining states, which means that the woman remains in the same health state as the previous year. Red blocks represent the progression states, which means the woman progressed to a more severe health state than last year.

6.9.1.2. Cycle lengths

Markov cycle lengths are then assigned to represent the minimum amount of time that any individual will spend in a state before they have the possibility of transition to another state (Gray et al., 2012). A cycle length of 12 months was chosen for the model as a reasonable assumption (Nguyen & Adang, 2018; Sun, Legood, Sadique, et al., 2018; Sun, Sadique, dos-Santos-Silva, Yang, & Legood, 2019; Wong et al., 2007) for the time women spent in a state before the possibility of transition to another state. Markov models usually model the transition to occur at a discrete point in time at either the beginning or end of a cycle, but in reality, the transition may occur at any time within a cycle (Gray et al., 2012). Therefore, the researcher used half-cycle corrections to compensate for the timing of the transition, making the assumption that state transition occurs about halfway through the cycle, hence reflecting the continuous nature of the timing of transitions within a cycle (Gray et al., 2012; Naimark, Bott, & Krahn, 2008).

6.9.1.3. Transition probabilities

The next step is to assign a transition probability to the model. Markov models are distinguished into two distinct types by the transition probabilities that are incorporated into the analysis (Briggs & Sculpher, 1998). Markov chain models use

constant transition probabilities over time. However, these assumptions may be inappropriate when the transition probabilities vary from cycle to cycle or are time dependent (Sonnenberg & Beck, 1993). Markov process models allow transition probabilities to vary over time. The probabilities are assumed to occur with equal probability across all cycles of the model (Briggs & Sculpher, 1998), which is an approach for assuming transition probability in this study. An example of a time-dependent transition probability would be tall-cause probability of death and the risk of developing breast cancer, as both increase with age (Fletcher et al., 1993). The model was populated using transition probability estimates derived from the literature presented in **Chapter 7.**

6.9.1.4. Starting probability

A separate starting probability of the population being modelled (such as in the Markov cohort) was then designated. It is assumed that the proportion of women diagnosed with ductal carcinoma in situ, or stage I, II, III or IV cancer were different, according to each alternative strategy (Groot et al., 2006). This intermediate outcome proportion was synthesized from published studies and then assigned to the model. For those with no cancer or a false-positive cancer result, the assumption is made that women can die from other causes or possibly get cancer at a later point (Tabár, Duffy, Vitak, Chen, & Prevost, 1999).

6.9.1.5. Rewards and the stopping rule

Having an estimate of health costs and utility value, these parameters were incorporated into the model. Costs are attached to individual health states to reflect the cost of a patient's procedure in the given health state for one cycle. The cost component should consider the transition costs. However, the researcher assumed a none-off cost incurred in the model due to data limitation. Utility values attached to

each state reflect the severity of the state. A utility is assigned to each state to represent the relative value of occupying it for one cycle. Attaching weighted quality-of-life on a standard 0–1 scale to the Markov states, generated a quality-adjusted life-years score when summed over all model cycles (Gray et al., 2012). The period that the model should be run was assumed for 80 years because the starting age of the cohort is 40 with an annual cycle length, and the current estimate of the life expectancy (at birth) is 73.6 years for women in Indonesia (for the period 2015–2020). It is assumed that if the model is run for 40 cycles, effectively all the cohort would have reached a dead state.

6.9.1.6. Analysis and evaluation of the Markov model

A cohort simulation was used to evaluate the model. The hypothetical cohort is distributed among the possible states in the model according to the starting probabilities using different proportions of breast cancer stages, then follows the cohort's transition among the states from one cycle to the next, depending on the transition probabilities. To calculate the proportion starting in the next cycle, the cohort's proportion ends in one state multiplied by the relevant transition probabilities attached to that state. The major outputs reported after the Markov analysis are lifetime costs, life expectancy, percentage of the subject in each Markov stage, incremental cost-effectiveness in terms of cost per life-year gained, and costs per quality-adjusted life-year.

6.10. Summary

This chapter has described development of the model structure on an organized screening strategy undertaken based on the stages in constructing, analyzing and evaluating the decision-tree incorporated with Markov models for economic

evaluation. Parameters to populate the model and a. base-case model are presented in **Chapter 7.**

Chapter 7: *Ex-ante* cost-effectiveness analysis for organized screening strategies within the Indonesian healthcare setting

7.1. Overview

In **Chapter 6,** the structure of the decision–analytic model for this study was constructed to initially assess the implementation plan of an organized strategy. This chapter describes the inputs used to populate the model, followed by the results of a base case model. As explored in **Chapter 5 (section 5.8)**, parameters for the participation of the target population and adherence to diagnostic tests were obtained from local data sources. While costs data on early-detection programs at the primary health centre were collected from the program implementers during study consultative processes, costs data on breast cancer treatment were calculated based on patient data billing provided by the National Cancer Center at Dharmais Hospital. However, when reliable data was not available from the local database, information was collected from other sources. The age specific breast cancer incidence and prevalence data for Indonesia were obtained from published country data profiled on the Institute Health Metric Evaluation IHME website. The sensitivity and specificity of the screening test modalities (clinical breast examinations and diagnostic mammography tests) were based on reviewed articles for selected Asian countries (presented in **Chapter 3**). Parameters for intermediate endpoint screening (such as cancer stage distribution), transition probability and utility score were obtained by the researcher from published articles, while selecting comparable country settings. A manuscript currently is in progress to finalize

Popy Yuniar, Suzanne Robinson, Rachael Moorin, Marshall Makate, Richard Norman. ***Establishing* ex-ante *evidence-informed decision-making of organized breast cancer screening in Indonesia toward quality improvement.***

7.2. Epidemiological and clinical data

Evaluating the cost-effectiveness of screening requires an estimation of the average probability of an event occurring in members of the simulated cohort, such as developing breast cancer and being diagnosed with breast abnormality through screening, as well as the stage distribution of incident cases (de Koning et al., 1991; Groot et al., 2006).

7.2.1. Breast cancer prevalence

The proportion of women who have already been diagnosed with breast cancer before screening takes place is determined by prevalence data (Tabár et al., 1999). Once diagnosed, women will generally not be part of any screening program. However, due to the risk of recurrence and the development of second primary breast tumours, women in remission are commonly included in a medical surveillance program (Wojcinski et al., 2011).

Population-based cancer registries can provide the number of most recently diagnosed cases (Zheng, Zeng, Zhang, Chen, & Chen, 2016) but the cancer registration practices in Indonesia are still immature (Soehartati Gondhowiardjo et al., 2020). The baseline rate of breast cancer prevalence by age group was retrieved from the Institute for Health Metrics and Evaluation, IHME, and downloaded from http://ghdx.healthdata.org/gbd-results-tool. Breast cancer prevalence estimates for 2018 and the proportion of woman stratified in five-year age groups are

presented in **Table 7. 1** The data shows that cancer cases are more prevalent among the non-elderly adult group (40–64 years) than in the younger group (<39 years) and elderly group (≥65 years).

Table 7. 1 Breast cancer prevalence in Indonesia, 2018

Age group	Prevalence					
	Number	Upper	Lower	Proportion (per 100,000)	Upper	Lower
20–24	4,989	6,153	4,106	46.9	57.9	38.6
25–29	13,257	16,405	10,670	130.4	161.4	105.0
30–34	25,236	30,741	20,739	250.4	305.0	205.8
35–39	39,102	47,572	32,398	386.0	469.6	319.8
40–44	59,844	73,436	49,823	629.6	772.5	524.1
45–49	67,840	82,263	56,213	807.9	979.6	669.4
50–54	57,083	67,819	47,835	794.7	944.1	665.9
55–59	47,031	55,666	40,100	802.0	949.2	683.8
60–64	37,926	44,384	32,178	851.7	996.8	722.6
65–69	26,294	30,925	22,404	842.0	990.3	717.5
70–74	16,857	20,128	14,227	775.3	925.7	654.3
75–79	10,409	12,774	8,625	712.9	874.9	590.7
80 +	8,133	10,256	6,623	617.0	778.1	590.7

7.2.2. Probability of having a positive clinical breast examination

The probability of Indonesian women aged 25–64 years being cancer-positive at clinical breast examination was 8.1% (Idaiani & Delima, 2018; National Institute of Health Research and Development Ministry of Health Republic of Indonesia, 2016). Clinical diagnosis of breast tumour(s) (being CBE-positive) was examined through the national community-based survey conducted by the Ministry of Health from July to August 2016, representing urban areas in 34 provinces. The survey aimed to obtain information on breast-tumour prevalence, demographic characteristics of respondents with breast tumours, and specific risk factors for breast cancer among

women in Indonesia. A higher prevalence of breast tumours was observed in respondents with a family history of breast cancer (14.6%), ovarian cancer (15.6%), and other cancers (10.7%) than those without any family history of cancer. Furthermore, a family history of first and second-degree cancer was linked with a higher prevalence of breast tumours (13.4 and 13.2%, respectively) than those without (7.8 and 8%, respectively). From 948 women aged 25-64 years old interviewed for this survey, 271 women (6.1 per 1000 or 0.6%, 95% CI 0.5–0.8%) had been diagnosed with breast cancer.

7.2.3. Stage-cancer distribution

Table 7. list plausible data of stage distribution in the presence and absence of extensive breast cancer programs from various studies, including standard treatments, breast-awareness programs, and early case-finding through the screening program.

Table 7. 2 Plausible data of stage distribution in the absence and presence of an extensive screening program

No.	Author	Country/Region	Design study	No. of study subjects	Setting of service delivery	Duration of study/ follow-up	Subject categories	Evidence on stage at diagnosis
1.	(Groot et al., 2006)	Asia	Model simulation	1,279,005	NA	10 years	Extensive population	Stage distribution / Extensive Program (%): Presence / Absence I: 49.00 / 9.40 II: 37.40 / 14.20 III: 8.60 / 58.00 IV: 5.00 / 18.40
2	(Ng et al., 1998)	Singapore	Randomized trial	166 600	Hospital	2 years	1. Women screened 2. Not invited (control) 3. Non-respondents (could not be contacted for screening)	Stage / Screened (%) / Not invited (%) / No response 0: 26 / 6 I: 38 / 20 IIA: 17 / 27 IIB: 14 / 21 IIIA: 1 / 7 IIIB: 1.5 / 3 IV: 1 / 8
								Stage / Screened (%) / Not invited (%) / No response 0: 26 / 6 I: 38 / 20 II: 33 / 48 III: 2 / 18 IV: 1 / 8

								RR for two years screened versus not invited = 1.2; 95% CI = (1.0–1.4)		
3.	(Murillo et al., 2016)	Colombia	Cluster randomized trial	7436 intervention vs 8419 control	Down-staging program;	2008–2012 with two years of follow-up	1. Modified opportunistic (intervention arm) 2. Usual care	Stage 0 I IIA IIB IIIA IIIB IV	opportunistic intervention (%) 14.3 42.9 14.3 14.3 4.8 9.5 0	Usual care control (%) 0 7.7 38.5 38.5 0 15.4 0
								Stage 0 I II IIIA IV	opportunistic intervention (%) 14.3 42.9 28.6 14.2 0	Usual care control (%) 0 7.7 77 15.3 0
4.	(Teh et al., 2015)	Malaysia	Retrospective study Screened detected vs symptomatic breast cancer	2510	Tertiary hospital in an urban setting — screening program	January–December 2010	1. The opportunistic 2. The high risk (targeted) 3. The diagnostic mammogram	Stage 0 I II III IV	Opportunistic and targeted (%) 23.0 30.8 30.8 15.4 0	Diagnostic (%) 2.6 23.4 35.1 18.2 20.7
5.	(Huang et al., 2012)	China	Trial	Organized = 2471 Opportunistic = 557	Community and central hospital	One year of follow-up	Oprganized screening population and opportunistic screening population	Stage I II III IV	Organized (%) 21.4 57.1 21.4 0	Opportunistic (%) 0 36.8 63.2 0

6.	(Miller, 2008)	Egypt	Phase I: Pilot study / non-randomized trial Phase II: cluster randomization	Phase I = 4116 Phase II = 1924	Health centers and community hospitals in the urban area	One year of follow-up	The active screening group The control group (received only health education)	Stage I II III IV	intervention (%) 30 43 20 7	control (%) 8 18 44 30

7.2. Deaths from other causes

The model is, by necessity, a simplified, real-life representation that only includes the clinical outcomes that are directly affected by the intervention. It is also necessary for the model to take into account that people within the cohort can die due to causes other than breast cancer (Chiang, 1991). Other causes of mortality are calculated as all-cause mortality minus breast cancer mortality (**Table 7. 2**).

The most recent data (as of 2018) on the number of deaths due to breast cancer and other causes of mortality by age group (at five-year intervals) were obtained from the Institute for Health Metrics and Evaluation, IHME, and downloaded from http://ghdx.healthdata.org/gbd-results-tool.

Table 7. 2 Breast cancer, other-cause and all-cause mortalities by five-year age group for Indonesian women, 2018

Age group	All-cause mortality (per 100,000 person-year)	Breast cancer mortality (per 100,000 person-year)	Other-cause mortality (per 100,000 person-year)[a]
25–	85.45	4.98	80.47
30–	113.94	11.86	102.08
35–	170.04	20.24	149.80
40–	264.41	33.10	231.00
45–	426.13	44.90	381.23
50–	693.96	50.36	643.60
55–	965.55	53.25	912.30
60–	1505.76	56.45	1449.31
65–	2392.16	59.56	2332.60
70–	3985.12	64.53	3920.59

Age group	All-cause mortality (per 100,000 person-year)	Breast cancer mortality (per 100,000 person-year)	Other-cause mortality (per 100,000 person-year)[a]
75–	6577.91	73.82	6504.09
80+	14063.78	90.07	13973.71

[a] The other cause mortality was defined as death from all the other causes except for breast cancer and was calculated as other cause mortality = all-cause mortality of the national average — breast cancer mortality

7.3. Effectiveness of screening

Clinical breast examination (CBE) is widely recommended and practised as a breast cancer screening modality in limited-resourced countries (Bobo, Lee, & Thames, 2000; Panieri, 2012; Cheng Har Yip & Anderson, 2007). However, the effectiveness of CBE is dependent on its accuracy (such as sensitivity and specificity) (Barton, Harris, & Fletcher, 1999). Sensitivity refers to the probability that a patient tests positive if they have the disease (Bovbjerg, 2020; Maxim, Niebo, & Utell, 2014). The result of sensitivity measure reflects the test's ability to correctly identify all people with a condition of interest by those people testing positive on the test (Trevethan, 2017). In contrast, specificity is the probability that a patient tests negative if they do not have the disease (Bovbjerg, 2020; Trevethan, 2017). In probability notation, sensitivity is written as follows:

$$Sn = P(Test - positive \mid Disease - positive) = True - positive \div (True - positive + \text{False} - \text{negative})$$

In probability notation, specificity is written as follows:

$$Sn = P(Test - negative \mid Disease - negative) = True - negative \div (True - negative + \text{False} - \text{positive})$$

The accuracy of CBE in this study was determined by both patient and examiner factors such as the duration of the examination, the use of correct CBE technique

(such as a systematic search pattern, thoroughness, varying palpation, three fingers, finger pads and circular motion), examiner experience, age, breast characteristics and cancer characteristics (Barton et al., 1999). The sensitivity and specificity results of CBE are derived from published articles (Barton et al., 1999; Bobo, Lee, & Thames, 2000; Elmore, Armstrong, Lehman, & Fletcher, 2005; Huang et al., 2012; Oestreicher, White, Lehman, Mandelson, & et al., 2002; Trevethan, 2017) and presented in **Table 7. 3.**

Table 7. 3. Studies on the performance of clinical breast examination

Population (Reference)	Participant and setting	Ages	Screening modalities	Sensitivity (%)	Specificity (%)
Pooled analysis of clinical trials (Barton et al., 1999)	- Participants in RCT (health insurance plan) (Shapiro, 1997), - Canadian National Breast Screening Study (NBBS1) - NBBS 2	40–64 40–49 50–59	- Clinical breast examination and mammography - CBE only; CBE and MMG - CBE only; CBE and MMG	54.1 (95% CI = 48.3 to 59.8)	94.0
U.S. National Breast and Cervical Cancer Early Detection Program (Bobo et al., 2000)	Low-income women enrolled in the National Breast and Cervical Early Detection Program	≥40	CBE and MMG	36.1	96.2
(Huang et al., 2012)	- Organized screening population recruited from the Qing yang community - Opportunistic screening population — outpatients recruited from Chengdu Women's and Children's Central Hospital	≥25	- CBE alone - CBE followed by MMG when indicated - CBE followed by ultrasonography when indicated	- 66.7 (95% CI = 48.2 to 82.0) - 69.7 (95% CI = 51.3 to 84.4) - 60.6 (95% CI = 42.1 to 77.1)	- 99.2 (95% CI = 98.8 to 99.5) - 99.4 (95% CI = 99.1 to 99.7) - 99.7 (95% CI = 99.4 to 99.8)

Mammography as a diagnostic test is regarded as providing definitive information about the presence or absence of breast cancer (Trevethan, 2017). Recent studies have shown that the sensitivity of mammography increases with age, whereas specificity varies little with age (IARC, 2002; Zeeshan, Salam, Khalid, Alam, & Sayani, 2018). The sensitivity of mammography is predominantly dependent on breast-tissue density; a denser breast density is common among premenopausal women than postmenopausal women, which reduces the ability of the technology to detect lesions if they exist (IARC, 2002; Medical Advisory, 2007; Ray, Price, & Joe, 2017). The model inputs assumed that the sensitivity and specificity of diagnostic mammography were similar to mammography screening. The sensitivity and specificity of mammography populate in the model was derived from a study of long-term effectiveness and cost-effectiveness of breast cancer screening in the Austrian healthcare setting compared opportunistic screening and an organized breast cancer screening program (Schiller-Fruehwirth et al., 2017) **(Table 7. 4.** and **Table 7. 5).** Schiller-Fruehwirth et al. incorporated lower age-specific sensitivity values for opportunistic screening compared to organized screening settings due in part to low technical quality assurance, the absence of double-reading and no mandatory training. This assumption is considered reasonable in Indonesia setting.

Table 7. 4. Sensitivity and specificity of mammography in organized screening

Age	Sensitivity	95% CI (Sensitivity)	Specificity	95% CI (Specificity)
40–49	84.7%	0.725; 0,924	93.9%	0.934; 0.9435
50–54	87.2%	0.8342; 0.9054	97.5%	0.9738; 0.976
55–59	92.9%	0.9071; 0.9473	97.7%	0.976; 0.9777
60–64	91.7%	0.8914; 0.9389	98.0%	0.9789; 0.9808
65–69	91.8%	0.8878; 0.9416	98.1%	0.9799; 0.9819
70+	91.2%	0.867; 0,947	93.4%	0.931; 0.937

CI = Confidence interval

Table 7. 5. Sensitivity and specificity of mammography in opportunistic screening

Age	Sensitivity	95% CI (Sensitivity)	Specificity	95% CI (Specificity)
40–49	71.9%	0.6933; 0.7437	89.10%	0.8902; 0.8919
50–54	76%	0.7414; 0.778	89.60%	0.895; 0.8965
55–59	80.0%	0.71855; 0.86175	90.0%	0.897; 0.903
60–64	83.6%	0.78198; 0.88029	90.3%	0.9006; 0.9062
65–69	86.9%	0.81061; 0.90958	90.9%	0.9063; 0.9125
70+	83.1%	0.76546; 0.88648	91.5%	0.9121; 0.9188

CI = Confidence interval

7.4. Participation in the screening program

The effectiveness of the screening program is judged by the outcome of the program and its impact on public health as well as the organization, implementation, execution and acceptability of the program (Perry et al., 2008). A population's acceptance of a screening program is reflected by the level of participation (Jacobsen & von Euler-Chelpin, 2012). Additionally, women who participated in an organized breast cancer screening had a 60% lower risk of dying from breast cancer within 10 years after diagnosis compared to the non-participant (Tabár et al., 2019).

The input parameters indicated that the participation of women younger than 50 years of age in organized screening was assumed to be 62.5% per year. This figure was based on the attendance rate of an organized screening program for women aged 45 to 69 years in the state of Tyrol, Austria (Schiller-Fruehwirth et al., 2017), which was similar to the response rate of women aged 26 to 64 years old attending clinical breast examination in a breast-tumour prevalence survey conducted across 36 urban areas in Indonesia (62.5%) (National Institute of Health Research and Development Ministry of Health Republic of Indonesia, 2016). The organization's proactive approach before the survey, such as sending invitations and reminders to

respondents was the hypothetical factor for a high response rate of the eligible population to screening, but in practice several studies reported the opposite – a limited screening coverage (Kim et al., 2013; Mardela et al., 2017).

The probabilities of attendance in an opportunistic screening context were derived from monthly report data on CBE in 44 primary health centres (known as PUSKESMAS) in five sub-areas of Jakarta province **(Table 7. 6).** To simulate the opportunistic screening arm, it was then assumed that 40 per cent of women get one screen in their lifetime at the age of 40.

Table 7. 6. Percentage of age-specific attendance of the opportunistic screening population of the clinical breast examination program (SADANIS) in Jakarta province, 2017

Age group	No.	%
25–34	7255	33.1
35–44	8704	39.8
45–54	4618	21.1
55–64	1315	6.0

Source: Routine report of SADANIS — Jakarta Provincial Health Office, 2017

7.5. Utility estimation of health states

There were numerous studies investigating the utility values associated with a range of breast cancer health states such as screening related researches adverse events, treatment and metastatic breast cancer (Bonomi et al., 2008; Bromley et al., 2019; Chou, Chiang, & Ko, 2020; Yang et al., 2020). However, they show a considerable variation in the results. For example, values for metastatic breast cancer ranged from –0.52 to 0.882 (Peasgood, Ward, & Brazier, 2010), which explained two causes. Firstly, an individual might experience diverse health states related to different treatment regimens, different responses to treatment and different possible

side-effects of treatment. Secondly, different methods for generating utility scores may produce different values for the same health state (Brazier et al., 2019; Weinstein et al., 2009).

Health utilities in breast cancer states have been shown to vary significantly depending on valuation method, health states, the provider of the preference weight (for example, patients with health condition of interest versus the general population) and location (Brazier et al., 2019; Peasgood et al., 2010). In terms of valuation methods on health-state utility values, all 49 published papers synthesized by Peasgood et al., showed that the visual analogue scale was the most frequently used method to estimate the utility of *early* breast cancer followed by the standard gamble, the EuroQol (EQ-5D) and the time trade-off. Meanwhile, the most common method to estimate the utility of metastatic breast cancer health state was SG, followed by EQ-5D, VAS and time trade-off (Brazier et al., 2019; Peasgood et al., 2010).

7.5.1. Literature search of health-state utility values

The utility parameters for this thesis were determined via literature search for conditions related to the 10 categories of health-state utility values of breast cancer: 1) ductal carcinoma in situ; 2) invasive breast cancer stage I; 3) invasive breast cancer stage II; 4) invasive breast cancer stage III; 5) invasive breast cancer stage IV; 6) remission stage I; 7) remission stage II; 8) remission stage III; 9) local recurrent and 10) distant recurrent. In addition to the appropriateness of reviewing the data of HSUVs, the location of studies was specified for Asian countries which represent similar study populations to the modelled population (Brazier et al., 2019).

The utility values were searched in two types of studies. The first is the economic modelling studies which used the utility weights from secondary sources. These included the reviewed studies in Chapter 2. Secondly, the Centre for the Evaluation of Value and Risk (CEVR) health cost-effectiveness analysis registry was searched using the keyword breast cancer and the instrument type utilities (https://cevr.tuftsmedicalcenter.org/databases/cea-registry). Due to limited access to the CEVR database, only 100 articles were able to be retrieved. Four out of 100 articles referred to the application of utility weights in an economic model located in Asia (Diaby et al., 2020; L. Sun, Legood, Sadique, et al., 2018; L. Yang, Wang, Cheng, Wang, & Lu, 2018; Ye, Lu, Yang, & Wu, 2018). **Table 7. 7** summarizes the findings related to the use of utility weight in economic modelling studies in breast cancer treatments.

Table 7. 7. Utility weights used in modelling studies and their sources

Authors	Country setting	Source of utilities value	Sample for utility elicitation	Method/ instrument for utility elicitation	Utility value
(Wong et al., 2007)	Hong Kong	(Mandelblatt et al., 2004)	*African American women*	Not clear	- DCIS = 0.95 - Stage I = 0.9 - Stage II = 0.8 - Stage III = 0.7 - Stage IV = 0.3
(Haghighat et al., 2016)	Iran	(Wong et al., 2007)	Not clear	Not clear	- DCIS = 0.95 - Stage I = 0.9 - Stage II = 0.8 - Stage III = 0.7 Stage IV = 0.3

Authors	Country setting	Source of utilities value	Sample for utility elicitation	Method/ instrument for utility elicitation	Utility value
(Yang et al., 2018)	China	(Wong et al., 2007)	Not clear	Not clear	- DCIS = 0.95 - Stage I = 0.9 - Stage II = 0.8 - Stage III = 0.7 - Stage IV = 0.3
(Huang, Li, Torres-Rueda, & Li, 2020; Shi et al., 2016; Sun et al., 2018)	China	(Shi et al., 2016)	- General population (n=11 699) - Individuals who had attended single cancer screening (n=11 805) - Individual who attended multiple screening (n=6838) - Patients with precancerous lesions (n=1942) - Patients with cancer (n=14 110)	Q-5D (EuroQol 5-dimensions) SF-12 (12-item Short-form health survey A cancer-specific instrument, FACTs (functional assessment of cancer therapy)	- Stage I = 0.79 (0.77–0.80) - Stage II = 0.79 (0.78–0.80) - Stage III = 0.77 (0.76–0.79) - Stage IV = 0.69 (0.65–0.72)
(Özmen et al., 2017b)	Turkey	(Milne et al., 2006)	- Women aged 25-69 years, randomly selected from the New Zealand general public	- Time trade-off and visual analogue scale valuations - UK EQ-5D social tariffs.	- With recurrent = 0.60 - Without recurrent = 0.78
(Diaby et al., 2020)	Taiwan	(Lloyd, Nafees, Narewska, Dewilde, & Watkins, 2006)	- Expert interviews - Members of the general public of England and Wales	- EQ-5D - Visual analogue scale and the standard gamble	- Metastatic cancer progression = 0.248 - Progression-free breast cancer under treatment = 0.786

Authors	Country setting	Source of utilities value	Sample for utility elicitation	Method/ instrument for utility elicitation	Utility value
(Ye, Lu, Yang, & Wu, 2018)	China	(Sorensen, Brown, Benedict, Flood, & Revicki, 2004)	- Women aged 55–70 years in the United Kingdom and the United States with a history of stage I or II operable early breast cancer and experience with adjuvant hormonal therapy	Chained SG	- Disease-free, no adverse event = 0.965 - Breast cancer recurrence (local/regional = 0.766 - Breast cancer recurrence (Distal) = 0.642

The authors' transparency on how they derived or modified their utility values in the first type of studies (Haghighat et al., 2016b; Wong et al., 2007; Yang et al., 2018) was occasionally lacking, making it difficult to verify or understand the value (Brazier et al., 2019). Therefore, the researcher conducted a further search for the second type of study where researchers reported on the generation of utility weights. Google Scholar and the SCOPUS search engine were utilized using the keyword 'health-state utilities' and 'breast cancer' and specified at least using one of standardized assessment methods (such as SG, time trade-off, VAS, EQ-5D) specified in Asian countries**.** The summary of four studies identified on the elicitation of utility weight in breast cancer health states is provided in **Table 7. 8.**

Table 7. 8. Key features of primary studies to generate utility weights

Authors	Country setting	Source of utilities health state value	Sample for utility elicitation	Method/ instrument for utility elicitation	Utility value
(Chou, Chiang, & Ko, 2020)	Taiwan	The expert panel (medical oncologist and clinical pharmacists)	Adult breast cancer patients (≥20 years old)	- Time trade-off - Visual analogue scale	- Progression-free metastatic breast cancer (MBC) VAS = 0.32 (SD=0.29); TTO = 0.43 (SD = 0.45) - Progression MBC VAS = 0.16 (SD=0.24); TTO = 0.22 (SD = 0.43) - Palliative MBC VAS = 0.15 (SD=0.25); TTO = 0.04 (SD = 0.47)

Authors	Country setting	Source of utilities health state value	Sample for utility elicitation	Method/ instrument for utility elicitation	Utility value
(Yang et al., 2020)	China	Mapping the functional assessment of cancer therapy — breast (FACT-B) to the five-level EuroQoL group's five-dimension questionnaire (EQ-5D-5L) utility index in a multi-ethnic Asian population	Adult breast cancer patient age≥18	The EQ-5D-5L The EQ-VAS Non preferred disease-specific FACT B	- Without cancer recurrent and metastasis = 0.81 (SD = 0.23) - With cancer recurrence within a year = 0.90 (SD = 0.12) - With primary and recurrent breast cancer for the second year and above = 0.78 (SD = 0.31) - Metastatic = 0.74 (SD = 0.27)

(Kim et al., 2017)	Korea	- The 5th Korean guideline for the management of breast cancer - American Joint Committee on Cancer (AJC 7th)	Adult aged ≥19 years	- Standard gamble - VAS	- Non-invasive breast cancer with mastectomy (stage 0) VAS = 0.68 (SD=0.199); SG 0.804 (SD=0.26) - Invasive breast cancer with surgery, radiation therapy and / or chemotherapy (stage I, II) SG = 0.731 (SD = 0.255); VAS = 0.579 (0.20) - Locally advance breast cancer with radical mastectomy and radiation therapy (IIIA, IIIIB) SG = 0.610 (SD 0.261); VAS = 0.435 (SD= 0.178) - Inoperable locally advance breast cancer (stage IIIC) SG=

Authors	Country setting	Source of utilities health state value	Sample for utility elicitation	Method/ instrument for utility elicitation	Utility value
					0.587 (SD = 0.259); VAS = 0.415 (SD = 0.173) - Loco-regional recurrent breast cancer SG = 0.496 (SD = 0.260); 0.333 (SD = 0.170) - Metastatic breast cancer IV SG = 0.352 (SD = 0.275); VAS = 0.170 (SD = 0.22)

(Shih, Chan, Xie, & Ko, 2012)	Singapore	The expert panel (oncologists and oncology nurses)	Oncology nurses age ≥21 years old and two years experience in oncology	VAS SG	- Current health (VAS=0.941; SG = 0.973) - No recurrence with no side effect (VAS = 0.86; SG = 0.77) - No recurrence with common side effect (VAS = 0.730; SG = 0.588) - Loco-regional recurrence with no side effects (VAS = 0.491; SG = 0.473) - Distant recurrence with no side effects (VAS = 0.40; SG = 0.371) - Loco-regional with side effects (VAS = 0.473; SG = 0.336) - Distant recurrent with chemotherapy side effects (VAS = 0.365; SG = 0.356) - Distant recurrent with

Authors	Country setting	Source of utilities health state value	Sample for utility elicitation	Method/ instrument for utility elicitation	Utility value
					hormonal side effect (VAS = 0.370; SG = 0.299)

As noted, the National Institute for Health and Care Excellence (NICE) reference case specified that health-state utility values should be derived from standardized and validated generic instruments that use a choice-based method (either TTO or SG) and take preferences from the general public (Brazier et al., 2019; Manchanda et al., 2018; Peasgood et al., 2010). Therefore, the utility parameters for the base case were derived from recent primary studies literature to generate utility weight or referred to modelling studies that have clear transparency about the source of the utility value (Sun et al., 2018). The 10 categories of breast cancer health states for the model structure were adopted from Sun et al. (2018) and others (Nguyen & Adang, 2018) are non-invasive/DCIS = 0.80, invasive breast cancer stage I = 0·79; invasive breast cancer stage II = 0.78; invasive breast cancer stage III = 0.76; invasive breast cancer stage IV = 0.69; remission stage I = 0.78; remission stage II = 0.78; remission stage III = 0.73; local recurrent = 0.496; and distant recurrent = 0.356.

7.6. Costs

The primary analysis for cost was carried out from the perspective of healthcare providers. The methodology used for the cost input was the bottom-up or ingredients-based approach, whereby each resource that required the cost of the intervention program and an individual was identified and valued. This approach was adopted from the Choosing Interventions that are Cost-Effective (CHOICE) project — the World Health Organization (WHO-CHOICE CEA) (Bertram et al., 2017; Edejer, 2003). The CHOICE project is a WHO initiative developed in 1998 to provide policymakers with evidence for deciding on interventions and programs that maximize health using available resources (Baltussen et al., 2004). Relevant costs in the analysis included an estimation of resource utilization linked to activities aimed

at supporting the quality of delivery of breast cancer screening (Bertram et al., 2017; Johns & Baltussen, 2004). **Table 7. 9** presents the resource use based on the screening strategies characteristics. The scope of program costs and cost categories required for the SADANIS program are illustrated in **Table 7. 10.** Cost data were collected in Indonesian rupiah (IDR) and adjusted for inflation using a domestic price index inflator. The adjusted price year 2016 was then converted to US dollars to reflect the 2018 Purchasing Power Parities value (https://eppi.ioe.ac.uk/costconversion)

Table 7. 9. Resource use based on screening delivery strategies

Area of work	Applicable screening strategy
Health promotion on breast cancer awareness	All screening scenarios
Invitation letter to SADANIS	Organized screening
Reminder for SADANIS invitation	Organized screening
Patient navigation for follow-up diagnostic test	Organized screening
Clinical breast examination in routine consultation	Opportunistic screening
Mammography screening	Opportunistic screening
CBE	All screening scenarios
CBE result interpretation	All screening scenarios
Diagnostic mammogram outside the screening program	Opportunistic screening
Diagnostic mammogram at the referral hospital	Organized screening

Table 7. 10. Scope of program support costs

Area of work	Cost item
Cost directly related to individual intervention delivery (patient cost)	Screening tests, diagnostic tests, and health-facility visit unit costs.
Costs related to the delivery of a health program	- Personnel - Materials and supplies - Media - Transport - Equipment - Maintenance - Utilities

7.6.1. Cost of screening

The estimated mean cost of one-off organized clinical breast-examination screening includes the incremental cost associated with an invitation, CBE and diagnostic tests. The screening program for patient navigation may also generate additional costs for referral diagnostic tests or additional tests for further testing for risk assessment of breast cancer. However, as these costs are not directly associated with the screening program, they are not included in the primary analysis. The impact of having the cost of patient navigation is examined in the sensitivity analysis. The data representing costs of organized screening characteristics were estimated from the national prevalence survey on breast tumours in 2016 and mobile mammography screening.

The costs of opportunistic screening were calculated based on the costs of activities incurred at the existing program required to carry out a CBE procedure at a primary healthcare facility. The information related to the costs of organized and opportunistic screening strategies was obtained from the semi-structured in-depth interview with key stakeholders (see **Chapter 5). Table 7. 11** shows the estimated program cost paid in 2017 for organized and opportunistic screening strategies with an adjustment to reflect 2018 consumer price index. The cost of organized screening program obtained a prevalence survey of breast tumour – from the Ministry of Health in 2016 with a total of 43 948 respondents. The researcher collected the cost of the opportunistic screening program from implementing the SADANIS program in Jakarta Province in 2017. Referring to **Table 5. 8.** , a total of 21 892 target population were engaged in the SADANIS program in 2017.

Table 7. 11. Program costs (in US$) and the cost distribution profile of organized and opportunistic screening strategies for breast cancer in primary healthcare facilities in Jakarta, 2018

Type of cost	Organized screening	%	Opportunistic screening	%
Direct cost				
Human resources	19 009.45	47.77	12,368.58	49.99
Medical equipment	12 301.17	27.44	6,675.66	26.98
Invitation and health promotion	2 547.40	5.80	1,326.78	5.36
Maintenance	1 054.45	2.36	1,054.45	4.26
Stationary	675.33	1.51	215.19	0.87
Subtotal direct costs	**35 587.80**	**84.88**	**21,640.66**	**87.46**
Indirect costs				
CBE training	4 398.14	9.86	2,160.21	8.73
Patient navigation	1 002.94	0.22	NA	NA
Household visit	1 297.78	0.22	NA	NA
Recording and reporting	98.87	2.19	98.87	0.41
Monitoring and evaluation	77.41	0.17	NA	NA
Subtotal indirect costs	**6 875.14**	**12.66**	**2,259.08**	**9.14**

The nature of the screening program potentially indicates four possible outcomes: true-positive, true-negative, false-positive and false-negative, which incur different costs according to the intervention.

True-positive on the screening test

Women who tested true-positive on the screening would need to undergo follow-up interventions, such as diagnostic mammography and preoperative verification for further therapeutic decisions (Pisano et al., 2001).

Accordingly, the potentially incurred cost to women with true-positive screening tests included the costs of a screening test interpreted by a general practitioner plus a diagnostic test assumed to be interpreted by a radiologist, and a biopsy result interpreted by the patient's oncologist. Women with the first-degree or second-

degree family history of breast cancer or any other type of cancer are charged an additional cost for blood tests due to risk assessments for the breast cancer gene-1 (BRCA1) and breast cancer gene-2 (BRCA2) gene mutations (Pruthi, Gostout, & Lindor, 2010).

True-negative on the screening test

Women with a true-negative result for the screening test would need follow-up interventions. In an organized screening strategy, this result was translated to incremental costs for follow-up monitoring to detect potential cancer development. In the current practice (opportunistic screening), no incremental costs nor further benefits were received by these women.

False-positive on the screening test

Women with an initial false-positive result on the screening test were assumed to later receive a diagnostic mammography test, fine-needle aspiration biopsy (FNAB), or core-needle biopsy (CNB) (Łukasiewicz et al., 2017; Yii, Read, Tan, Ng, & Bennett, 2018), which then correctly identified that they did have breast cancer (Ibikunle, Omotayo, & Ariyibi, 2017). All these individuals were incurred the cost of screening tests plus the cost of mammography or ultrasonography diagnostic and biopsy tests interpreted by a radiologist. It should be noted that some false-positives may be diagnosed when people have benign tumours (e.g., microcalcification) (Alsheh Ali, Czene, Hall, & Humphreys, 2019; Nalawade, 2009) and the corresponding people may receive some benefits from an organized screening program. However, corresponding benign tumours were not captured in the model for this study.

False-negative on the screening test

False-negatives on the screening test mean the women may have breast cancer but are not given reference for further diagnostic mammography tests. This includes women with a non-palpable condition at the time of the screening test (Skinner, Silberman, Sposto, & Silverstein, 2001). Therefore, they have incurred the cost of the screening test but without the future incremental costs and benefits that could have come from the test if it had been accurate.

7.6.2. Cost of diagnostic test

The assumed two diagnostic techniques for the preoperative procedure were fine-needle aspiration biopsy or core-needle biopsy (Łukasiewicz et al., 2017; Yii et al., 2018). In Indonesia, FNAB might be more common than CNB due to its lower cost and wider availability (Łukasiewicz et al., 2017). The use of CNB in corresponding breast disease was performed for Breast Imaging–Reporting and Data System score 4 and 5 focal lesions (Łukasiewicz et al., 2017).

7.6.2. Costs of breast cancer treatment and follow-up

The average cost per patient was estimated as a weighted average based on the standard of care for breast cancer patients. All patients' data for breast cancer cases diagnosed between January 2012 and December 2013 were generated from patients' billing, accessed through the hospital information system of the National Cancer Center at Dharmais Hospital.

A set of basic breast cancer treatments were confined to consider the standard care of breast cancer patients referred under the National Comprehensive Cancer Network (NCCN) treatment guideline (Gradishar et al., 2020; Groot et al., 2006)

(Table 7. 12). This treatment options might vary with the patient's stage of disease (based on tumour size, involvement of surrounding tissue and the number of affected axillary lymph nodes) and pathology.

Table 7. 12 Basic interventions for breast cancer diagnosis and treatment

	Type of intervention
Stage I treatment	Lumpectomy with axillary dissection supplemented with external radiotherapy to also receive endocrine therapy.
Stage II treatment	Lumpectomy with axillary dissection supplemented with external radiotherapy to the breast. Eligible patients also receive endocrine therapy.
Stage III treatment	Neoadjuvant chemotherapy followed by mastectomy with axillary dissection supplemented with adjuvant chemotherapy. External radiotherapy to the breast is also administered and eligible patients receive endocrine therapy.
Stage IV treatment	Systematic chemotherapy, supplemented with endocrine therapy for eligible patients. In this group of patients, these therapies are palliative.
Extensive program	Treatment of all stages as described above, plus a breast-awareness program and early case-finding through the screening program.

For each breast cancer case, information concerning direct medical costs attributable to breast cancer treatment was obtained according to the pattern of the treatment. The use of a resources pattern at the patient level for breast cancer treatment is shown in **Table 7. 13** However, it is worth noting that a specific phase-based description of breast cancer treatment (such as a follow-up phase 13–24 months after diagnosis) was not available to populate the model due to the limited capacity of the database to filter the patient's historical data. Therefore, the cost estimation extracted assumed only for the 0 to 12 months after diagnosis.
In addition, a study by Blumen et al. showed an estimation of the total cost of 13 to 24 months of resource use per diagnosed patient would be 20 per cent lower than the total costs of initial treatment.

Table 7. 13 Resource use for breast cancer treatment

Cancer stage	Category of resource	Average 0 to 12-month cost, by resource per diagnosed patient	
		Average cost, US$	First 12-month total, %
I	Breast cancer surgery	1 968.01	37.7
	Radio therapy	1 049.80	20.1
	Pharmacy (chemotherapy, central surgery, inpatient and outpatient)	792.02	15.2
	Clinical pathology	461.25	8.8
	Inpatient	324.42	6.2
	Radio diagnostic and MRI	275.44	5.3
	Outpatient	133.08	2.6
	Integrated diagnostic unit	82.35	1.6
	One day care	82.13	1.6
	Medical rehabilitation	47.81	0.9
Total		**5 216.31**	
II	Breast cancer surgery	2 056.26	34.7
	Pharmacy (chemotherapy, central surgery, inpatient and outpatient)	1 062.07	17.9
	Radio therapy	863.60	14.6
	Inpatient	435.27	7.3
	Clinical pathology	412.75	7.0
	Radio diagnostic and MRI	317.16	5.3
	Outpatient	186.75	3.1
	One day care	123.54	2.1
	Integrated diagnostic unit	66.40	1.1
	Medical rehabilitation	64.09	1.1
Total		**5 932.56**	
III	Breast cancer surgery	2 642.30	27.1
	Pharmacy (chemotherapy, central surgery, inpatient and outpatient)	2 461.51	25.2
	Radio therapy	2 447.80	25.1
	Inpatient	636.85	6.5
	Clinical pathology	524.51	5.4
	Outpatient	286.71	2.9
	Radio diagnostic and MRI	287.31	2.9
	Integrated diagnostic unit	246.80	2.5
	One day care	134.40	1.4
	Medical rehabilitation	86.26	0.9
Total		**9 754.46**	
IV	Pharmacy (chemotherapy, central surgery, inpatient and outpatient)	2 434.77	27.6
	Radio therapy	2 141.77	24.3
	Breast cancer surgery	2 028.69	23.0
	Inpatient	777.84	8.8
	Clinical pathology	523.09	5.9
	Radio diagnostic and MRI	348.96	4.0
	Outpatient	231.57	2.6
	Integrated diagnostic unit	201.71	2.3
	One day care	87.14	1.0
	Medical rehabilitation	39.07	0.4
Total		**8 814.76**	

To detect disease recurrence at its earliest stage, medical surveillance is conducted after the primary treatment of breast cancer that includes patient history and physical examination, complete blood cell counts, comprehensive blood chemistries, tumour marker tests, mammography and chest X-rays (Emens & Davidson, 2003). Data tracking resources for follow-up patients in remission or people who experienced a relapse of the original breast cancer (recurrence) were difficult to collect due to the unavailability of patient-level linkage data to trace or differentiate patient events.
A study by Karnon et al.,(2007) estimated healthcare costs for treating breast cancer recurrent events from United Kingdom–based patient-level analysis. Karnon et al., highlighted the aggregate five-year costs for patients' recurrent events, with attached resource associated with chemotherapy, hormonal therapy, and the average number of inpatient days. However, this produced relatively high estimates of treatment costs for the Indonesian setting because the standard costs were diferrent.

7.7. Transition probability

The transition probability of breast cancer progression has been derived from the literature. It was assumed that the transition probability between health states was not age specific as the number of involved lymph nodes and tumour size identified as significant contributing factors in improving the prognosis of breast cancer (Moons et al., 2009). Meanwhile, the likelihood of breast cancer incidence as well as the probability of all-cause mortality was time dependent because both risks increase with age (Fletcher et al., 1993; Tabar et al., 2002).

Table 7. 14. Summary of transition probabilities

Branch	Index	Transition probabilities	Baseline value	Range in sensitivity analysis	Remarks	Source
No breast cancer	1	Sustaining in no breast cancer**				
	2	Annual progression probability from no breast cancer to ductal carcinoma in situ	Incidence rate = 8.82	8.45–9.21	Observational cohort study England	(Mannu et al., 2020)
			RR = 2.51	2.14–2.93		(Castells et al., 2015)
			RR = 4.56	2.06–10.7	From patients proliferative benign with atypia	(Dyrstad, Yan, Fowler, & Colditz, 2015)
			RR = 3.58	2.61–4.91	From patients with proliferative benign without atypia	(Dyrstad et al., 2015)
			0.000001		Age 40–44	(Huang et al., 2020)
DCIS	3	Sustaining in DCIS**			Number of years DCIS patients remain at elevated risk for subsequent invasive cancer = 10 years	(Wong et al., 2007)
	4	Annual progression probability from DCIS to stage I	Relative risk (RR) = 2.02		Surveillance program, National Cancer Institute	(Sun et al., 2018; Wong et al., 2007)
			Cumulative incidence 2.4%	1.7–3.4%	A population-based study using a cancer registry. Follow-up year, five years.	(Habel et al., 1997)

Branch	Index	Transition probabilities	Baseline value	Range in sensitivity analysis	Remarks	Source
			Cumulative incidence 6.1%	4.4–8.6%	Population-based study using a cancer registry. Follow-up year, 10 years.	(Habel et al., 1997)
			Risk of developing subsequent ipsilateral invasive BC	0.69	Patient DCIS was treated with wild local excision. Follow-up 23 years.	(Cheung, Booth, Kearins, & Dodwell, 2014)
			Risk of developing subsequent ipsilateral invasive BC	0.22	Patient DCIS treated with mastectomy.	(Cheung et al., 2014)
			0.0268		Age 40–44	(Huang et al., 2020)
Cancer stage I	5	Sustaining in cancer stage I**				
	6	Annual progression probability from stage I to remission stage I	0.15		Pathological complete remission; clinical tumour stage T1; nine years follow-up	(Rocca et al., 2008)
			0.17		Pathological complete remission; clinical nodal stage 0; nine years follow-up	(Rocca et al., 2008)
	7	Annual progression probability from stage I to stage II	0.790		Age 40–44	(Huang et al., 2020)
			0.06			(Tsokos & Oğuztöreli, 1987) in(Sun et al., 2018)
Remission stage I	8	Sustaining in remission stage I**				

Branch	Index	Transition probabilities	Baseline value	Range in sensitivity analysis	Remarks	Source
	9	Annual progression probability from remission stage I to local recurrent	0.01		Age 45–49	(Gocgun et al., 2015) in (Hoang Lan, Laohasiriwong, Stewart, Tung, & Coyte, 2013)
			The cumulative incidence of 35%		In the group treated by lumpectomy alone	(Fisher et al., 1995)
			The cumulative incidence of 10%		In the group treated by lumpectomy and breast irradiation	
			The cumulative incidence of 32%		In node-negative patients treated by lumpectomy alone	
			The cumulative incidence of 12%		In node-negative patients treated by lumpectomy and breast irradiation	
			Recurrence rate = 1.6%		Radiation after conserving surgery; 62 months follow up	(Notani, Uchida, & Kitagaki, 2007)
	10	Annual progression probability from remission stage I to distance recurrent	0.000016		Age 45–49	(Nguyen et al., 2013)
Stage II	11	Sustaining in stage II**				
	12	Annual progression probability from stage II to remission	0.15		Pathological complete remission; clinical tumour stage T1; nine years follow-up	(Rocca et al., 2008)

Branch	Index	Transition probabilities	Baseline value	Range in sensitivity analysis	Remarks	Source
			0.17		Pathological complete remission; clinical nodal stage 0; nine years follow-up	(Rocca et al., 2008)
	13	Annual progression probability from stage II to stage III	0.345			(Huang et al., 2020)
			0.11			(Tsokos & Oğuztöreli, 1987) in(Sun, Sadique, dos-Santos-Silva, Yang, & Legood, 2019)
Remission stage II	14	Sustaining in remission stage II**				
	15	Annual progression probability from remission II to local recurrent	0.018			(Gocgun et al., 2015) in (Nguyen et al., 2013)
	16	Annual progression probability from remission II to distant recurrent	0.024			(Gocgun et al., 2015) in (Nguyen et al., 2013)
Stage III	17	Sustaining in stage III**				
	18	Annual progression probability from stage III to remission	0.137			(Krishnan, Al Awadi, Sreedharan, Sujith Nair, & Thuruthel, 2016)
	19	Annual progression probability from stage III to stage IV	0.22			(Huang et al., 2020)
			0.15			(Tsokos & Oğuztöreli, 1987) in (Sun et al., 2019)
Remission stage III	20	Sustaining in remission stage III**				

Branch	Index	Transition probabilities	Baseline value	Range in sensitivity analysis	Remarks	Source
	21	Annual progression probability from remission III to local recurrent	0.018			(Gocgun et al., 2015) in (Nguyen et al., 2013)
	22	Annual progression probability from remission stage III to distant recurrent	0.024			(Gocgun et al., 2015) in (Nguyen et al., 2013)
Stage IV	23	Sustaining in stage IV**				
	24	Annual progression probability from stage IV to distant recurrent	0.386		Age 45–49	(Gocgun et al., 2015) in (Nguyen et al., 2013)
			0.423		Age 50–59	(Gocgun et al., 2015) in (Nguyen et al., 2013)
	25	Annual dead probability of stage IV	0.23			(Wong et al., 2007)
			0.31		Age 40–44	(Huang et al., 2020)
			0.25		Age 45–49	
			0.26		Age 50–54	
			0.19		Age 55–59	
			0.12		Age 60–64	
			0.10		Age 65–69	
			0.10		Age 70–74	
Local recurrent	26	Sustaining in local recurrent**				
	27	Annual progression probability from local recurrent to distant recurrent	0.062		Age 45–49, stage I	((Gocgun et al., 2015) in (Nguyen et al., 2013)
			0.165		Age 45–49, stage II and III	
			0.052		Age 50–59, stage I	
			0.13		Age 50–59, stage II and III	

Branch	Index	Transition probabilities	Baseline value	Range in sensitivity analysis	Remarks	Source
Distant recurrent	28	Sustaining in local recurrent**				
	29	Annual dead probability of distance recurrent	0.386 0.423		Age 45–49 Age 50–59	

** Probability of sustaining states changed

7.8. Model parameters, value and data sources used in the base-case model

Table 7. 15. Model parameters, value, and data sources used in the base-case model

Opportunistic screening	Value	Organized screening	Value	Source
Prevalence of breast cancer (per 100 000)		Prevalence of breast cancer (per 100 000)		Institute for Health Metrics and Evaluation http://ghdx.healthdata.org/gbd-results-tool (country: Indonesia, data for the year 2019)
40–44	636.72	40–44	636.72	
45–49	820.03	45–49	820.03	
50–54	807.06	50–54	807.06	
55–59	816.12	55–59	816.12	
60–64	863.39	60–64	863.39	
65–69	852.54	65–69	852.54	
70–74	784.19	70–74	784.19	
75–79	720.46	75–79	720.46	
80+	655.04	80+	655.04	
Other-cause mortality (per 100 000 person-years)	231	Other-cause mortality (per 100 000 person-years)	231	IHME http://ghdx.healthdata.org/gbd-results-tool (country: Indonesia, data for the year 2019)
40–44	381.23	40–44	381.23	
45–49	643.60	45–49	643.60	
50–54	912.30	50–54	912.30	
55–59	1 449.31	55–59	1 449.31	
60–64	2 332.60	60–64	2 332.60	
65–69	3 920.59	65–69	3 920.59	
70–74	6 504.09	70–74	6 504.09	
75–79	13 973.71	75–79	13 973.71	
80+		80+		

Breast cancer mortality (per 100 000 person-years) 40–44 45–49 50–54 55–59 60–64 65–69 70–74 75–79 80+	 33.10 44.90 50.36 53.25 56.45 59.56 64.53 73.82 90.07	Breast cancer mortality (per 100 000 person-years) 40–44 45–49 50–54 55–59 60–64 65–69 70–74 75–79 80+	 33.10 44.90 50.36 53.25 56.45 59.56 64.53 73.82 90.07	IHME http://ghdx.healthdata.org/gbd-results-tool (country: Indonesia, data for the year 2019)
Participation in clinical breast examination (CBE) (%)	20%	Participation in CBE (%)	62.5%	Jakarta Provincial Health Office, 2017; report on breast-tumour prevalence survey in Indonesia, the Ministry of Health, 2016
Probability of attending mammography diagnostic test	20%	Probability of attending mammography diagnostic test	80%	The National Cancer Center — Dharmais Hospital, 2013; report on breast-tumour prevalence survey in Indonesia, the Ministry of Health, 2016
Effectiveness of screening - Sensitivity CBE paralleled with ultrasonography, followed by mammography when indicated - Specificity CBE paralleled with ultrasonography, followed by	0.681 0.968 0.848 0.979	**Effectiveness of screening** - Sensitivity CBE paralleled with ultrasonography, followed by mammography when indicated - Specificity CBE paralleled with ultrasonography, followed by	0.862 0.970 0.939	(Huang et al., 2012; Schiller-Fruehwirth et al., 2017)

mammography when indicated - Sensitivity mammography diagnostic test - Specificity mammography diagnostic test		mammography when indicated - Sensitivity mammography diagnostic test - Specificity mammography diagnostic test	0.980	
Breast cancer stage distribution (%)		**Breast cancer stage distribution (%)**		(Groot et al., 2006; Miller, 2008; Murillo et al., 2008; Teh et al., 2015)
Stage I	9.4	Stage I	49.0	
Stage II	14.2	Stage II	37.4	
Stage III	58.0	Stage III	8.6	
Stage IV	18.4	Stage IV	5.0	
Transition probabilities	0.00001	**Transition probabilities**	0.000001	(Huang, Li, Torres-Rueda, & Li, 2020)
- No cancer to stage 0 (ductus carcinoma in situ)	0.02 0.79	- No cancer to stage 0 (DCIS)	0.02 0.79	(Rocca et al., 2008)
- Stage 0 to stage I	0.34	- Stage 0 to stage I	0.34	
- Stage I to stage II	0.22	- Stage I to stage II	0.22	(Krishnan, Al Awadi, Sreedharan, Sujith Nair, & Thuruthel, 2016)
- Stage II to stage III	0.31	- Stage II to stage III	0.31	
- Stage III to stage IV	0.17 0.17	- Stage III to stage IV - Stage IV to death	0.17 0.17	(Huang et al., 2020) (Nguyen & Adang, 2018a)
- Stage IV to death	0.137	- Stage I to remission	0.137	
- Stage I to remission	0.01	- Stage II to remission	0.01	
- Stage II to remission	0.000016	- Stage III to remission	0.000016	(Gocgun et al., 2015; Nguyen & Adang, 2018a)
- Stage III to remission	0.018	- Remission stage I to local recurrent	0.018	
	0.024	- Remission stage I to distant recurrent	0.024	

- Remission stage I to local recurrent	0.018	- Remission stage II to local recurrent	0.018	
- Remission stage I to distant recurrent	0.024	- Remission stage II to distant recurrent	0.024	
- Remission stage II to local recurrent	0.386	- Remission stage III to local recurrent	0.386	
- Remission stage II to distant recurrent		- Remission stage III to distant recurrent		
- Remission stage III to local recurrent		- Stage IV to distant recurrent		
- Remission stage III to distant recurrent				
- Stage IV to distant recurrent				
Utility scores		- Utility scores		
- DCIS	0.84	- DCIS	0.84	(Kim et al., 2017; Sun, Legood, Dos-Santos-Silva, et al., 2018)
- Stage I	0.79	- Stage I	0.79	
- Stage II	0.79	- Stage II	0.79	
- Stage III	0.61	- Stage III	0.61	
- Stage IV	0.53	- Stage IV	0.53	
- Remission	0.76	- Remission	0.76	
- Local recurrent stage I	0.75 0.73	- Local recurrent stage I	0.75 0.73	
- Local recurrent stage II	0.70 0.40	- Local recurrent stage II	0.70 0.40	
- Local recurrent stage III		- Local recurrent stage III		
- Distant recurrent/ metastatic		- Distant recurrent/ metastatic		

Cost, US$		**Cost, US$**		
Program cost for CBE screening	23 899	Program cost for CBE screening	42 374	Breast-tumour prevalence survey, Ministry of Health, 2016; SADANIS program, Jakarta Provincial Health Office, 2017; mobile mammography, Dharmais Hospital, 2017
Breast cancer treatment	5 216	Breast cancer treatment	5 216	
Stage I	5 932	Stage I	5 932	
Stage II	9 754	Stage II	9 754	
Stage III	8 814	Stage III	8 814	
Stage IV		Stage IV		

7.9. Results of cost-effectiveness analysis

7.9.1. Model validation

Model validation was assessed by comparing the overall survival features of our model with that of Peisl et al. (2019) for the overall survival pattern of organized versus opportunistic breast cancer mammography screening. The initial probability constructed in the Markov model started with women diagnosed with breast cancer **(Figure 6. 2).** These women were distributed to the stages of breast cancer based on proportion, distinguished by the presence or absence of an extensive breast cancer program, as derived from Groot et al. (2006) and shown in **Table 7. 8.** Meanwhile, the survival probability for women with breast cancer, under organized and opportunistic screening are presented in **Figure 7. 1** and **Figure 7. 2.** Both figures illustrate a declining distribution of survival rate for women living with breast cancer. However, the organized screening arm sees a more favourable screening benefit than the opportunistic one.

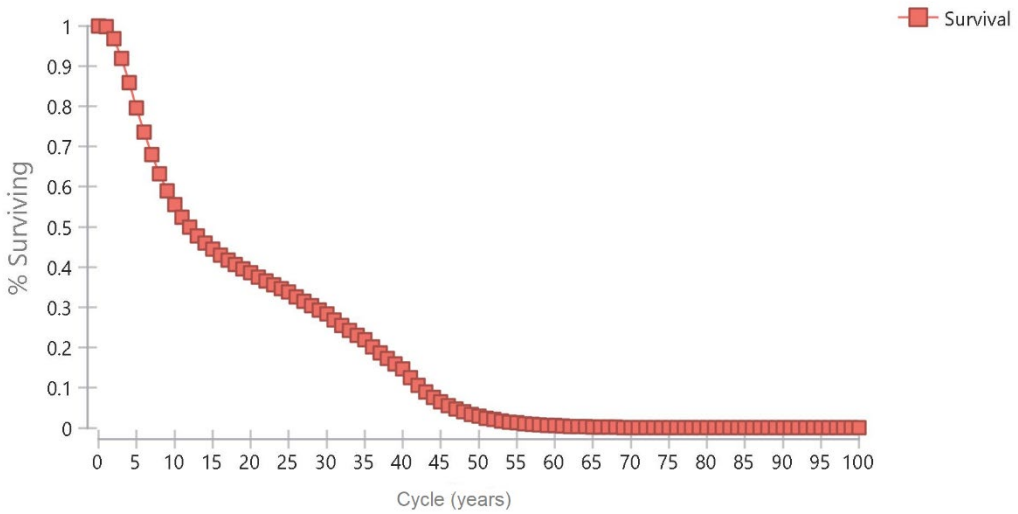

Figure 7. 1 Opportunistic screening survival curve

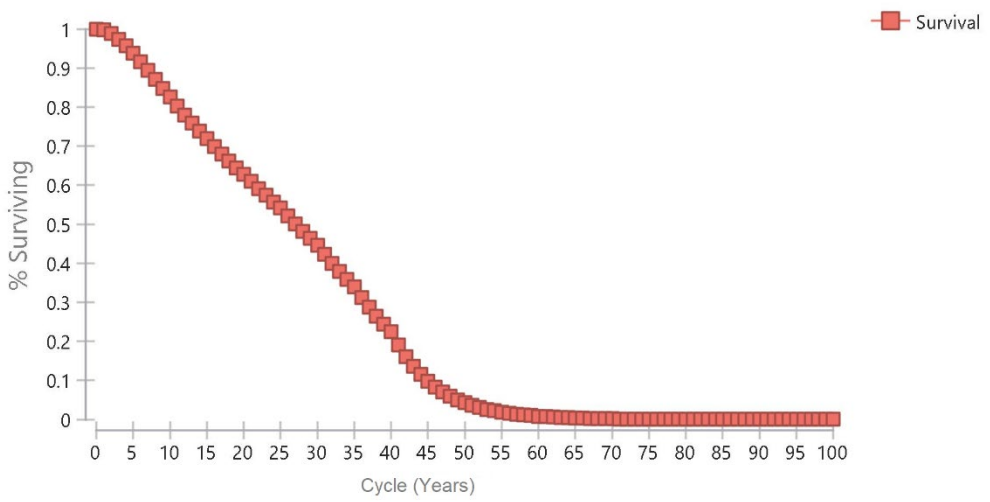

Figure 7. 2 Organized screening survival curve

It is evident that women with breast cancer, regardless of the screening strategy for detection, have the same survival rates in the early years. However, in the first five-year survival point, the opportunistic screening strategy sees a steeper decline in the survival rate as it slowly descends until it hits a plateau at the age of 60 onwards. Meanwhile, the survival rate of women under organized screening gradually declines, then falls with the same patterns as the opportunistic strategy. Both figures show that if women can survive due to effective treatment, they can live longer, but if their cancer is left untreated, higher levels of breast cancer death may ensue.

Furthermore, there is a different mortality rate due to breast cancer and other causes among women under organized and opportunistic screening. **Figure 7. 3** and **Figure 7. 4** illustrate the probability distribution of breast cancer states for a cohort of women from year-one up to 100-years in organized screening strategy and opportunistic strategy, respectively.

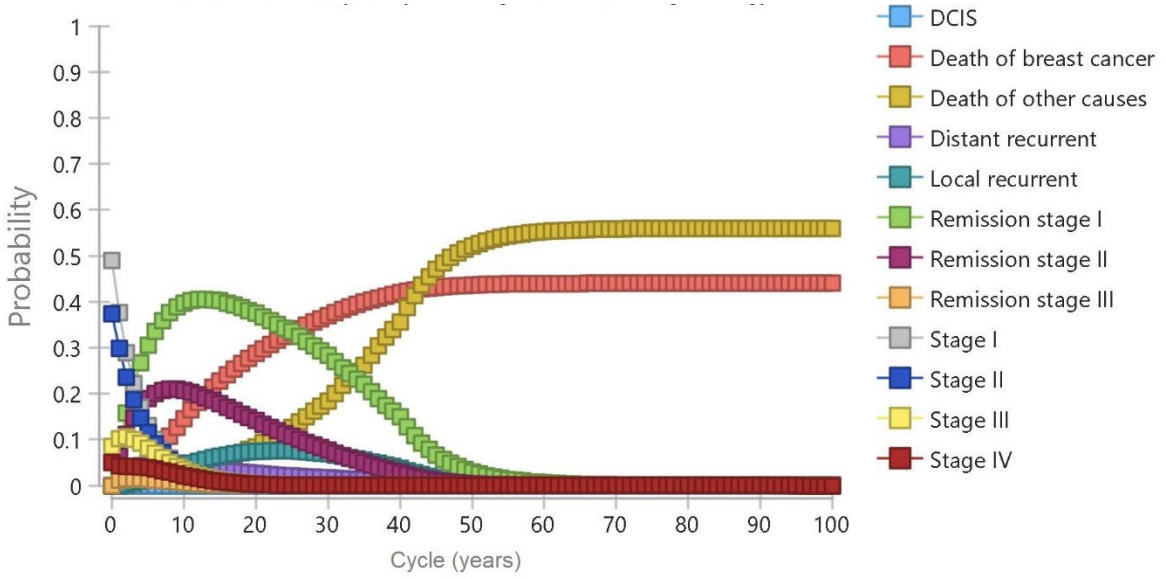

Figure 7. 3 Markov probability analysis for an organized screening strategy

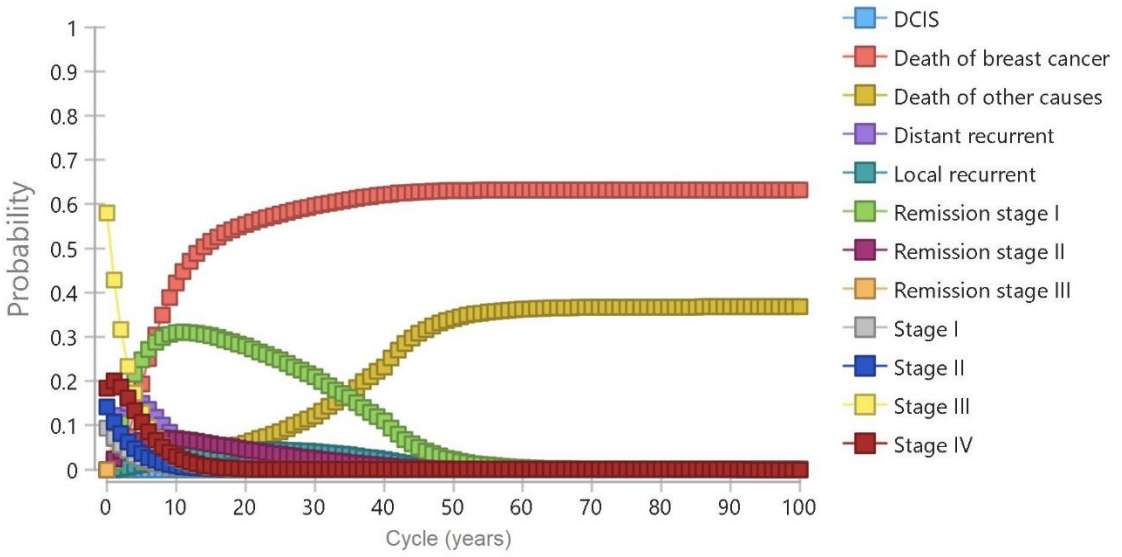

Figure 7. 4. Markov probability analysis for an opportunistic screening strategy

Figure 7. 3 shows that death from breast cancer from year 0 to 40 surpasses death from other causes but the trend reverses when the former remains steady at 40% while the latter reaches 50% until the end of the line at year 45. The cancer's remission stage I peaks in the first 10 years and continues to gradually decline until years 50–60. Meanwhile, **Figure 7. 4.** presents the opposite trend as being apparent in an opportunistic screening where the mortality rate due to breast cancer in the first 10 years has already increased up to 60% in year 10, a trend nearly six-fold of the other causes and remains levelled off until year 80. Remission at the early stage (stage I and stage II) is smaller than that in organized screening. From the model, the cohort summary illustrates that the proportion of early-stage breast cancer in the organized screening is higher than that in the opportunistic screening, but the percentage of the cohort at the late stage is slightly lower **Table 7. 17.**

Table 7. 16 Markov summary cohort

Stage	**% Cohort**	
	Organized screening	Opportunistic screening
I	0.000069	0.000036
II	0.0082	0.0033
III	0.00105	0.00175
IV	0.00137	0.00147

Table 7. 16 presents the disaggregate cost of breast cancer treatment. As indicated in **Figure 7. 3** and **Figure 7. 4**. when the organized screening test captured more people with early-stage breast cancer, the treatment cost would be higher for those states than in opportunistic screening. Meanwhile, treatment costs in opportunistic

screening are higher at a more advanced stage of breast cancer. In general, in both organizing and opportunistic screening, the cost of breast cancer stages at diagnosis is lower than in the remission and recurrent breast cancer.

Table 7. 17 Disaggregated breast cancer treatment costs

Item	Organized expenditure	Opportunistic expenditure	Difference	% Difference
Stage I	8 179.22	2 173.56	6 005.66	45.93
Stage II	5 431.40	3 134.96	2 296.44	17.56
Stage III	9 287.20	11 624.35	- 2 337.15	-17.87
Stage IV	4 157.61	7 945.49	- 3 787.88	-28.97
Remission stage I	3 344.11	5 246.59	- 1 902.48	- 14.55
Remission stage II	9 536.86	4 362.45	5 174.41	39.57
Remission stage III	15 246.59	23 344.11	- 8 097.52	-61.92
Local recurrent	10 484.03	9 056.50	1 427.53	10.92
Distant recurrent	5 241.46	10 943.80	-5 702.34	-43.61

7.9.2. Base-case analysis

Using the input parameter shown in **Table 7. 15** the expected cost and effectiveness of an organized or opportunistic screening strategy are estimated in the base-case and sensitivity analysis. The incremental cost-effectiveness ratios are calculated by dividing the difference in cost by the difference in effectiveness (Ramsey et al., 2005). Since in the Indonesian Guidelines for Health Technology Assessment does not contain the recommended threshold to determine whether an intervention is cost-effective as in representing good value for money (Ministry of Health Republic of Indonesia, 2017), the costs are less than three times as much as the national annual gross domestic product (GDP) per capita is used as the threshold (Griffiths, Maruszczak, & Kusel, 2015).

Table 7. 18. Cost-effectiveness analysis base-case results

Strategy	Cost (US$)	Incremental costs (US$)	Effect (quality-adjusted life-years)	Incremental effect (QALYs)	ICER (per QALY)
Opportunistic	14 562.94	——	20.10	——	——
Organized	19 340.44	4 777.48	20.72	0.62	7 727.88

As illustrated in **Table 7. 18.** the organized breast cancer screening strategy yielded slightly higher QALYs compared to opportunistic breast cancer screening (20.72 versus 20.10 QALYs) but was more expensive relative to the opportunistic strategy (US$ 19 340.44 versus US$14 562.94). The means of total incremental costs and total QALYs were present for each strategy at per capita GDP threshold was US$ 4135.56), as recommended by the World Health Organization for low- and middle-income countries (Woods, Revill, Sculpher, & Claxton, 2016). The discounted incremental cost-effectiveness ratio was US$ 7 727.88 per QALY, which was below the threshold of three times the Indonesian GDP per capita of US$12 406.71, indicating that organized breast cancer screening program was cost-effective.

Figure 7. 5. shows the cost-effectiveness graph with the dotted line of willingness to pay (WTP). The WTP was set at three times as much as per capita GDP (US$12 406.71). The cost effectiveness of the current screening strategy (opportunistic) is plotted as the red square and that of the alternative option (organized screening strategy) as the blue circle.

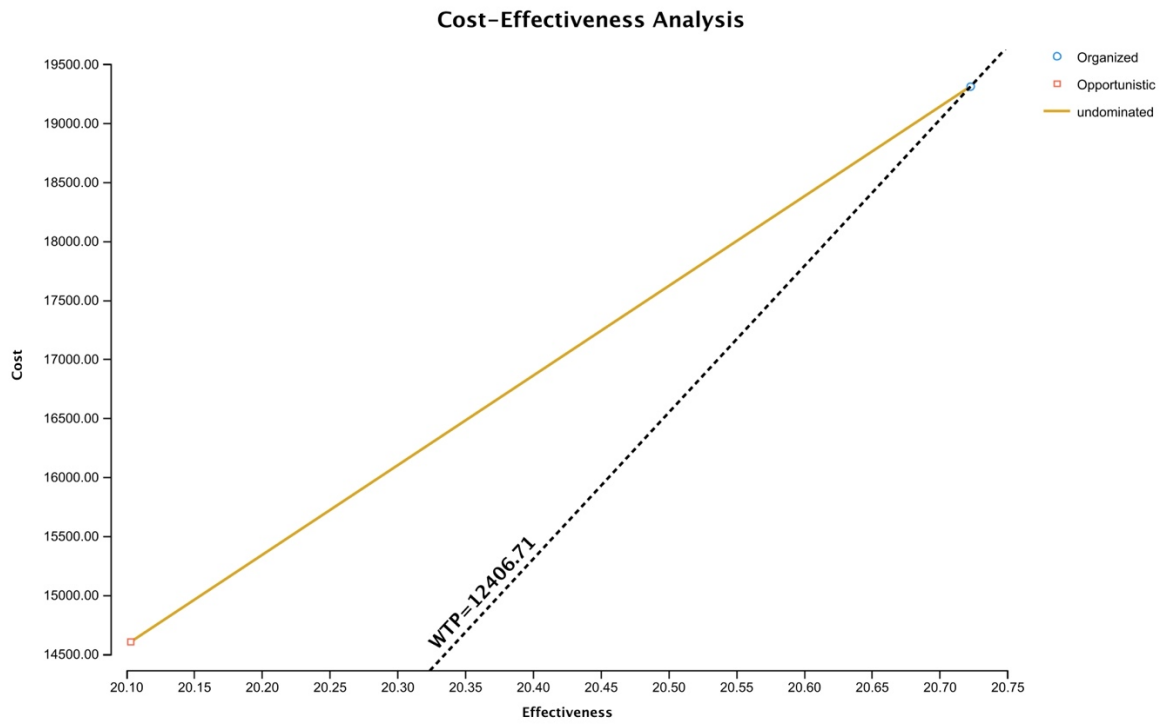

Figure 7. 5 Cost-effectiveness analysis

7.9.3. Sensitivity analysis

To assess parameter uncertainty, one-way and probabilistic sensitivity analyses were conducted. In one-way sensitivity analysis, key parameters were varied using minimum and maximum estimates.

Table 7. 19 presents the results from the sensitivity analysis for 1) prevalence of breast cancer, 2) participation,
3) sensitivity and specificity of CBE screening, 4) sensitivity and specificity of diagnostic mammography, 5) cost of clinical breast examination screening, and 6) treatment costs of breast cancer.

Table 7. 19. One-way sensitivity analysis

Parameter	Strategi	Cost (US$)	Incr cost (US$)	Eff	Incr Eff	ICER (per QALY)
Base-case model	- Opportunistic	14,607.3		20.10		
	- Organized	19,315.645	4,708.29	20.72	0.62	7,601.79
Prevalence						
0.0025	- Opportunistic	14,397.56		20.13		
	- Organized	19,295.76	4,898.20	20.73	0.60	8,168.52
0.30	- Opportunistic	16,006.63		19.88		
	- Organized	19,730.34	3,723.71	20.66	0.78	4,771.97
Participation						
0.60	- Opportunistic	14,562.94		20.10		
	- Organized	18,174.41	3,611.47	20.74	0.64	5,662.45
0.90	- Opportunistic	14,562.94		20.10		
	- Organized	21,672.45	7,109.51	20.68	0.58	12,227.79
Sensitivity - specificity (CBE paralleled with ultrasonography and, followed by mammography when indicated)						
Se: 0.56	- Opportunistic	14,254.11		20.15		
Sp: 0.98	- Organized	19,320.02	5,065.91	20.72	0.58	8,756.09
Se: 0.97	- Opportunistic	17,006.69		19.77		
Sp: 0.98	- Organized	19,501.87	2,495.17	20.70	0.65	2,677.20
Sensitivity - specificity (diagnostic. mammography)						
Se: 0.79	- Opportunistic	14,562.94		20.10		
Sp: 0.97	- Organized	20,528.83	5,965.90	20.70	0.60	9,9966.08
Se: 0.99	- Opportunistic	14,562.94		20.10		
Sp: 0.98	- Organized	19,034.69	4,471.75	20.73	0.62	7,174.84
Clinical breast examination screening costs						
(US$ 6)	- Opportunistic	14,531.16		20.10		
	- Organized	19,193.57	4,662.41	20.72	0.62	7,541.75
(US$20)						

	-	Opportunistic	14,598.54		20.10		
	-	Organized	19, 463.36	4,873.82	20.72	0.62	7,883.72
Treatment costs stage I Treatment (US$)							
	-	Opportunistic	15,682.11		20.10		
2,500.00	-	Organized	19,423.68	3,741.57	20.72	0.62	6,052.23
10,182.57	-	Opportunistic	13,416.49		20.10		
	-	Organized	19,255.14	5,838.65	20.72	0.62	7,748.31
Treatment costs stage II							
	-	Opportunistic	14,792.57		20.10		
3,019.00	-	Organized	19,439.15	4,646.58	20.72	0.62	7,516.14
10,417.89	-	Opportunistic	14,444.96		20.10		
	-	Organized	19,289.70	4,844.74	20.72	0.62	7,836.67
Treatment costs stage III							
	-	Opportunistic	19,597.99		20.10		
3,181.96	-	Organized	21,078.75	1,480.77	20.72	0.62	2,395.23
38,295.49	-	Opportunistic	13,451.83		20.10	0.62	8,904.67
	-	Organized	18,956.82	5,504.99	20.72		
Treatment costs stage IV							
	-	Opportunistic	19,165.54		20.10		
2,617.07	-	Organized	21,109.26	1,943.72	20.72	0.62	3,144.09
40,000.00	-	Opportunistic	17,832.46		20.10		
	-	Organized	20,596.94	2,764.48	20.72	0.62	4,471.72

Given that an organized screening strategy may be more effective to introduce in high-prevalence regions, an attempt was made to explore how this epidemiology profile may affect the results of the analysis. The change to prevalence parameters is consistent with the relative decision between organized and opportunistic strategies in the base-case model. However, it is notable that implementing an organized approach in areas with a higher prevalence of breast cancer area is considered more cost-effective than in the low-prevalence area. The ICER ranges

from US$ 4,771.97 with a related QALY of 20.66 for a prevalence rate of 30 per 100 000 population to US$ 8 168.52 with QALY value of 20.73 for a prevalence rate of 2.5 per 100 000 population.

Participation of the eligible population was evaluated, highlighting the potential increase in patient volume as a consequence of personal invitation. The results indicated that higher participations in organized strategy would cost more to save one quality-adjusted life-year than lower participation. Increasing the participation rate would change the results in terms of ICER, ranging from US$ 5 662.45 with a related QALY of 20.74 for a participation rate of 75% to US$ 12 227.79 with a QALY value of 20.68 for the participation rate of 90%.

To investigate the influence of screening test performance on decision-making, sensitivity and specificity of CBE and mammographic diagnostic tests were varied together, with a minimum value of both and maximum value of both. Under circumstances where CBE can reach more the target population, the highest level of organized strategy is more cost-effective, with the ICER decreased less than two GDP per capita. In contrast, when the CBE test is performed at the minimum level, the ICER of organized screening increases compared with the base-case result (US$ 7 727.88 versus US$ 8 756.09), which may occur due to a high number of false-positives.

As the economic situation is different among the regions in Indonesia, half and double of the baseline input of screening and treatment costs were tested to explore their effects on cost-effectiveness results. Primary screening costs of CBE are from US$ 6 to US$ 20. The underlying assumption is that the primary screening costs are positively associated with the local economy. The highest CBE screening cost at the

organized strategy slightly increased the ICER by more than three times the GDP per capita. When the treatment cost of stage I and stage II are the lowest, the base-case results of the organized strategy are considered cost-effective. When the treatment cost of stage III and stage IV were higher of the base-case analysis, the ICER of organized strategy increased more than three times the GDP per capita.

Figure 7. 6 illustrates a Tornado analysis of a total of nine tested variables which have a potential effect on the ICER. All tested variables are ranked by descending order of uncertainty prediction. Participation and prevalence of breast cancer as the top two on having an effect of the ICER predictions. Each of them accounts for 40%, and 30% of ICER results. Meanwhile, variables related to specificity mammography diagnostic had the weakest effect (less than 1%) on the ICER results.

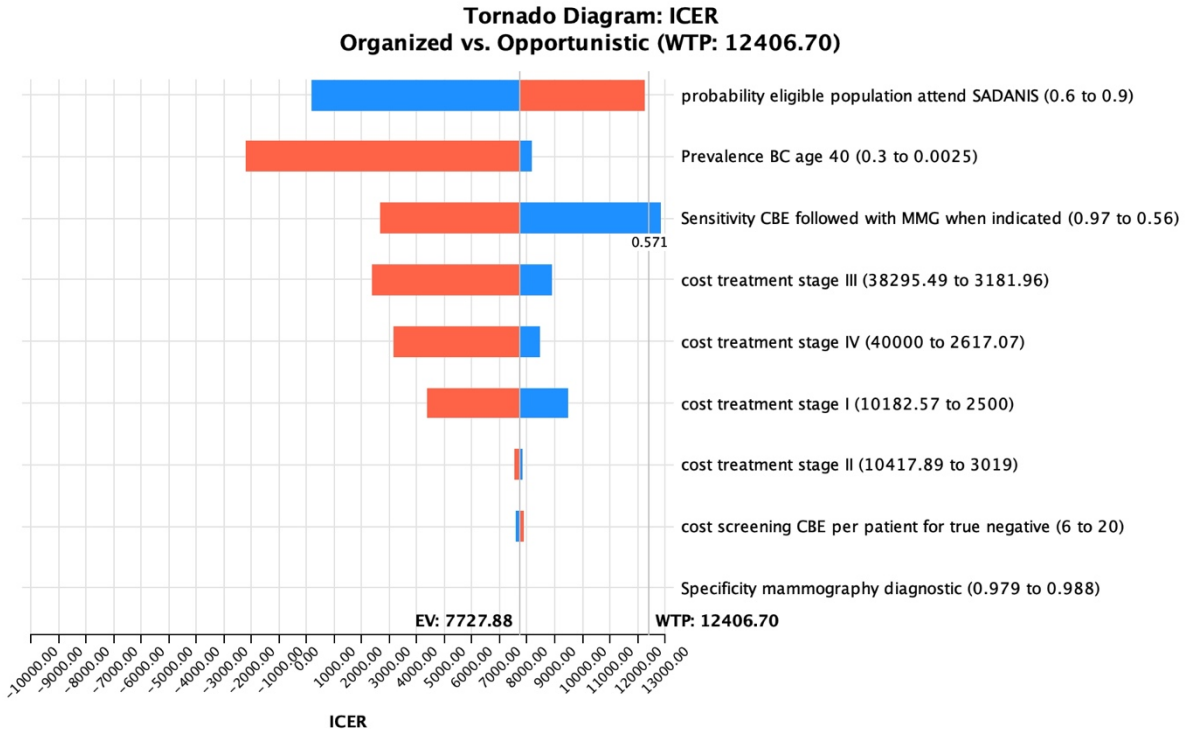

Figure 7. 6 Incremental cost-effectiveness ratio tornado diagram for organized versus opportunistic strategy

Three variables related to the participation of screening, the prevalence of breast cancer and the performance of CBE and are identified to be sensitive to the baseline CEA result. Whereas when making the strategies recommendation, special attention should be given to raise awareness among the target population to carry out breast cancer screening, selecting the areas with a high prevalence of breast cancer, and improve the performance of clinical breast examination.

7.9.4. Probabilistic sensitivity analysis

In probabilistic sensitivity analyses, incremental cost-effectiveness ratio was assessed across 95% confidence intervals while comparing organized screening versus opportunistic screening and is illustrated in cost-effectiveness plane figures **(Figure 7. 7.)**. A minimum acceptable willingness-to-pay for organized screening to be a cost-effective strategy is presented to provide reference information for policymakers on decision-making. The incremental cost-effectiveness plane shows Monte Carlo estimates of the incremental costs and benefits of having an organized screening strategy versus an opportunistic strategy **(Figure 7. 7.).** For each one of the 100 000 iterations, values for parameters were randomly selected from their distributions and an ICER was calculated. Descriptive statistics for the cost and effectiveness of organized and opportunistic screening is presented in **Table 7. 20.**

Table 7. 20. Monte Carlo descriptive statistics of cost-effectiveness

Statistics	Minimum	Mean	Median	Maximum	Standard deviation
Cost of organized screening	483.84	19 315.64	21 594.87	90 474.66	9 293.84
Cost of opportunistic screening	1 129.58	14 607.35	9 935.12	64 600.25	12 290.80
Quality-adjusted life-years of organized screening	16.63	20.72	20.71	21.06	0.17
QALYs of opportunistic screening	19.19	20.10	20.10	20.98	0.24

Organized screening was found to be a dominant strategy (less costly and more effective) in 33.07% of the simulation and cost-effective in 0.52 % of simulations at the willingness-to-pay threshold of US$12 406.70 per QALY. To allow for the possibility that the healthcare decision-maker faces different healthcare objectives and/or differing budget constraints, the result is presented in the form of a cost-effectiveness acceptability curve (CEAC), showing the probability of screening strategy being the optimal strategy for a range of willingness-to-pay thresholds . Given a maximum acceptable willingness to pay of $12,406 per QALY, the probability that organized screening is cost-effective compared to opportunistic screening is 0.157. In other word, there is a 51.7% chance that the additional cost of organized screening, compare with opportunistic screening, is at or below $12,406 per QALY.

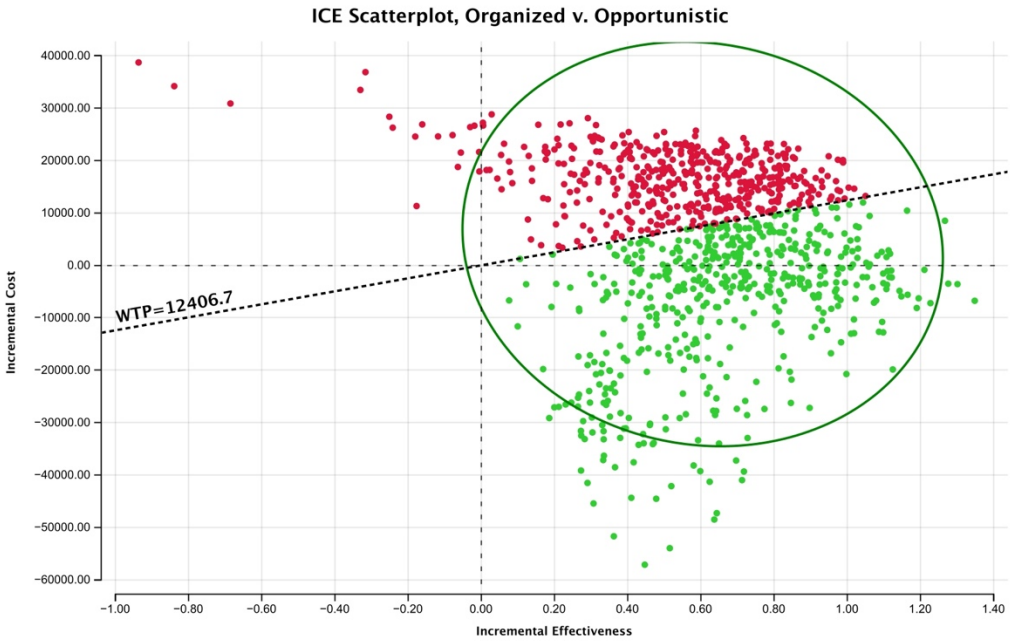

Figure 7. 7 The incremental cost-effectiveness plane for organized versus opportunistic strategy

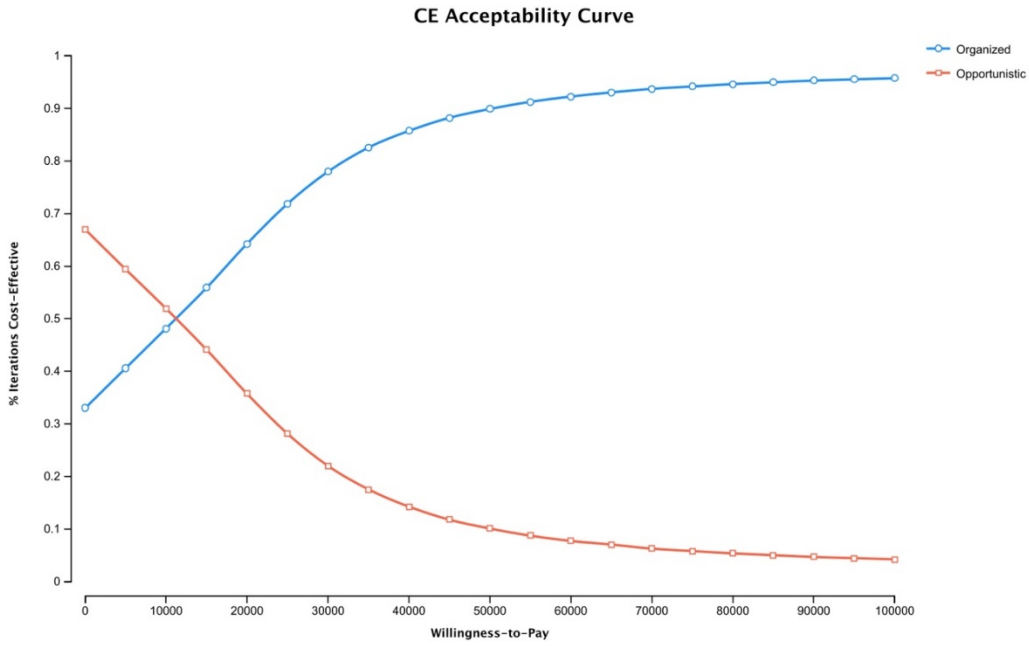

Figure 7. 8 Cost-effectiveness acceptability curve

7.10. Summary

This chapter has populated parameters collected from various data sources to simulate the model of an ex-ante evaluation of breast cancer screening within the Indonesia healthcare setting. In this study, the cost-effectiveness analysis of organized breast cancer screening is presented as an incremental cost-effective ratio in relation to opportunistic screening. Using three times the Indonesian per capita GDP in 2019 as an analytical threshold for ICER per QALY in comparison to opportunistic screening, the organized screening is a cost-effective option to be implemented in the setting of urban areas. One-way sensitivity analyses were performed in this thesis study to explore the possible effect of variable uncertainties on baseline cost-effective strategy recommendation. Variables related to screening participation, the prevalence of breast cancer and performance of clinical breast examination followed with mammography when indicated, cost treatment stages I, II, III and IV was tested. From all the above variables tested, participation in attending the screening, the prevalence of breast cancer and sensitivity CBE followed with mammography had a significant impact on the ICER in the baseline model.

The next chapter will discuss more detail on contribution of this thesis, policy implication, future research needed and conclusion to response the overall research questions.

Chapter 8: Discussion

8.1. Overview

This chapter highlights the contribution made by the present study to constructing the decision-analytic model of breast cancer early detection in Indonesia and the added-value to the body of knowledge.

8.2. Empirical evidence of economic evaluation in a country-specific setting

The systematic literature review (SLR) conducted and published in this thesis either as an individual article or part of a cumulative dissertation phase (Yuniar et al., 2020) contributes a state-of-the-art synthesis of evidence to the limited but growing literature on economic evaluation of community-based secondary prevention for breast cancer control in Asia. As a standalone paper, this review has objectively summarized a large amount of information as well as identified the benefit of health economics studies and the gaps in population-based breast cancer screening programs in Asia. This evidence generated from the literature review is useful for research, policy and the broader public who are interested in this topic area. The researcher has addressed two review questions to consolidate the topic area in order to establish the status quo of the current research. In addition, the SLR produced a more diverse set of dimensions about the research field based on geographic and methodological specifics.

As a cumulative dissertation, the systematic review as part of this dissertation has elaborated on the methodological issues and data inputs to populate the model after collecting a wide array of data on the extent to which the decision–analytic model in breast cancer early detection is constructed. From the data synthesis of model parameters, the researcher revealed that none of the reviewed studies addressed transferability in interpreting the study result. Nevertheless, there is a growing body of literature about transferability issues in various methodological guidelines for economic evaluation, and the researcher has made recommendations for good practice (Drummond et al., 2015, 2009b). The economic evaluation of breast cancer early detection is considered a mature field of research, and a growing research subject (Ahmadian & Samah, 2012; Anderson, 2010; Nelson et al., 2016). However, a large amount of recent literature on this issue is published in developed countries including Netherland, Germany, Australia (Beemsterboer et al., 1998; Harry J. de Koning et al., 1991) and very few studies conducted in Asian countries, thus reflecting the immaturity of this research field in the latter countries. The present study included only 15 articles out of 1 445 published studies on breast cancer screening undertaken in Asian countries. Furthermore, findings from the reviewed articles indicated that in Asia, there has been limited amount of evaluation of economic research that focused on the cost and cost effectiveness of breast cancer early detection strategies. The evidence suggests that organized mammography screening for women under 50 years old may be economically attractive in Asia, but there is relatively limited evidence regarding opportunistic screening strategies and early diagnosis strategies. Given the increased incidence of breast cancer and lack

of evidence of established policy of early detection strategy, it is essential to undertake an extensive economic analysis with better data transparency and comprehensive screening strategies in Asia, to make it relevant and adaptable to other Asian countries.

8.3. Integrate the local context into an evidence-informed decision-making model of breast cancer early-detection strategies

An increasing number of scholars have advocated for qualitative data to be incorporated into and documented thoroughly in an economic evaluation study to strengthen economic evaluations in the context of implementation research (Dopp, Mundey, Beasley, Silovsky, & Eisenberg, 2019).

The second qualitative phase of this study, the contextualization phase, is crucial to understand the success and challenges of the existing practice, the impacts and necessary improvement. The involvement of local decision makers and clinical expertise in this research, as well as the inclusion of local context has increased the useability and usefulness of relevant evidence for decision-makers, bridging gaps in translating research findings into healthcare practices (Robinson et al., 2020). In addition, involving local data in economic evaluation allows for greater transferability of evidence into policy and practice (Michael Drummond et al., 2009b). Two streams of knowledge gained from the contextualization processes in this study have formed an integral part of the real-world program evaluation.

The first stream is the appropriate framework to facilitate a comprehensive assessment of the program landscape. The second stream is the practical experience of addressing context through an iterative qualitative approach and embracing co-production evidence with engaged stakeholders. The subsections below discuss the relevance of the knowledge gained throughout the contextualization process.

8.3.1. Enable the usefulness of contextualization frameworks and their applicability to assist with breast cancer early-detection program evaluation

Engaging the World Health Organization's standard evaluation components for cervical cancer to improve the availability and use of high-quality data for decision-making in low- and middle-income countries (WHO, 2018), the researcher worked with stakeholders to develop assessment tools and a modified framework including seven domains of essential information related to contextual factors that influence the implementation of breast cancer early detection and six domain data sources to inform the economic evaluation **(See Figure 4. 1).** In addition, an extended logic model **(see Figure 5. 1)** was produced that depicted the overall local-contextual themes emerging from the inductive analysis of qualitative data, categorized as inputs, activities, outputs and outcomes of breast cancer early-detection program in Indonesia (the SADANIS program). The framework and logic model developed through this research study can be used in other decision contexts to inform the economic modelling components of the economic analysis and to support decision makers in policy development and evaluation. Furthermore, involving decision

makers and stakeholders in the contextualization and model building phase can contribute more knowledge and foster support for translating of evidence into practice.

8.3.2. Increase usability and adoption of research implementation through co-creating knowledge of local contexts with the engaged stakeholders

Stakeholder engagement in this research has made a valuable contribution to the iterative co-creation of the knowledge based on the researcher's perspective. The identification and interaction with opinion leaders employed in this research are both critical activities because the nature of breast cancer screening research involved multi-and transdisciplinary stakeholders. Thus, the researcher identified and actively engaged with opinion leaders, including the working groups for breast cancer early detection at the National Cancer Centre (NCC) at Dharmais Hospital, before the data collection phase to build institutions or individual trust.

As a result, the opinion leaders become more aware of their contributions and roles in supporting this study, namely, to motivate and influence other stakeholders to undertake policy deliberation, execute a strong influence, and ensure a high level of interest in improving the implementation of community-based breast cancer early detection in Indonesia. They also realized that this study is parallel with their research plan and potentially provides scientific merit to the economic evaluation of breast cancer early-detection strategies. These characteristics may be related to the attributes and capacity of opinion leaders at NCC, a teaching hospital and the only national referral cancer hospital.

Involving opinion leaders in the study is starting point for this research framework and aided the researcher in framing better research questions and integrating more relevant evidence into the model development. Additionally, stakeholder engagement with opinion leaders is the key component of pragmatic approach to research that may produce valuable and applicable research. The knowledge obtained about the value of transdisciplinary research as it related to decision–analytic model development in country-specific settings such as Indonesia is helpful to inform the development of a set of suitable designs for stakeholder engagement for more advanced research on breast cancer early-detection programs, especially in other developing countries.

8.3.3. *Ex-ante* cost-effectiveness analysis of breast cancer screening

Both opportunistic and organized screening strategies are likely to yield favourable health benefits to the population (Peisl et al., 2019). Therefore, it is relevant for public health decision-makers to draw comparisons between both strategies prior to establishing an appropriate guidelines for screening policy (Neeser, Szucs, Bulliard, Bachmann & Schramm, 2007). The pattern of overall survivals among women with breast cancer undergoing either opportunistic or organized screening in this thesis (**Figure 7. 1 and Figure 7. 2 .**) confirms a declining distribution in both screening strategies. Fortunately, the organized screening arm in the model saw more favourable benefits than the opportunistic one, which were similarly reported in studies in Switzerland (de Gelder et al., 2009; Peisl et al., 2019). The possible explanation of such findings may be attributed to the elements of the organized

screening strategy that form a coherent structure and offer a standardized system of care. In addition, a systematic management of the organized screening would have implemented more clear guidelines which defined who should be invited, how frequently they should be screened, and how any screen-detected abnormalities should be followed up and treated (Chamot et al., 2007; Madlensky et al., 2003) (Amendoeira et al., 2013),

The result of the baseline analysis in this thesis showed that organized breast cancer screening strategy, compared to the opportunistic screening, led to slightly higher QALYs (20.72 versus 20.10 QALYs) but imposed a higher cost (US$ 19,340) versus US$14,562). The discounted incremental cost-effectiveness ratio (ICER) was US$ 7,727 per QALY or below the threshold of three-fold Indonesian per capita GDP (US$12 406.71), indicating the cost-effectiveness of organized breast cancer screening program. These findings are aligned with breast cancer early detection strategies identified in selected Asian countries, including Japan, Korea, Vietnam, Hong Kong, Iran, and China (Chapter 3). Despite different context in the implementation of breast screening programs between the model in this study and the reviewed literature, it is relevant to compare the ICER because Asian countries have similar epidemiology background of breast cancer among Asian countries. The range of ICER of organized breast cancer screening in Asian countries is $ 3 816 to $ 89 552. The variation of ICER in most studies was influenced by the starting and ending age of the target population in the screening program. For example, in Hong Kong, mammography screening is a cost-effective strategy for women starting to get screened between the age of 40 to 69 years. However, when screening is extended

up to the age of 79, ICER can increase by four times. The evidence in China found that in a scenario where only 70% of detected cases were treated, the ICER yielded a higher ICER per QALY ($ 11 844) compared to that in the baseline model ($8 739 per QALY). In Vietnam, the ICER for mammography screening at 50-54 years is the most cost-effective option ($3 816.81) compared to at 45 or 60 years old, which could not be considered cost-effective.

Regardless the primary modalities used in breast cancer screening, the organized screening is recommended because the cost-effective strategy has been evident to reduce the late-stage breast cancer in some neighbouring countries, such as Malaysia and Vietnam (Devi, Tang, & Corbex, 2007; Nguyen & Adang, 2018). However, before a jurisdiction initiate a resource-appropriate population-based screening program, it is imperative to establish four prerequisite approaches. These approaches are 1) establishing a systematic triage approach to diagnose palpable breast disease; 2) strengthening resource-adapted, stage-appropriate treatment planning using navigation processes to reduce access barriers; 3) scaling up targeted educational interventions for public and private healthcare staff audiences to promote the downstaging of clinically detectable disease; and 4) systematically upgrading image-based diagnostic systems for managing nonpalpable disease as a prerequisite to the mammographic screening program (Duggan et al., 2020).

8.4. Summary

Having evidence on the effectiveness and cost-effectiveness of breast cancer screening programs, it is important to support policy making which aimed at reducing high incidence and mortality of breast cancer in Indonesia and other low-and middle-income countries in Asia. The inclusion of relevant stakeholders throughout this research has been important in increasing the research quality and supporting the translation of research into policy and practice.

Chapter 9: Conclusion

The previous chapter has provided an in-depth discussion to increase the transparency in developing evidence-informed decision-making for breast cancer early detection in healthcare system of Indonesia. This final chapter presents a summary of the study and highlights the significance and original contributions. The strength and limitations of the three research objectives are provided. This chapter concludes with a range of recommendation for future policy and research.

9.1. Summary of the study aims

This study responds to two substantial issues of public health in a low- and middle-income country. The first addresses the global call on equities of breast cancer early detection to increase breast cancer survival rates. The second responds to the need to build a Health Technology Assessment (HTA) framework by reflecting transparency in developing a cost-effective model for breast cancer screening in Indonesia. This section outlines each chapter of this thesis.

As highlighted in Chapter Two, breast cancer is a global burden in which the suboptimal population-based screening program exacerbates breast cancer cases in low-middle-income countries. In addition, lack of utilization of HTA in breast cancer screening programs in Indonesia has resulted in limited evidence to improve screening services. The systematic review in Chapter Three elaborates the limited number of scientific publications of the economic evaluation of breast cancer screening in selected Asian countries. The reviewed literature also indicates the

parameters used to populate the economic evaluation model derived from references in other countries to compensate lack of data availability and quality.

As detailed in Chapter Four, this study employed explanatory mixed method across three consecutive approaches to contextualizing the domains of epidemiology, policy, service availability and utilization, human resources, and economic and health information system in implementing early detection programs in Indonesia. An organized strategy is defined through stakeholder engagement as the alternative strategy for improving opportunistic breast cancer screening in Indonesia, which is currently being applied as an existing strategy. **Chapter 5** contains the contextualization results, which inform the milestones in the cancer control program, a showcase of implementation in Jakarta Province, participation and patient adherence to diagnostic tests and the sources of accessible data to inform the economic model. Findings in each chapter responded to two research objectives that include identifying parameters to construct the cost-effectiveness model. **Chapter 6** outlines the model structure that reflects the local context of economic evaluation of breast cancer screening in Indonesia. Chapter Seven elaborates the cost-effectiveness analysis using the Markov Model. The analysis results indicate that an organized breast cancer screening program is cost-effective, although it is close to the borderline of willingness-to-pay (WTP). The results of this model provide insight that organized screening is an alternative to the current systematic screening which can improve the quality of early detection of breast cancer within the local context in Indonesia. While systematic screening strategy is most likely to achieve

early detection for a broad population segment, it is also the most resource-intensive approach. Therefore, infrastructure and clarity of guidelines needed to ensure before implementing organized screening.

Chapter **8** consolidated the findings to provide the context of transparency in model development before proposing recommendations for policy implication and future research as highlighted in chapter 9. The model development process includes collecting evidence related to the variation of breast cancer early detection approach, model parameters and policy processes through stakeholder engagement to define alternative interventions in creating a framework ex-ante cost-effectiveness model.

Given the importance of preparing resources for implementing an organized breast cancer screening program and scientific reasoning for policy choices, the following section will discuss policy implications with a focus on advancing breast cancer early detection program in Indonesia

9.2. Strength and limitations of the study

This thesis has both strengths and limitations. Below is the analysis of the research objectives raised in **Chapter 1** , addressing the strengths, and limitations of the study were addressed.

Objective 1. *To undertake a systematic review of the effectiveness and cost-effectiveness of breast cancer screening in Asian countries that focuses on*

a) reviewing the evidence from different approaches to breast cancer screening;

and b) assessing the requirements of plausible parameters for the development of the economic model.

Rich insights from the Asia-specific body of literature have enabled the researcher to synthesize authors' recommendations of region-specific comparative evidence on the variability of the economic analysis of breast cancer early detection. However, this review is not without limitations. Despite having similar epidemiologic background, the reviewed studies provided insufficient information about the patters of early-detection practice, types of economic study and aspects of practical guidance which are crucial for the researcher to draw conclusion of the relevance and full applicability and transferability within and between Asian countries. There is also relatively limited evidence regarding opportunistic screening strategies. Indeed, a contributing factor to the difficulty of apprising opportunistic screening is the scarcity of available data for such a strategy (Madlensky et al., 2003). In addition, despite being able to compare the quality of reviewed articles based on the completeness of reported economic evaluation of the Consolidated Health Economic Evaluation Reporting Standards (Husereau et al., 2013), the researcher did not use the scientific journal rankings in the search strategy as the inclusion criteria. In other words, less stringent inclusion criteria show that most of the evidence in the reviewed studies did not put randomize controlled trials (RCT) at the highest level of importance as evidence.

Objective 2. *To contextualize the decision problem of breast cancer early detection in the Indonesian healthcare setting to align between relevant model structure and the decision needs of end-users.*

This study demonstrated in detail the mechanics of a mixed method economic evaluation that merges strengths and perspective of a quantitative approach and contextually interrelated qualitative methods. The results are contextual domains at macro level and meso level. The macro-level domain includes the existing policies, guidelines, regulations and directives of breast cancer early-detection programs. The meso-level domain showcases how the current macro-context is operationalized in Jakarta province and how the policy process to plans an alternative strategy for screening improvement. A dedicated process to determine context at the micro-level (such as the eligible population for screening) would have been valuable if additional time and resources had been allowed. A limitation of this research is the potentially overgeneralized results that stems from the context-dependent nature of engaging Jakarta province as the only in-depth case study to capture policy implementation. Without any comparative regions, this limitation means results are highly context dependent and therefore difficult to generalize the results of the study.

Objective 3. *To develop cost-effectiveness analysis for breast cancer screening strategies in Indonesia.*

The setting of *ex-ante* evaluation of a predevelopment organized service delivery to improve the quality of breast cancer early detection in Indonesia provides strategic information about potential service changes to be pursued, revealing the evidence

that an opportunistic early-detection approach could not possibly be cost-effective even under the most optimistic assumptions (Chamot et al., 2007; de Gelder et al., 2009; Peisl, Zimmermann, Camey, Betticher, & Bouchardy, 2019). While the stakeholders and program implementers are planning the implementation of organized breast cancer screening, the *ex-ante* evaluation in this study is seeks to clarify whether this choice will yield the most significant benefits from the intended investment. Ex-ante evaluation may also be useful for studying different scenarios and the effects of chance in certain parameter assumptions during implementation (Samset & Christensen, 2017). More importantly, *ex-ante* process of evaluation and decision-making is potentially much more efficient to assess the expected returns from promoting any further chance in clinical management or health policy through the use of the valuable tools of implementation analysis (Hoomans & Severens, 2014). Despite the benefits of identifying the potential cost-effectiveness and avoiding ineffective solutions in early breast cancer detection strategy, the *ex-ante* evaluation in this research setting, encounters many unavoidable limitations. First, although the structure of the decision–analytic model for this study was built on the standard screening pathway and natural history of breast cancer used in many cost-effectiveness studies (Nguyen & Adang, 2018; Sun, Legood, Sadique, Dos-Santos-Silva, & Yang, 2018; Wong, Cowling, Schooling, & M Leung, 2007), there were practical challenges to develop the base-case model associated with insufficient breast cancer screening data. Secondly, selecting an organized early-detection strategy as an alternative option in the model does not represent a robust comparator due to non-existent endpoint data on early-detection interventions. Also,

different utilities for non-invasive and different invasive stages of this study were retained using data available in the Tuft cost-effectiveness registry database rather than the more representative sample sets of Indonesian women. In addition, there are inaccurate cost estimation for systematic screening strategies due to unavailable retrospective estimation of implementation cost data to calculate resources for organized and opportunistic screening. Accordingly, the absence of these empirical values has made large variation intervals used in the cost-effectiveness analysis be subjected to rigorous probabilistic sensitivity analysis.

9.3. Policy Implications

9.3.1. Develop national guidelines, a clear pathway of care and efficient referral protocols for early diagnosis and screening

To focus on effective, organized breast cancer early detection, it is crucial to have national guidelines, a clear pathway of care and efficient referral protocols for early diagnosis and screening are necessary. Protocols need to include the circumstances for detection, compliance with recommendations for diagnostic follow-up testing, and the initiation of treatment for both early diagnosis and screening as part of the pathway-of-care to ensure that people with a screen-positive or abnormal result get referral to follow-up treatments without long delays. The early diagnosis of symptomatic individuals (also called case-finding) focuses on recognizing possible warning signs of cancer followed by taking prompt actions. Employing fast-track pathways may support early-diagnosis intervention to improve clinical pathways (Koo et al., 2021). A breast-care service platform to equip the primary healthcare

level with specialized diagnostic and surgical capabilities has been practiced in Zambia to overcome structural barriers (Mutumba Songiso et al., 2020). As a result, it successfully minimized the time interval between initial presentation and performance of clinical diagnosis, receipt of definitive pathologic diagnosis and initiation of surgery, and receipt of a definitive pathologic diagnosis and referral (Mutumba Songiso et al., 2020).

Meanwhile, for systematic use of testing across an asymptomatic population to detect and treat cancer, formal organizational activities should be attached at the service points to benefit the detection of the eligible population. The screening pathways need to be mapped onto a country's health system to describe how people should move through the screening pathway, flagging how they are identified, invited, screened and referred, and what further investigations and treatment or interventions they will receive (WHO, 2020). The test is systematically offered based on a register of the eligible population using a call-and-recall system to increase participation and limit inequities in socioeconomic levels (WHO, 2020). Additionally, patient navigation involving trained health educators and nurses should be promoted to minimize structural barriers and reduce the number of health encounters and unnecessary steps to receiving appropriate care (WHO, 2020). These navigators play a key role in guiding patients through the screening process to ensure diagnosis and completion of treatment for patients with cancer (Sivaram et al., 2018).

9.3.2. Apply measures to evaluate the organized screening program

Applying metrics and measures that can systematically evaluate screening phases, performance, costs, and outcome measures is essential for the successful implementation of an organized screening program. The evaluation of screening phases should include patient identification activities, screening or rescreening, diagnostic follow-up and treatment (Zapka et al., 2003). Performance indicators include the domains of clinical effectiveness, safety, facilities and resource (Muratov et al., 2020). The measures for both intermediate and long-term outcomes of intervention are clinic-level indicators such as screening rates, case detection, breast cancer incidence and mortality (Subramanian et al., 2018), economic indicators, access to finances for health care, public transportation costs and location of health facilities (Ginsburg et al., 2020). According to WHO, the following information should be routinely collected: demographic and socioeconomic data, legal data (consents and authorizations), financial data related to fees, and clinical patient data (WHO, 2002). Documentation of breast cancer-specific data should also include specific sites and sizes of the tumours and the type of treatment (WHO, 2002).

9.3.3. Integrate the cancer registry with an early-detection registry system

Currently, the multinational contribution data for cancer estimation in Indonesia is extrapolated by those of other nations with good cancer registration systems. Therefore, hospital-based cancer registry (HBCR) centres are now focusing on developing a cancer registry with high coverage and robust data to contribute to

IARC's registry program. Establishing HBCR units to support the quality of cancer registry data was a significant initial step before the Indonesian government embraced the population-based cancer registry in Indonesia. In addition to improving the quality of cancer registry data, the government and stakeholders can prepare a strategy for implementing an organized breast cancer screening, namely establishing the screening registry system, and creating interoperability between the cancer registry and the cancer registry system. This integrated, highly interoperable early-detection registry system would generate high-quality data that can be used for quality assurance, and program monitoring and evaluation. On the other hand, lack of interoperability may prevent the operators of the early-detection programs from effectively identifying eligible for screening, operating call and recalling systems, recording who has seen the test patient, implementing patient-tracking systems and evaluating the endpoint of the effectiveness of an early-detection program. Therefore, based on the need for clear pathways and definition of the variable data, the current cancer data registry can be upgraded for better structural and semantic interoperability using more defined formats, syntax of data exchange, standard codification and data interpretation which altogether produce additional useful results, as defined by the end-users (Shah, Leider, Luo, & Kaur, 2016).

9.3.4. Maintain sustainability and scale up the pilot of decentralized, organized breast-care services pilot

It is crucial to maintain sustainability and scale up the pilot of decentralized organized breast-care services at the national or sub-national levels with a high

prevalence of breast cancer in order to improve the healthcare system. This can be achieved through support and commitment from the local government. Pilot trials should be based on the best demonstrated evidence. For example, an early consultation between the National Cancer Center working group and the LRCB-Ductch Expert Center (Danielle van der Waal, Mireille Broeders, & Ruud Pijnappel, personal communication, 2018) recommended that breast cancer screening should be performed to Indonesian women aged 45–64 years, with a two-year interval. This decision was made after considering data on breast cancer incidence, age distribution of the overall female population in Indonesia, and life expectancy. In addition, large cohort studies have shown that the mortality reduction, indicative of screening effectiveness, is smaller in women aged 40–45 years compared to older women (Hellquist et al., 2011). Data of breast cancer incidence data from two neighbouring countries, Malaysia and Brunei Darussalam, which may have reflected similar breast cancer incidence patterns to those in Indonesia, showed a low incidence of expected breast cancer in women younger than 45 years old. Meanwhile, a sharper increase of incidence appears to women aged 45–49 years than the 40 - 44 years, which may result in an unfavourable balance between benefits and the harms of screening the latter age group.

The recommended screening stopping age in a population depends on life expectancy (van Ravesteyn et al., 2015). According to the Indonesian Central Bureau of Statistics (2015-2020), the current estimates of woman life expectancy (at birth) in Indonesia is 73.6 years. The remaining life expectancy of women aged 45 years at baseline is 32.4 years. Based on this estimated life expectancy in

Indonesia, screening up until 75 years old is not recommended because the closer women are to the average life expectancy, the greater is the risk of overdiagnosis (Kerlikowske, Salzmann, Phillips, Cauley, & Cummings, 1999).

9.3.5. Confirm the feasibility of national screening tests and investigations

It is crucial to have assurance of the feasibility of national funding to cover screening tests and further investigations that included feasible funding sources for diagnostic tests, additional mammographic views, breast ultrasounds, and fine-needle aspirations of the breast. As mandated through Presidential Regulation No 82/2018 on Health Insurance, Minister of Health Regulation No 71/2013 on Health Services in the National Health Insurance, and Health Minister Regulation No 52/2016 on Standard Tariffs for Health Services in the Implementation of Health Insurance Program, the reimbursement rate for screening and diagnostic services for the members of national health insurance member (known as the Social Security Management Corporation for the Health Sector or BPJS) is capped at BPJS scheme funding that covers only for early-diagnosis and opportunistic clinical breast examination screening. Fundings are also available to cover some of the diagnostic tests for a woman might need to reach a definitive diagnosis after an abnormal CBE test. However, the legislation prohibits the use of program fundings for screening tests through the personal invitation to eligible populations. To address this issue, there should be a dialogue forum to discuss possibilities of expanding the universal Health Coverage package to the scale-up integration of people-centre services for secondary prevention of breast cancer. Meanwhile, the alternatives of financing

schemes could be multiple funding sources from mainly domestic donors (Ginsburg et al., 2017) or government-initiated subsidy for targeted population. Historically, cancer services have been funded by long-term sustainable funding, such as expanding government funding via the use of a public-finance health system, compulsory prepayment funding sources (such as taxation), or compulsory health insurance (Jones, 2021). In the absence of these funding schemes, low- to middle-income countries might consider utilizing the current resources and services, namely integrating breast cancer early detection into the primary clinics for cancer and infectious diseases, or collaborating with non-communicable disease programs and maternal and child health services to educate the community about primary and secondary prevention of breast cancer (Sivaram et al., 2018).

9.4. Future research

Future research can include an *ex-post* economic assessment to extend the decision–analytic model by comparing multiple alternative strategies that are considered effective for breast cancer early detection. A meta-analysis of the probability of early-stage shifting is needed to evaluate the impact of adherence to regular schedule of breast cancer screening. The necessary research to appraise the potential costs of intervention design and local adaptation, initiation, scale-up and maintenance for the sustainability of community-based breast cancer early-detection programs would be beneficial for improving the cost-effectiveness analysis of health interventions in resource-limited settings (Sohn, Tucker, Ferguson, Gomes, & Dowdy, 2020). A study involving a deliberative dialogue approach to secure the

commitment and readiness of government and stakeholders to pilot an implementation phase of systematic breast cancer early detection also seems vital, given the increasing emphasis on using implementation science research to narrow the identified research evidence into a routine practice gap (Lobb & Colditz, 2013). The development of the research area and policy agenda is needed to allow the process of transforming strategies to improve the quality of breast cancer detection in limited-resource countries.

9.5. Summary

The findings from this study address existing knowledge gaps and provide recommendations for future policy and research.

Appendix A: Paper 1

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Systematic Review

Economic Evaluation of Breast Cancer Early Detection Strategies in Asia: ASystematic Review

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ABSTRACT

Objective: This article aims to support the development of practical guidelines for early detection of breast cancer in Asia by systematically reviewing economic evaluation studies of such early detection strategies in Asian countries.

Methods: A systematic literature review was conducted following the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols checklist. The quality of reviewed studies was examined using theConsolidated Health Economic Evaluation Reporting Standards statement.

Results: A total of 15 articles on the economic evaluation of breast cancer early detection based in Asia were reviewed. Cost-effectiveness was used in all the studies as the analytic method to compare the cost and consequences of different screening policies. Ten studies were categorized as incorporating the modeled approach. Fourteen studies analysed the cost- effectiveness of the organized population-based approach, in which mammography screening was the prevailing screening modality. Only one study evaluated the cost-effectiveness of early diagnosis for breast cancer patients in orderto provide early treatment. The results from the identified economic evaluations, and consequent recommendations concerning optimal early detection strategies varied among studies, and depended on key parameters and assumption used, as well as differences in inter-country health resources, breast cancer incidence, prevalence and early detection pathways.

Conclusions: The economic evaluation of breast cancer early detection programs is still limited in Asia. Policy decisions on organized mammography screening in women ¸50 are economically attractive in the region, despite the lack of evidence to provide recommendations on opportunistic screening strategy and early diagnosis strategy. Future studies need to provide better transparency of the data used and cover more comprehensive strategies, to make them relevant and adaptable to other Asian countries, resulting in clear policy recommendations on breast cancer early detection strategies.

Keywords: Asia, breast cancer, early detection, economic evaluation.

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Introduction

The health and financial burdens of breast cancer remain sig- nificant, despite considerable efforts to address them.[1,2] Asia, facing high and increasing strain from the disease, is a geographic region that has been less researched than Europe or North America. This absence of region-specific evidence poses a significant threat, in that findings around safety, effectiveness, and cost-effectiveness may differ substantially. This affects both the pathway women experience in the detection and management of the disease, and the resource capacity for implementing early detection strategies.[3,4]

Given the significant prognostic benefit of detecting breast cancer at early stages, early detection is a potentially fundamental strategy in minimizing the burden of the disease. It comprises 2 components, namely early diagnosis and screening.[5] Existing work concerning interventions across the breast cancer contin- uum of care has predominantly been from Western countries.[6,7]

Many Asian countries have been struggling to improve the implementation of early detection strategies due to funding barriers, an absence of evidence to guide programs, and a lack ofappropriate investment in healthcare infrastructure.[8] Addressing the scarcity of healthcare resources in the face seemingly unlimited demand, the feasibility of using economic evaluation is gaining more attention from policymakers in Asia.[9] However,

there are challenges to using economic evaluation in the region due to barriers related to data limitations, as well as users' mini- mum comprehension on economic evaluation, and political and ethical considerations in resource allocation.[9,10]

Economic evaluation can be used as a tool to assist decision- makers in allocating healthcare resources and making choices about the planning and provision of healthcare.[11,12] The central principle of economic evaluation is to estimate the costs and outcomes associated with 2 or more approaches to care in a particular populationand to compare these costs and outcomes simultaneously to understand the trade-offs made when moving between these competing strategies.[13]

There has been a need to develop an Asia-specific body of literature around economic evaluation[6,14,15] to support the development of practical guidelines on early detection and reduce the incidence of breast cancer and the mortality rate in Asia. Several recent reviews have summarized the evidence on the economic evaluation of different aspects of breast cancer con- trol.[15–18] However, these have not been explicitly conducted in an Asian setting, and generally have a broader scope than the simple identification of cases. Given that there is considerable uncertainty when generalizing results from developed Western nations to Asia, it is essential to have region-specific comparative evidence on the variability of the economic analysis of strategies for the early detection of breast cancer. Therefore, this review will pro- vide new knowledge concerning the economic studies which evaluate breast cancer early detection strategies in Asian coun- tries, and synthesize the availability and variability of the health- related economic evaluations undertaken.

Methods

Aim and Objectives

This systematic review aims to assess the variability in eco- nomic analysis of breast cancer early detection strategies in an Asian setting by focusing on the following 3 specific objectives: (1) assess strategies for detecting breast cancer at an early stage; (2) assess the variability of economic evaluation methodology; and
(3) assess the differences in the way the costs and effectiveness of early detection strategies are estimated.

Study Design

The protocol was designed in accordance with the Cochrane Handbook, the reporting standard checklist of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS), and the Preferred Reporting Items for Systematic reviews and Meta- Analysis Protocols checklist. This protocol study is registered with the international prospective register of systematic reviews (PROSPERO, registration number CRD42018115419).

Search Strategy

A systematic literature search was conducted in Medline (via PubMed); EMBASE, using the OvidSP platform; the Cumulative Index to Nursing and Allied Health Literature using the EBSCO platform; Scopus, the Health Economic Evaluation Database (via EBSCO) from its inception up to September 2018, but limited to studies written in English (Appendix 1). In addition, the grey literature was searched using the website of selected organizations and networks, including the International Agency for Research on Cancer and the World Health Organization. The search was expanded by identifying studies from the reference lists of identified relevant studies.

The key definitions used in this review are "economic evalu- ation," "early detection of breast cancer," "strategies," and "Asian countries." These definitions are shown in Table 1.

Eligibility Criteria

Types of early detection strategies

For the review, early detection was defined either as early diagnosis or screening. Early detection without screening entails education of the population and healthcare providers to respond to the first signs or symptoms of breast cancer. Because screening modalities can be delivered through organized or opportunistic approaches, depending on the country's setting, the types of early detection strategies for the review included opportunistic or organized screening using screening modalities such as clinical breast examination (CBE); magnetic resonance imaging, mammography; ultrasonography; or a combination of 2 or moreof these, health promotion of symptoms and signs of breast can- cer; breast self-examination.

Types of studies

Studies were included if they used one or more of thefollowing types of full economic evaluation: (1) cost-effectiveness, cost-benefit, cost-utility, or cost minimisation, evaluating any of the strategies for early detection of breast cancer noted above focused on populations in Asian countries; (2) economic analyses measuring the performance of national breast cancer control programs, programmatic approaches (ie, organized or opportu-nistic), the benefit of particular screening modalities to reduce morbidity, mortality, or any other intermediate outcome, as wellas the evaluation of specific diagnostic imaging equipment to support early diagnosis strategies; and (3) inclusion of the outcome indicators from experimental studies, observational studies, or mathematical models.

Studies were excluded if they met any of the following criteria:
(1) did not present original data; (2) were not a full-text publi- cation; (3) were in the form of comments, letters to the editor, descriptive studies, case reports, or conference papers; (4) did not include information on health outcomes; (5) did not include

Table 1. Operational definition and terms were used in the search strategy.

The systematic review aimed to identify studies that report on the economic evaluation of early detection strategies of breast cancer in Asian countries. The operational definition and terms are defined as follows:
Economic evaluation: articles are eligible if they were dealing with 1 of 4 main types of economic evaluation studies, cost-effectiveness, cost-benefit, cost-utility, and cost minimization.
Early detection of breast cancer: the 2 approaches that enable timely diagnosis and treatment of breast cancer: (1) early diagnosis, that is the recognition of symptomatic cancer inpatient and (2) screening, which is the identification of asymptomatic disease in a healthy target population.

Strategy: initiative, approach, or activities that aim to either: (1) strengthen national breast cancer control program by planning an effective and appropriate early detection program; (2) improve healthcare provision of timely diagnosis and treatment of breast cancer.

information on intervention costs (only gross economic benefitwas estimated); or (6) were not published in English.

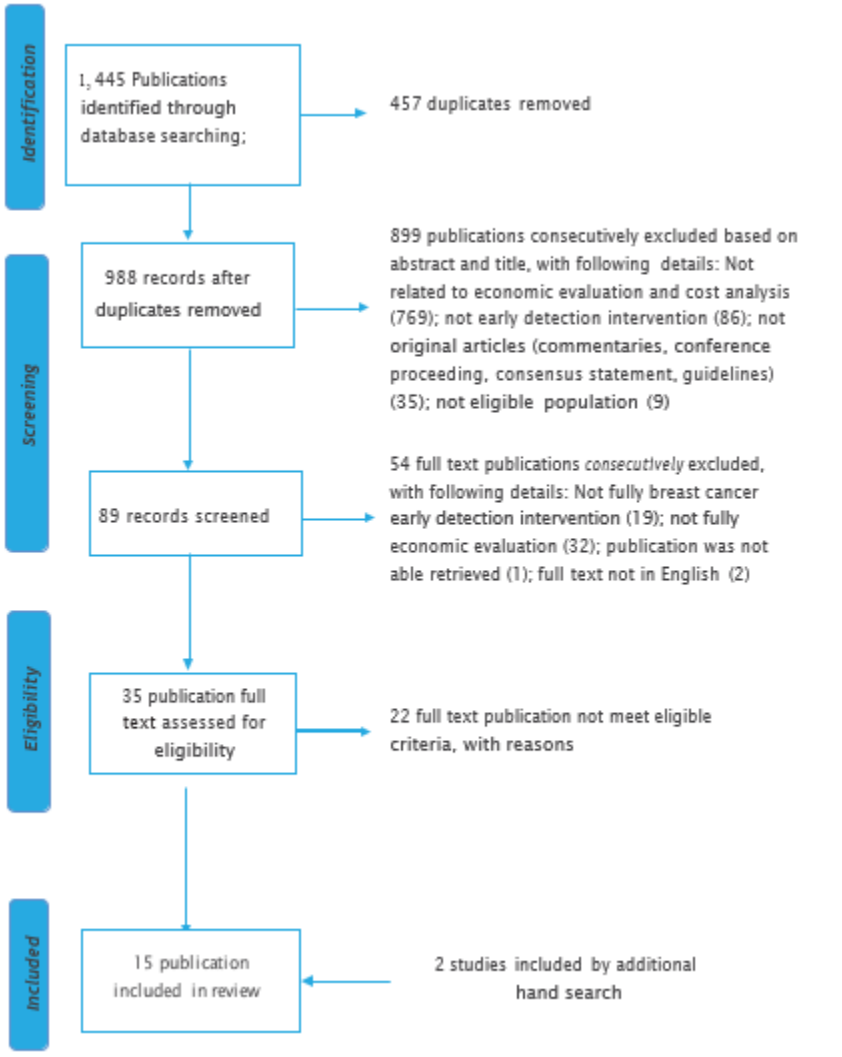
Data Extraction

The study characteristics were extracted from all reviewed studies, these being the country or region, the base year of cost, year of publication and study population. Methodologic charac- teristics that were extracted included the following information: type of economic evaluation, study design, perspective, time ho- rizon, and outcome measure for effectiveness. Information on cost, discount rate, the source of estimation effectiveness, the source for estimation of resources utilization, value, and references used for the study parameter are also listed. The results of the studies were captured using the economic evaluation results obtained by the authors

Data Synthesis

Descriptive characteristics of the eligible studies were extrac- ted and reported in a systematic format, together with the results of their standard reporting appraisal. The variety of early detectionstrategies and epidemiologic backgrounds were explored to frame the policy consideration in the implementation of breast cancer early detection program. Across the studies, based on the author's description, a common theme of early detection strategies was

Figure 1. Flow diagram of the study selection phases.



identified, whether it was screening program or early diagnosis. The study design involved in the economic evaluation of studies was also discussed to consider the methodologic approaches. To facilitate data synthesis, the result of economic evaluation was converted to US dollars and inflated to 2018 prices (http://www. bls.gov/cpi/).

Reporting Quality Assessment

The quality of study reporting was examined using the CHEERS statement.[19] This contains a checklist of 24 items intended to establish the minimum information that should be included when reporting economic evaluations of health strategies; each publication included in this review was assessed against these criteria.[19] Three scale responses were used to appraise each item. Pub- lications scored 1 point for each point fully met, 0.5 for each partially met, and 0 when very little or no information was re- ported. A percentage score was then generated, and the sum of scores divided by the total of domain scores, giving all criteriaequal weight. Studies that scored 75% or more were categorized ashigh quality, scores in the 50% to 74% range were ranked as me- dium, and scores below 50% were ranked low.[20] Because 2 of the reporting criteria may depend on the publisher (source of funding and conflicts of interest), percentage score excluding these criteria were also generated, but this had minimal impact on the categorizations.

Results

Search Results

The systematic selection criteria for the articles are shown in Figure 1. The articles were exported to EndNote X7 (Clarivate Analytics, Philadelphia, PA), with duplicates removed. The title and abstract of the retrieved articles were then uploaded to Rayyan, a free web app for systematic review.[21] The research strategy initially yielded 1445 studies, including 556 from Med- line, 36 from EMBASE (Ovid), 117 from Cumulative Index to Nursing and Allied Health Literature (EBSCO), and 736 from PubMed. After excluding any duplicates, the total number of hits was reduced to 988 records. The application of filters to the titles, abstract and full texts resulted in 15 articles that fully met the criteria.

Study Characteristics

Eight studies based in East Asia, 5 in West Asia, and one each inSouth Asia and Southeast Asia were retrieved in the review. Based on the income classification by the World Bank, 3 of the East Asian countries were categorized as high-income (Japan, Korea, and Hong Kong), 3 were categorized as upper-middle-income (China, Turkey, and Iran), and 2 as lower-middle-income (India and Vietnam).

Table 2 shows the characteristics of the studies based on the elements of economic evaluation reported in them. All conducteda full economic evaluation and cost-effectiveness analysis. A va- riety of perspectives were used, including that of the payer[22–25]; society[26–29]; healthcare provider[30,31]; health system[32]; govern-ment[33–35]; and program perspective.[36] Time horizons to capture benefit, cost, and resources were reported in 13 studies, in the range of 5 months to a lifetime. Nine of the studies included in- formation on the cost and outcomes in future years over specific time horizons, discounted at 3% for both cost and effect; one studyonly discounted cost at an annual rate of 5%; while the discounted rate percentage was not specified in 4 studies. The base year of thecost data was generally from 2000 onward, with only one study before 2000, and one that could not be identified.

Twelve studies included only direct and recurrent costs, having excluded any start-up costs,[22–28,30–34,36] while 3 studies were considered to have included indirect costs in their analysis.[28,29,34]In terms of health outcomes, 9 studies reported one of the following primary health outcomes: years of survival, life expec- tancy, number of breast cancer deaths averted, mortality reduc- tion, or disability-adjusted life-years (DALY).

Intermediate outcomes measured included the number of detected cases[24,30,31] and participation rate.[35] One study in Japan used economic evaluation alongside a randomized control trial (RCT).[35] Two studies in Iran and one in Turkey use used a pilot study as their primary data sources to calculate the parameters of cost and the effectiveness of screening programs.[25,28,31] In addi- tion, other studies combined data sources from existing datasets, including cancer registries, hospital data, and the International Agency for Cancer Research.[27,30,33,34,36]

Sensitivity analysis was conducted to handle uncertainty around the cost-effectiveness ratio. Table 2 outlines the analytical methods used in the included studies to deal with such uncer- tainty. Fourteen studies performed sensitivity analysis, 7 of which involved a single method, either one-way sensitivity anal- ysis,[24,30,34] scenario analysis,[22,31,33,36] or probabilistic sensitivity analysis.[26] Six studies applied a combination of techniques; 3 combined one-way sensitivity analysis with probabilistic sensi-tivity analysis,[23,29,32] and 3 combined scenario analysis and multi- way analysis.[25,27,28] One RCT study, which deployed the statistical analysis approach did not demonstrate the method for exploring any study uncertainty.[35]

The parameter values of breast cancer screening effectiveness were referenced in accordance with the results of screening trials conducted within the country of origin of the studies, or from other countries (Appendix 2). Three studies from Japan,[22,27,33] one from Korea,[30] one from China,[29] and one from Iran[25] were refer- enced for the values of sensitivity and specificity of screening modalities from the reports of a pilot study and an observational study within the country. On the other hand, the studies fromHong Kong, Vietnam, and India used references from studies in the United States, Japan, and the Netherlands, respectively.[23,26,36] Only one study used expert opinion to justify the values of mammography sensitivity and specificity.[32] Parameters related to relative risk of invasive breast cancer, stage distribution, and sur- vival were obtained from the Surveillance, Epidemiology and End Results program, randomized trials, and simulation studies.[26,28,32]

Early Detection Strategies

Table 3 provides information on the different strategies of early detection intervention for reducing breast cancer incidence and mortality. The most common was 2-yearly population-based screening program[26–28,30,33–36]; other strategies included deploy- ment of a reminder system to enhance screening rates within the nonadhering population.[35] The main screening modality used was mammography testing,[23–32,34,35] while 3 studies included com- bined mammography and clinical breast examination.[22,33,36] One study evaluated the cost-effectiveness of early diagnosis to allow patients with breast cancer to receive early treatment.[24]

A range of starting and terminating ages was used to report thetarget population; 10 studies evaluated starting and terminating age-specific cost-effectiveness measures. Nine of these studies simulated the model with a starting age range in the 40s, while 4 started with a younger age range (30-35 years old). The range of terminating ages reported was between 59 and 75. In one study in

Appendix B: Interview guideline

DOMAIN 1: DEMOGRAPHICS AND EPIDEMIOLOGY

For each subset (demographics, mortality and vital statistics, breast cancer early detection epidemiology) where data are available, ask the following questions:

1.1 What are the structures and processes to obtain and report data on population demographics, mortality, vital statistics, and breast cancer early detection epidemiology?

Probes:

- What are the data sources, and how are the reported numbers derived?
- How are the data aggregated and analyzed? Are paper-based or electronic systems (or registries) in use? What is the system name, what entity maintains it, and who are the users?
- Are there guidelines for reporting data into the system (or registry)? What are data quality checks in place for these data?
- What is the quality of these data in the following six dimensions: Completeness, Conformity; Accuracy, Duplication; Integrity, and Timeliness?
- Are the systems integrated or linked to any other systems (e.g., system for vital registration linked to the cancer registry; cancer registry related to health management information system)?

1.2 How and by whom have these data been used in the past 12 months?

Probes:

- Are they used for program planning, development, or improvement?
- Are they used for policy development or modification?
- Are you used to determining resource allocation?
- Is it used to produce an internal or external report or presentation?

For each subset where data are available but are NOT current, ask the following question (in addition to the questions above):

1.3 What are the barriers to collecting or obtaining current data on population demographics, mortality, vital statistics, and breast cancer early detection epidemiology?

Probes:

- Is this an issue of data accessibility or availability?
- If there is an access issue, who currently has access to these data? What is the process to expand access?
- If there is an issue of availability, are there other systems or processes that could potentially

be leveraged to collect more current data?
- Is timeliness impacted by the availability of resources to collect and manage these data?

For each subset where data are NOT available, investigate further by asking:

1.4 Why are these data not available?

Probes:

- Is this an issue of access or availability?
- Are there systems and processes to provide specific programs with the necessary epidemiological and surveillance data for planning, management and targeting?
- What data and systems are other programs using for planning, monitoring, and determining impact?

1.5 Please describe any other registries, systems and sources of surveillance or epidemiological data relevant to breast cancer early detection that were not described above.

Probes:

- Are there routinely conducted population-based surveys (e.g., DHS, STEPS, etc.)?
- Are there surveys to collect: mortality data? Breast cancer data? Breast cancer early detection data/information? When was the last survey, and when will the next poll be?
- Where there is a cancer registry, is it paper-based or electronic? Are there guidelines for reporting invasive breast cancer early detection data? Are there guidelines for monitoring and quality control of the data?
- Where there is a breast cancer early detection screening registry, is it paper-based or electronic? Are there guidelines for reporting? Are there guidelines for monitoring and quality control of the data?
- Where there is a registry capturing community-based breast cancer early detection screening, is it paper-based or electronic? Are there guidelines for reporting? Are there guidelines for monitoring and quality control of the data?
- Who reports into the systems, who has access to the data, and how has the data been used in the past 12 months?
- Are these systems integrated with or linked to any other methods? Can information readily be shared between systems? Please describe the process.
- What is the quality of these data?

DOMAIN 2: GOVERNANCE, MANAGEMENT, AND INFRASTRUCTURE

Where information and data on infrastructure are available, ask the following:

How is the healthcare sector addressed and prioritized in government structures to deliver essential infrastructure and telecommunications and ensure government effectiveness?

2.1 How is the healthcare sector addressed and prioritized in government structures to deliver essential infrastructure and telecommunications and ensure government effectiveness in delivering breast cancer early detection?

Probes:

- Does the basic framework include infrastructure specific to healthcare service provision? What are some gaps in this infrastructure? What, if any, efforts are in place to strengthen these domains?
- What percentage of facilities with access to essential infrastructure domains and telecommunications technology? What efforts, if any, are in place to strengthen these domains?
- Are there critical examples in the healthcare sector of leveraging available ICT for programming (e.g., data collection and management, patient follow-up, etc.)?

Where information and data on infrastructure are NOT available, ask the following:

2.2 What are some of the most significant gaps experienced by the healthcare sector in terms of basic infrastructure (e.g. electricity and water) and telecommunications (e.g., telephones and mobile networks, computers, and internet)?

Probes:

- Are there certain healthcare system levels with better access to basic infrastructure and telecommunications? Do private or NGO facilities typically have better access than government/public facilities?
- Is there political will behind prioritizing the delivery of basic infrastructure and telecommunications elements to the healthcare sector?
- Are there critical examples in the healthcare sector of leveraging available ICT for programming (e.g., data collection and management, patient follow-up, etc.)?

Where there is an organizational structure for national healthcare governance, ask the following:

2.3 Are there any key strengths or weaknesses in general health care or breast cancer early detection /screening service delivery or programming because of the healthcare governance structure?

Probes:

- Has this structure recently changed or been adapted? What impact did this have on service provision and access to healthcare services?
- Is there a different ministry/department that oversees health care financing? Human resources for health? Information technology for health?
- Do the different ministries/departments that oversee health care, and information technology have standing coordination meetings, working groups or other collaborative opportunities?

Where there is NOT an organizational structure for national healthcare governance, ask the following:

2.4 Please describe how health care is provided.

Probes:

- Are there specific organizations, institutions, or agencies responsible for providing health services? Are they private (for-profit)? Do they provide health care to the entire country, or only to specific subnational areas?
- Who is responsible for healthcare financing and the provision of primary healthcare infrastructure?
- What is the relationship between any entities providing health services, health-care infrastructure or financing and the government?

2.5 Please describe the organization and management of breast cancer early detection prevention and control activities within the MoH. If an organogram is available, please provide a copy.

Probes:

- How many units/depts. have authority over breast cancer early detection activities?
- Do the units/depts. Also, have authority over other disease areas? What areas?
- Is there staff dedicated to breast cancer early detection at the department, section, unit, or program level? Is this number of staff sufficient?
- What decisions regarding breast cancer early detection prevention and control programming are made at the centralised National level? Subnational level? Program level?
- In high BREAST CANCER prevalence contexts: What is the

level of integration between breast cancer early detection prevention and control programming?

2.6 Please describe the level of interaction between different programs/units and other stakeholders.

Probes:

- How do the breast cancer early detection screening, and invasive breast cancer diagnostic and treatment communicate (e.g. regular meetings/forums)?
- Are data routinely exchanged between different sections/units? If applicable, are data exchanged with the BREAST CANCER EARLY DETECTION program?
- What is the level of interaction between breast cancer early detection prevention, screening, diagnostic, and treatment of invasive breast cancer early detection management programs and units or departments responsible for Health Information Systems and ICT?
- Is there a national stakeholder forum for breast cancer early detection (prevention screening or treatment)? Are any stakeholders designing or supporting systems for data collection around breast cancer early detection?

DOMAIN 3: POLICIES, PLANS, STRATEGIES AND CLINICAL GUIDELINES

3.1 Please describe the policies, plans and strategies that govern breast cancer early detection.

Probes:

- How many different policies, plans or strategies govern breast cancer early detection? What is the level of integration between screening, diagnostic and invasive breast cancer treatment?
- Have the plans or strategies been fully costed?
- How widely are the policies, plans and strategies disseminated?
- Does service provision at all levels follow the policies, plans and strategies? In private facilities as well?
- What is the scope of recommendations in the policies, plans and strategies? Are they detailed enough to offer appropriate guidance for service provision?
- Who is responsible for drafting and updating plans or policies? Please briefly describe the process.
- Do any of the plans or strategies include a monitoring and evaluation plan?

3.2 Please describe the clinical practice guidelines for breast cancer early detection (screening, diagnostics, treatment of invasive breast cancer).

Probes:

- How many different clinical practice guidelines are endorsed by MoH for breast cancer early detection prevention and control services? What is the level of integration between screening, diagnosis, and treatment of invasive breast cancer early detection?
- Are there clinical practice guidelines that address BREAST CANCER EARLY DETECTION/ SCREENING?
- Are the guidelines developed at the National level? Subnational level? Program/facility level? Partner level? What department, section or unit is responsible for updating and drafting the guidelines?
- How widely are the guidelines disseminated?
- Does service provision at all levels follow the guidelines? In private facilities as well?
- Are the guidelines detailed enough to guide service provision?
- If clinical practice guidelines do not exist, how do providers make decisions about patient care (e.g. are there other supportive resources in use)?

DOMAIN 4: SERVICE AVAILABILITY AND UTILIZATION

4.1 Please describe the availability and general status of early detection programs and services for breast cancer screening, diagnostic and treatment.

Probes:

- What breast cancer detection and early detection services are offered (national and subnational)? Are these the same as outlined in national policies, plans or strategies?
- Are breast cancer screening services available through mobile units? Are these units tied to specific facilities or programs?
- Are the services designated to be provided at each health care facility level provided with regularity and without interruption?
- Are there enough facilities providing services to meet population needs?
- What type of service/location of service provision is the most accessible to women seeking services (e.g., at a facility, mobile unit, or campaign)?
- How do private facility service availability and provision differ from the public sector (e.g., Do private facilities use mammograms? Is it primarily public facilities that offer mobile mammography services?)

Where data are available, ask the following questions:

4.2 What are the structures and processes to obtain and report data on health facilities and their services?

Probes:

- What are the data sources? Are these data routinely collected and reported as part of program service delivery or through periodic health facility censuses or surveys and assessments of service availability and facility readiness?
- Is there a national Master Facility List or Registry?
    - Does the list include all facilities in the country (public/government, NGO, faith-based, private, etc.)?
    - Does the list capture breast cancer early detection services provide?
    - What data elements are captured?
- What entity is responsible for collecting and maintaining information on health facilities (including location and distribution) and their services?
- How are these data used? Who has access to these data?
- If these data are derived from routine data collection, how are the data aggregated, analyzed and transmitted?
    - If electronic systems are in use, what is the system name, what entity maintains it, and who are the users?
- Are these data linked or accessible to other systems (?

How are they related? To what systems?

4.3 What is the quality of these data?

Probes:

- Please describe data quality in the following six dimensions: Completeness, Conformity, Accuracy, Duplication, Integrity, and Timeliness.
- What are data quality checks in place for these data? Are routine data audits or updates conducted?
- Is there a backup system for these data?

Where data are available but are NOT current, ask the following question (in addition to the questions above):

4.4 What are the barriers to collecting or obtaining current data? What are potential opportunities for strengthening?

Probes:

- Is this an issue of data access or availability?
- Are resources available for conducting more timely periodic surveys or assessments?
- Are there existing systems or periodic surveys or assessments which could be better coordinated or leveraged to collect these data?

Where data are NOT available, investigate further by asking:

4.5 Why are data not available?

Probes:

- Is this an issue of data access or availability?
- If there is an access issue, what are the barriers to obtaining these data for decision-making? Who currently has access to these data?
- If there is an issue of availability, are there existing systems or periodic surveys or assessments which could be leveraged to collect these data for breast cancer early detection?
- What data and systems are other programs and healthcare areas using for planning and monitoring service delivery and distribution?

Where data are available, ask the following:

4.6 What are the structures, processes, and systems in place to collect data on service delivery at the client/ facility level and to aggregate and report these data?

Probes:

- What is the level of standardization of existing structures and processes, and what entities are responsible for coordination and management (e.g. National level? Subnational level? Program or facility status?)?
- How are the numbers reported in the survey responses derived/obtained? What are the data sources?
- Who has access to these data?
- How are these data used (e.g., for patient management; for program

or policy development, resource allocation; to inform research; to develop a report, etc.)? Are data used frequently and routinely?
- Are the data stored securely to maintain privacy and confidentiality?
- Are there standardized forms, registers, or systems for collecting client-level data? And for summarizing and reporting facility-level data to the national or subnational level?
    - Is there a standardized set of minimum data elements to be collected?
    - Is this information sufficient for both patient management and program monitoring?
- How do systems collect client-level data exchange information with data aggregation systems?

4.7 What is the quality of client-level data?

Probes:

- Please describe data quality in the following seven dimensions: Completeness, Conformity, Consistency, Accuracy, Duplication, Integrity, and Timeliness.
- What are data quality checks in place for these data? Are routine data audits or updates conducted?
- What is being done to improve the data quality?
- Is there a backup system for these data?

4.8 What is the quality of aggregate data?

Probes:

- Please describe data quality in the following seven dimensions: Completeness, Conformity, Consistency, Accuracy, Duplication, Integrity, and Timeliness.
- What are data quality checks in place for these data? Are routine data audits or updates conducted?
- What is being done to improve the data quality?
- Is there a backup system for these data?

Where data are available but are NOT current, ask the following question (in addition to the questions above):

4.9 What are the barriers to collecting or obtaining current data?

Probes:

- Is this an issue of data access or availability
- Are there specific data elements that create a barrier to the timely reporting of summarized facility data?
- What are the significant challenges with data collection, management, and aggregation?
- Is there a demand for these data for decision-making? For patient and program management?

Where data are NOT available, investigate further by asking:

4.10 Why are data not available?

Probes:

- Is this an issue of access or availability?
- If there is an access issue, what are the barriers to obtaining these data for decision-making? Who currently has access to these data?
- Are there systems and processes to provide specific programs with the necessary data for planning, management and targeting?
- What data and systems are other programs and healthcare areas using for planning, monitoring, and determining impact?
- Can the systems, structures and processes utilized by other programs and health areas be leveraged for breast cancer early detection?

4.11 What are the systems and processes for tracking women referred to services following a positive screen or breast cancer early detection diagnosis?

Probes:

- Do referral mechanisms work promptly? If not, please identify the significant gaps as you understand them.
- Is there integration or cross-referral between public and private facilities? For what services?
- Are there standardized paper forms or electronic systems and processes for referral mechanisms and tracking women through the continuum and between facilities? What are the primary gaps in these systems and processes?

DOMAIN 5: HUMAN RESOURCES

5.1 Please describe the availability of trained healthcare service providers – focusing on those relevant to the provision of breast cancer early detection screening, diagnostic and treatment of invasive breast cancer.

Probes:

- What cadres of providers generally provide breast cancer early detection services?
- Are specific cadres outlined in early detection policies, plans, strategies, or clinical guidelines for breast cancer? Are the providers currently providing services the same as those outlined?
- Are training needs or qualifications for breast cancer early detection service providers outlined in policies, plans, strategies, or clinical guidelines for breast cancer early detection?
- Are these providers typically trained inside or outside of the country/province/district?
- Is the number of trained service providers sufficient to meet the population's needs?
- What are the significant gaps in the availability of trained service providers? How do these gaps impact service provision? Is anything being done to address these gaps?
- What entity is responsible for ensuring the training and distribution of a sufficient number of service providers?
- Are there opportunities that can be leveraged to increase the availability of trained breast cancer early detection/screening service providers?

Where data are available, ask the following question:

5.2 What are the structures and processes to obtain and manage data on healthcare provider training, certification programs, continuing education, and capacity building?

Probes:

- Is there a central system to track the training of breast cancer early detection/screening service providers? Please describe the system: what are the data sources? What entity is responsible for maintaining the system? What entities report into the system?
- Is there a central system for tracking continuing medical education programs? Please describe the system.
- Do systems include all available education and training opportunities (e.g. public/government, NGO, faith-based, private, etc.)?
- Are the systems for tracking provider training and certification integrated with or connected to the methods for managing human resource distribution (e.g. health provider registry or list)?

- How often is this information updated? What are the processes for updating, and how is the information validated?

Where data are available but are **NOT** current, ask the following question (in addition to the question above):

5.3 What are the barriers to collecting, obtaining, or maintaining current data? What are potential opportunities for strengthening?

Probes:

- Is this an issue of data access or availability?
- Are there existing systems or periodic surveys or assessments which could be better coordinated or leveraged to collect and update these data?
- If there is an access issue, what are the barriers to obtaining these data for decision-making? Who currently has access to these data?

Where data are NOT available, investigate further by asking:

5.4 Why are data not available?

Probes:

- Is this an issue of data access or availability?
- If there is an access issue, what are the barriers to obtaining these data for decision-making? Who currently has access to these data?
- If there is an issue of availability, are there existing systems or periodic surveys or assessments which could be leveraged to collect these data for breast cancer early detection?
- What data and systems are other programs and healthcare areas using for planning and monitoring service delivery and distribution?

Where data are available, ask the following question:

5.5 What are the structures and processes to obtain and report data on healthcare service providers?

Probes:

- What are the data sources (e.g., systematic collection and reporting; periodic surveys and assessments of service availability and facility readiness; etc.)?
- Is there a national Master Provider List or Registry?
    - Does the list include all cadres of providers in the country (public/government, NGO, faith-based, private, etc.)? Or does it have only limited cadres (e.g. surgeons and doctors, but not nurses?)?
    - What data elements exist within this provider registry (e.g. qualifications, location, services, training)?
    - Who has access to this provider list/registry?
- Is the national list or registry integrated with healthcare provider training data or facility data?
- What entity is responsible for collecting and maintaining

information on service providers (including location and distribution) and their qualifications?
- If these data are derived from routine data collection, how are the data aggregated, analyzed and reported?
- If electronic systems are in use, what is the system name, what entity maintains it, and who are the users?
- What are data quality checks in place for these data?
- What is the quality of these data in terms of the following dimensions: Completeness, Conformity; Accuracy, Duplication; Integrity, and Timeliness?

Where data are available but are NOT current, ask the following question (in addition to the question above):

5.6 What are the barriers to collecting or obtaining current data? What are potential opportunities for strengthening?

Probes:

- Is this an issue of data access or availability?
- Are resources available for conducting more timely information updates through periodic surveys, assessments, or other systematic means?
- Are there existing systems or periodic surveys or assessments for general health care which could be better coordinated or leveraged to collect these data for breast cancer early detection?

Where data are NOT available, investigate further by asking:

5.7 Why are data not available?

Probes:

- Is this an issue of data access or availability?
- If there is an access issue, what are the barriers to obtaining these data for decision-making? Who currently has access to these data?
- If there is an issue of availability, are there existing systems or periodic surveys or assessments which could be leveraged to collect these data for breast cancer early detection?
- What other programs and healthcare areas use data and systems to plan and monitor healthcare provider availability, qualifications, and distribution?

DOMAIN 6: EQUIPMENT, SUPPLIES AND MEDICINES

6.1 Please describe the availability of equipment and supplies for breast cancer early detection screening, diagnostic and treatment of invasive breast cancer services

Probes:

- What equipment, supplies, medicines, or commodities present the most significant barrier to providing breast cancer early detection services without interruption?
- Are supplies and medicines for breast cancer early detection on the essential national supplies and medicines lists? If not, what are the processes for including them? What are the barriers?
- Are the available equipment and supplies sufficient to meet the population's needs?
- Are our equipment, supplies, and medicines more regularly available at certain healthcare system levels? Or at private versus public facilities?
- Are medicines for invasive breast cancer, early detection, pain management, and palliative care available to out-patients as oral prescriptions? Are these medicines only available to in-patients? What are barriers to out-patient availability?
- Are the line item costs available for breast cancer early detection supplies and commodities?

DOMAIN 7: LABORATORY and RADIOLOGY

7.1 Please describe the availability, organization, and management of laboratory and radiology services for breast cancer early detection screening, invasive breast cancer early detection diagnostics and treatment.

Probes:

- How is the laboratory/radiology system in the country organized? Are most breast cancer early detection services provided by government or private laboratories?
- Are most laboratories/radiology connected to hospitals or health facilities? Or are they standalone? is this organization service-dependent?
- Please provide a summary of the laboratory strategy and plan. If no system exists, is there a future for such a strategy?
- Are there enough laboratories/ radiology to meet the demand for breast cancer early detection screening and diagnostic services?
- What are the primary gaps in the laboratory system?
- Please describe the processes, plans or guidelines for laboratory and radiology accreditation and quality and performance evaluations for breast cancer early detection screening and diagnostic test services.

Where data are available, ask the following questions:

7.2 What are the structures and processes to obtain and report these data?

Probes:

- What are the data sources? Are there data periodic censuses or surveys and assessments of laboratory service availability and readiness?
- Are there systems for tracking laboratory/laboratory accreditation and quality and performance evaluations for breast cancer early detection screening and diagnostic test services? Please describe the systems.
- What are data quality checks in place for these data?
- What entity is responsible for collecting and maintaining information on human laboratory resources (including location and distribution), the services they provide and their level of accreditation/ qualification?
- What entity is responsible for collecting and maintaining laboratory information (including location and distribution), the services they provide and their level of accreditation/ qualification?
- How are data on laboratory/radiology human resources, service availability and accreditation used? Who has access to these data?

Where data are available but are NOT current, ask the following question (in addition to the questions above):

7.3 What are the barriers to collecting or obtaining current data? What

are potential opportunities for strengthening?

Probes:

- Is this an issue of data access or availability?
- Are resources available for conducting timely periodic surveys, assessments, or other systematic updates?
- Are there existing systems or periodic surveys or assessments which could be better coordinated or leveraged to collect these data?

Where data are **NOT** available, investigate further by asking:

7.4 Why are data not available?

Probes:

- Is this an issue of data access or availability?
- If there is an access issue, what are the barriers to obtaining these data for decision-making? Who currently has access to these data?
- If there is an issue of availability, are there existing systems or periodic surveys or assessments which could be leveraged to collect these data for breast cancer early detection?
- What data and systems are other programs and healthcare areas using for planning and monitoring laboratory service delivery, distribution, and quality?

7.5 Please describe the procurement and distribution of laboratory supplies for breast cancer early detection screening and diagnostic services.

Probes:

- Who is responsible for procuring and distributing laboratory supplies for breast cancer early detection diagnosis within the country? Are the same entities accountable for procuring health facilities' supplies, commodities, and medicines?
- What system is used to procure & track the inventory of laboratory supplies for breast cancer early detection? Is this an electronic or paper-based system? Who enters inventory information, and who has access?
- What is the level of government ownership of this system? How broadly is it used?
- Are the systems for managing inventory for laboratory/laboratory supplies and commodities linked to those for procurement of supplies, items, and medicines for health facilities? Are these systems linked to systems capturing information on service utilization?
- How is inventory managed to prevent stockouts at laboratories, and how are stockouts monitored and addressed? What are the strengths and weaknesses of the inventory management system?
- Are periodic surveys or assessments conducted to determine the availability of laboratory supplies for breast cancer early detection and functionality of the procurement system and supply chain?

7.6 Please describe the systems and processes for documenting and communicating laboratory and diagnostic test results.

Probes:

- Is there a national Laboratory Information System that includes client level laboratory results data? What entity is responsible for maintaining and updating this system?
- What are the standards for documenting and reporting cytology results? Biopsy results? Is the standard terminology used consistently?
- Are there guidelines for collecting and reporting laboratory results data?
- What is the quality of these data in terms of the following dimensions: Completeness, Conformity, Accuracy, Duplication, Integrity, and Timeliness? Are data quality checks in place?
- What information is exchanged between the laboratory and health facility? What information accompanies the sample? What information is provided back to the facility and the provider?
- Please describe the flow of results information from the laboratory to the client? Is this direct or via the health facility/provider?
- Is feedback provided to the facility/provider on inadequate or unusable samples?
- Are there forms or systems to facilitate timely information exchange between health facilities/ providers and laboratories? Are there specific laboratory-based tests or processes which delay results reporting?

DOMAIN 8: FINANCING, BUDGET, AND COSTING

8.1 What opportunities and threats resulting from the current financing and budgeting structure for breast cancer early detection, early detection services, programming, and human resources?

Probes:

- Is the current funding stream sustainable? Are there specific risks associated?
- If there is not a dedicated breast cancer early detection budget, is there a regular percentage allocation for breast cancer early detection services and programming?
- Who is involved in developing the breast cancer early detection (i.e., Are program personnel involved? Service providers or clinicians? A national costing and planning unit not specific to breast cancer early detection?)?
- Are there resources allocated explicitly to supporting capacity building and provider training? Are these resources sufficient?

8.2 What are the systems and processes for breast cancer early detection, early detection budgeting, and costing?

Probes:

- Are breast cancer early detection costing data systematically

collected and managed? Is collecting cost data an ongoing process, or was it done as a one-time activity?
- How are line-item costs for breast cancer early detection estimated or determined? How are service costs per individual estimated? How often are line-item fees updated?
- Who has access to these data and systems?
- Are the systems and processes for budgeting and costing linked to other systems (e.g. those for procurement and supply management)?

8.3 Where costing data (i.e., line-item costs, service costs per individual, overall budget requests and allocations) are available, how have these data been used in the past 12 months?

Probes:

- For program budget forecasting?
- Inventory and stock maintenance?
- Cost-effectiveness or efficiency analyses?
- Program or impact evaluation?
- Planning for service introduction or scale-up?
- Service feasibility studies?

DOMAIN 9: HEALTH INFORMATION SYSTEMS OVERVIEW

Where a national policy, plan or strategy for ICT exists, ask the following:

9.1 Please describe the national ICT policy, plan, or strategy.

Probes:

- What pillars or focus areas are prioritised? Does the plan directly address health? And breast cancer early detection prevention and control?
- Does it outline a clear framework or strategy for implementation? For monitoring implementation?
- What are some of the activities outlined in the policy, plan, or strategy?
- What are the expected outcomes? Is there a timeline associated with implementation and outcomes?

Where a national policy, plan or strategy for eHealth exists, ask the following:

9.2 Please describe the national eHealth policy, program, or design.

Probes:

- What does the plan hope to achieve? Is there a clear goal or vision?
- Is there an implementation framework or roadmap that reflects country priorities? What are the key priorities?
- Does it include a plan to monitor implementation? Assess opportunities and gaps?
- Are required components and resources identified?
- Is breast cancer early detection prevention and control addressed?

Where there are no national policies, plans, or strategies for ICT or eHealth, ask the following:

9.3 What are the barriers to developing a national policy, plan, or strategy for ICT or eHealth?

Probes:

- Are resources available for development?
- Needs such as a policy, plan or strategy have been identified.
- Are there plans to draft such a policy, program, or design?
- What currently guides ICT and eHealth development and implementation?

9.4 Please describe the organisational structure of eHealth and ICT and any key strengths or weaknesses.

Probes:

- Is there an eHealth coordinator? What Ministry or department is responsible for eHealth coordination?
- Is there one unit or multiple units that oversee health information systems?
- Are there established eHealth coordination structures specifically for breast cancer early detection on a national or subnational level?
- Do these structures engage all key stakeholders at the district/municipality level?
- Is there a sufficient staff to support national ICT and eHealth needs? Are staff adequately and appropriately distributed?
- Are there resources allocated to ICT and eHealth? How are they financed, and who is responsible for budget development?
- What are some of the critical opportunities or threats that the structure poses for high-quality breast cancer early detection data systems?

Where a national M&E plan for breast cancer early detection exists, ask the following:

9.5 Please describe the M&E plan for breast cancer early detection prevention and control

Probes:

- Is the M&E plan for screening and treatment integrated with the M&E plan for invasive breast cancer early detection? If no, please describe each (use probes below for each project).
- How widely is the plan disseminated?
- Are action plans included in the M&E strategy/plan?
- Do the plan outline process, timelines, and responsibilities? Please describe.
- Does the plan outline specific indicators and a plan for data collection, analysis, and reporting?
- Is capacity building for M&E staff addressed? Is the development of data systems and tools addressed?

Where a national M&E plan for breast cancer early detection does not exist, ask the following:

9.6 What are the barriers to developing a national M&E plan for breast cancer early detection prevention and control?

Probes:

- Are resources available for development? Does the technical

capacity for the plan's development exist?
- Needs an M&E plan been identified?
- Are there plans to develop an M&E plan for breast cancer early detection?
- What currently guides breast cancer early detection monitoring and evaluation?

9.7 Please describe the team responsible for M&E of breast cancer early detection prevention and control programming, noting any strengths, challenges, and gaps.

Probes:

- How is this team structured? Are there protocols and lines of authority for these individuals?
- Is M&E for breast cancer early detection screening and precancerous lesion treatment integrated with M&E for invasive breast cancer early detection?
- What are the responsibilities and outputs of the M&E team?
- Are M&E efforts harmonised between public and private entities? Between national government and their implementing partners?
- Is there an active M&E working group, and are there minutes to demonstrate their work?
- Is there a dedicated budget allocation for M&E? What entity (or entities) finances M&E at the national level?
- Are M&E staff adequately and appropriately distributed in the country? Is there any bias toward distribution at the mid-level?
- Does the number of staff meet needs? What are some of the critical gaps in staffing?
- Is there harmonization between units/departments? And across the health system levels?

9.8 Please describe the availability of trained personnel to support data and data systems.

Probes:

- Are staff adequately and appropriately distributed in the country? Is there any bias toward distribution at the mid-level?
- Does the number of staff meet needs? What are some of the critical gaps in staffing?
- Is there harmonisation between units/departments? And across the health system levels?
- Are there IT staff or developers specifically dedicated to breast cancer early detection data and systems?
- Are staff to support data systems primarily MoH employees? Or contractors? Or external consultants?

This question focuses primarily on information relevant to client-level data systems and processes; responses to 4.7–4.11 provide additional detail on data access and use, health information exchange, and data quality.

9.9 Please describe the client-level data systems in use, noting any key strengths and gaps.

Probes:

- Is the system exclusive to breast cancer early detection or part of a

comprehensive client-level system?
- Do these systems collect data from static facilities only? From fixed facilities and mobile units? From campaigns or outreach?
- Are campaign data shared with other care settings? Which ones and how are they transmitted?
- Are there exemplar programs that manage client-level data well? If yes, which programs?
- Are the data collected at the client level mostly free text or coded?
- If electronic systems exist, what is the level of MoH endorsement of strategy, and what stage of maturity (early design, pilot, scaling, no longer operational)?
- What are the plans for national/subnational client-level systems? What are the anticipated opportunities and challenges?
- If any systems have changed, what strategies are in place to integrate historical data?

These questions focus primarily on data systems and processes for aggregating and reporting service delivery and program monitoring data; responses to 4.7–4.11 provide additional detail on data access and use, health information exchange, and data quality.

9.10 Please describe the data systems and processes for aggregating and reporting data, highlighting the strengths and weaknesses of these systems and any plans for M&E.

Probes:

- Is the system exclusive for breast cancer early detection? Or a national health information system that collects breast cancer early detection and early detection data and other health data?
- What data are reported into these systems and by whom (e.g. static facilities, mobile units, campaigns, hospitals, etc.)?
- Is feedback on the quality of reported data provided from the higher program levels (e.g. national and subnational level) to the facility level?
- Do these systems allow for the calculation of breast cancer early detection indicators? Which indicators?
- Are aggregate data systems electronic or paper-based? Is aggregation manual?
    - If electronic systems exist, what is the level of MoH endorsement of strategy, and what stage of maturity (early design, pilot, scaling, no longer operational)?
- Are these data transmitted to the MoH, and through what process?
- Are there exemplar programs that manage aggregate data well? If yes, which programs?
- Are the data reported and entered into aggregate systems mostly free text or coded?
- What are the plans for national/subnational aggregate systems? What are the anticipated opportunities and challenges?
- If any systems have changed, what strategies are in place to integrate historical data?

9.11 What indicators are currently used to monitor breast cancer prevention and control (screening, early diagnosis and invasive breast cancer early detection treatment and management)? Please provide the list.

Probes:

- Is the system exclusive for breast cancer early detection? Or a national health information system that collects breast cancer early detection data and other health data?
- What data are reported into these systems and by whom (e.g. static facilities, mobile units, campaigns, hospitals, etc.)?
- Is feedback on the quality of reported data provided from the higher program levels (e.g. national and subnational level) to the facility level?
- Do these systems allow for the calculation of breast cancer early detection indicators? Which indicators?
- Are aggregate data systems electronic or paper-based? Is aggregation manual?
    - If electronic systems exist, what is the level of MoH endorsement of strategy, and what stage of maturity (early design, pilot, scaling, no longer operational)?
- Are these data transmitted to the MoH, and through what process?
- Are there exemplar programs that manage aggregate data well? If yes, which programs?
- Are the data reported and entered aggregate systems mostly free text or coded?
- What is the future for national/subnational aggregate systems? What are the anticipated opportunities and challenges?
- If any systems have changed, what strategies are in place to integrate historical data?

9.12 How widespread is the adoption of the nationally standardised indicators?

Probes:

- What proportion of breast cancer early detection programs in the country routinely utilise these indicators for program M&E?
- Are these indicators regularly reported from facilities/regions to the MOH (e.g. at least annually)?
- Are there facilities or regions that are more compliant with reporting than others? If yes, which ones, and why?
- Do private facilities or other facilities outside of the government health system monitor and report on these indicators?

Data System Themes:
Systems and Processes; Data Access and Use; Health Information Exchange; Data Quality

9.13 What kinds of systems are used for breast cancer early detection, clinical consultation, and referral?

Probes:

- Are there protocols in place for client referrals?
- Are there data systems to support these across the continuum of breast cancer early detection prevention, screening, and treatment?
- What is the predominant system used within the country for referral screening services? To treatment services?
- What level of organization exists around these referral mechanisms?
- Describe whether telemedicine systems are synchronised/real-time or synchronised?
- Are there any mobile device-based systems for prevention, screening, and treatment?
- Are there exemplar referral, mobile-based or telemedicine systems?

9.14 Please describe any decision support systems relevant to breast cancer early detection early detection

Probes:

- What breast cancer do these systems address early detection components?
- How does each decision support system work?
- What are some exemplar decision support systems around breast cancer early detection or other care related CDSS?
- If any decision support systems exist that do not have breast cancer early detection components, what are the opportunities to integrate breast cancer early detection decision support within those systems?

9.14 Please describe any decision support systems relevant to breast cancer early detection Probes:

- How routine and formal are these efforts?
- Are there individuals tasked with understanding and improving data quality gaps within the country?
- Is there routine supervision and data audit?
- Are data quality improvement efforts conducted in a systematic or ad hoc fashion?
- Is there a formal written policy for quality improvement (please get the documentation, if available)?

9.14 What efforts are in place to improve the quality of M&E data?

Probes:

- How routine and formal are these efforts?
- Are there individuals tasked with understanding and improving data quality gaps within the country?
- Is there routine supervision and data audit?
- Are data quality improvement efforts conducted in a systematic or ad hoc fashion?
- Is there a formal written policy for quality improvement (please get the documentation)?

9.15 Please describe the structures and processes for backing up

breast cancer early detection data.

Probes:

- How routinely are the backups performed?
- What guidelines and processes are in place for backups breast cancer early detection data?
- Is the backup method standardised or variable across institutions and regions? Is it within or outside of the country?
- Are there backup security mechanisms in place?
- Who has access to and controls the data backed up and abreast of early detection of cancer?

9.16 What are the different legacy systems relevant to breast cancer early detection screening and treatment?

Probes:

- Are legacy data reported on a national level?
- Are there efforts to integrate legacy systems into current systems?
- How are legacy data represented in national reporting systems?
- Are legacy data standardised to meet current standards and guidelines?

Data System Themes:
Health Information Exchange

9.17 What is the status of health information exchange in the country?

Probes:

- What methods are in use for health information exchange?
- What is the level of interoperability of existing systems? Is there a health enterprise architecture?
- What is the horizontal integration of patient information across points of care (e.g. lab, pharmacy, etc.)?
- What is the stage of maturity (e.g. early design, pilot, scaling, no longer operational)?
- Which data standards are used? What hardware is required for use?
- What is the level of customisation or continuous development required?
- What mechanisms are in place to measure the quality of data?

9.18 What methods are used (or planned for use) to identify clients uniquely?

Probes:

- Are IDs standardised across systems (e.g. across clinics, registries)?
- What systems are in place to generate and store identifiers?
- Are there guidelines on how identifiers are generated and issued?
- Are there systems for managing legacy identifiers?
- What national or subnational level initiatives are there for standardising identifiers? Are there models for client ID systems?
- Are biometrics used?

9.19 Is there shared terminology, vocabulary or coding utilised in

breast cancer early detection program data systems and exchange?

Probes:

- Who is responsible for establishing terminology?
- How often is the language updated?
- Is the terminology aligned with international standards, and if so, which standards are these?
- Does the MoH endorse the terminology?
- If there is shared terminology/definitions, is there an electronic version of the dictionary?

9.20 Please describe how facility-level systems integrate or share information with national Ministry level systems (e.g. M&E and reporting systems).

Probes:

- What is the level of accessibility of these systems? Are they user-friendly?
- What are the timelines of data uploaded?
- How do the systems integrate with the M&E system or with registries?
- Are breast cancer early detection indicators incorporated into the national HMIS?
- What are the available vertical data aggregation systems for the early detection of breast cancer (e.g. DHIS2)? What is the level of MoH endorsement and ownership level?
- What are examples of systems with good vertical integration?

Appendix C: Guideline for documents selection

Domain 1. Demographics and Epidemiology

- Census data report
- Population-based survey reports or fact sheets
- Cancer registry reports
- Program data summary reports
- Breast cancer prevalence and incidence modelling

Domain 2. Governance, Management, and Infrastructure

- Organogram for the national Ministry
- Organogram for the breast cancer program
- List of key NGOs and partners working in breast cancer. Includes organizations working in research, training, service provision, surveillance, health promotion, etc.

Domain 3. Policies, Plans, Strategies and Clinical Guidelines

- Strategic health plan for the country
- National cancer prevention and control policy
- Breast cancer early detection/ screening policy or strategic plan
- National breast cancer treatment policy or strategic plan
- Policy relevant to any aspect of breast cancer early detection
- National clinical practice guidelines for breast cancer early detection/screening
- Clinical practice guidelines for breast cancer early detection specific to BREAST CANCER screening
- National clinical practice guidelines for the management of invasive breast cancer
- Policies and clinical practice guidelines used for breast cancer screening and treatment of invasive breast cancer

Domain 4. Service Availability and Utilization

- Documents and strategic plans outlining the breast cancer prevention, screening, and treatment programs
- Cancer registry, national monitoring and other reports with breast cancer screening, treatment, and invasive cancer indicator data
- Service availability surveys, health facility census reports, and facility registry
- Standardized forms and registers for individual/client level breast cancer screening data; standardized summary and reporting forms; data dictionary for electronic client level systems (e.g. EMR)

Domain 5. Human Resources for Health

- Reports from human resource management information systems, or health worker registry
- Report on medical schools, training, specialty training
- Strategy for health worker capacity building or continuing education

Domain 6. Equipment, Supplies and Medicines

- Essential supply list and essential medications list
- Lists of breast cancer supplies and equipment available (e.g. inventory reports, orders, etc.)
- Guidelines, standard operating procedures (SOPs) or technical specifications for system used to procure and distribute equipment and supplies for breast cancer
- Reports or findings from health facility surveys (e.g. service availability and facility readiness surveys)

Domain 7: Laboratories and Diagnostics

- National policy, plan or strategy for laboratory development and management
- List of laboratories offering breast cancer screening services
- Guidelines for national quality assessment program for cytology and histopathology
- Quality assurance (QA), control (QC) and improvement
- (QI) strategies, guidelines, or SOPs for laboratories
- Sample cytology and histology request and results return forms

Domain 8. Budgeting, Financing and Costing

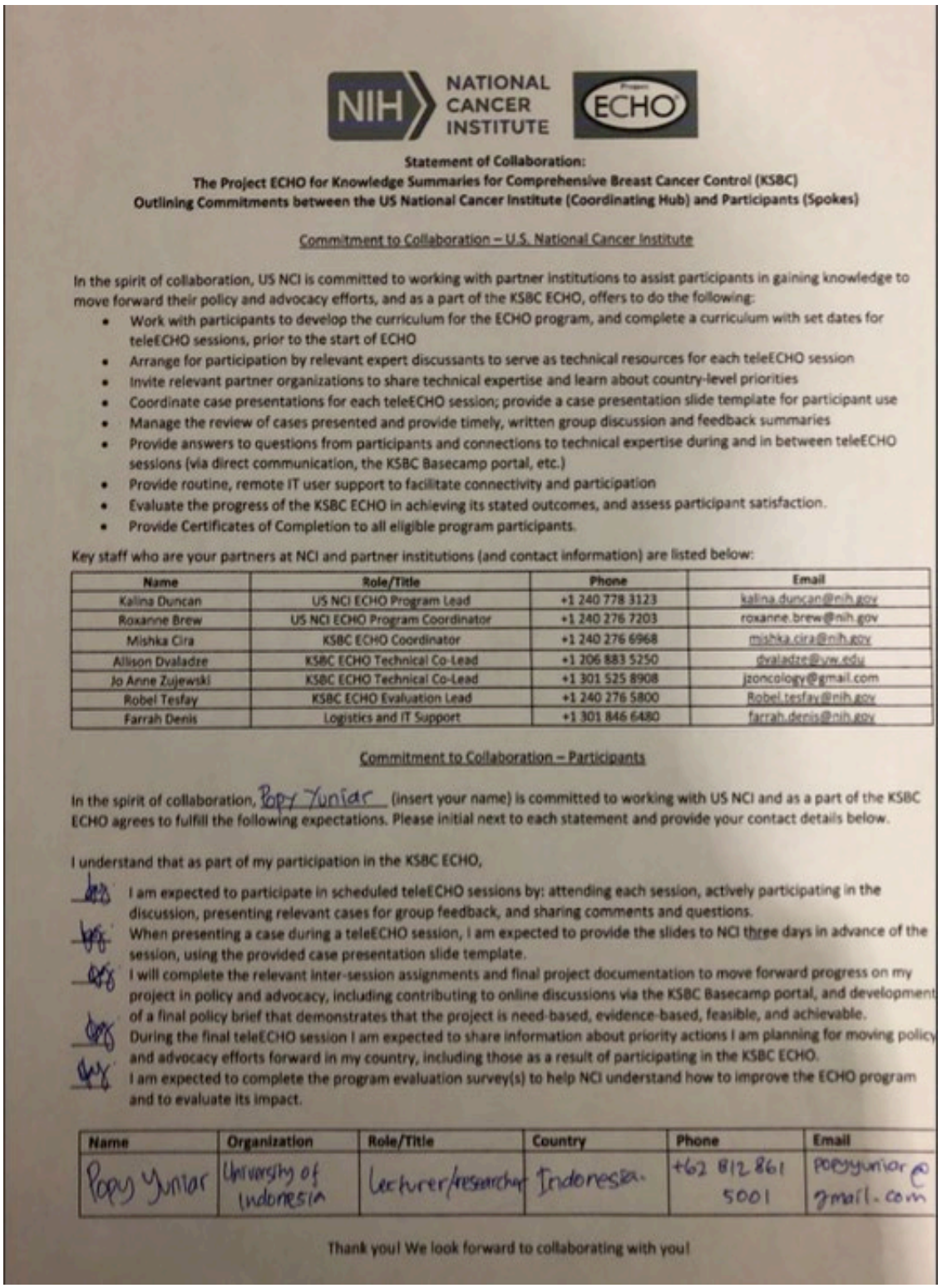
- Salary structure for government health personnel
- Donor country operations plans or memorandums of understanding showing budgetary commitments
- Previous program budgeting or costing activity documents (e.g. spreadsheets or summary reports)
- Cost analysis and planning documents or reports (e.g. cost effectiveness analysis, analysis of average cost of services per individual)

Domain 9. Data and Data Systems

- Data management policies, plans or guidelines
- National eHealth and ICT strategy, policy or plan
- mHealth policy, strategy or plan
- National M&E plan for breast cancer

- List of standardized national indicators for breast cancer
- Organogram for breast cancer M&E
- Document showing budget allocations for breast cancer data systems and M&E efforts
- Reports of specific evaluations that have been conducted on breast cancer information systems
- Reports of evaluations, assessments, and audits conducted on health information systems and breast cancer information systems
- Data access policies and guidelines
- Predefined formats or standards for M&E and indicator data; national health information system technical notes and data dictionary
- Standardized forms and registers for individual/client level breast cancer data; standardized summary and reporting forms; data dictionary for electronic client level systems (e.g. EMR)
- Guidelines for reporting data into HPV vaccine and cancer registries, and for monitoring and quality control of registry data
- Terminology or vocabulary in breast cancer systems (e.g. comprehensive shared terminology/definitions; national concept dictionary)

Appendix D: **The researcher's commitment to collaboration**



NIH NATIONAL CANCER INSTITUTE — ECHO

Statement of Collaboration:
The Project ECHO for Knowledge Summaries for Comprehensive Breast Cancer Control (KSBC)
Outlining Commitments between the US National Cancer Institute (Coordinating Hub) and Participants (Spokes)

Commitment to Collaboration – U.S. National Cancer Institute

In the spirit of collaboration, US NCI is committed to working with partner institutions to assist participants in gaining knowledge to move forward their policy and advocacy efforts, and as a part of the KSBC ECHO, offers to do the following:

- Work with participants to develop the curriculum for the ECHO program, and complete a curriculum with set dates for teleECHO sessions, prior to the start of ECHO
- Arrange for participation by relevant expert discussants to serve as technical resources for each teleECHO session
- Invite relevant partner organizations to share technical expertise and learn about country-level priorities
- Coordinate case presentations for each teleECHO session; provide a case presentation slide template for participant use
- Manage the review of cases presented and provide timely, written group discussion and feedback summaries
- Provide answers to questions from participants and connections to technical expertise during and in between teleECHO sessions (via direct communication, the KSBC Basecamp portal, etc.)
- Provide routine, remote IT user support to facilitate connectivity and participation
- Evaluate the progress of the KSBC ECHO in achieving its stated outcomes, and assess participant satisfaction.
- Provide Certificates of Completion to all eligible program participants.

Key staff who are your partners at NCI and partner institutions (and contact information) are listed below:

Name	Role/Title	Phone	Email
Kalina Duncan	US NCI ECHO Program Lead	+1 240 778 3123	kalina.duncan@nih.gov
Roxanne Brew	US NCI ECHO Program Coordinator	+1 240 276 7203	roxanne.brew@nih.gov
Mishka Cira	KSBC ECHO Coordinator	+1 240 276 6968	mishka.cira@nih.gov
Allison Dvaladze	KSBC ECHO Technical Co-Lead	+1 206 883 5250	dvaladze@uw.edu
Jo Anne Zujewski	KSBC ECHO Technical Co-Lead	+1 301 525 8908	jzoncology@gmail.com
Robel Tesfay	KSBC ECHO Evaluation Lead	+1 240 276 5800	Robel.tesfay@nih.gov
Farrah Denis	Logistics and IT Support	+1 301 846 6480	farrah.denis@nih.gov

Commitment to Collaboration – Participants

In the spirit of collaboration, Popy Yuniar (insert your name) is committed to working with US NCI and as a part of the KSBC ECHO agrees to fulfill the following expectations. Please initial next to each statement and provide your contact details below.

I understand that as part of my participation in the KSBC ECHO,

- I am expected to participate in scheduled teleECHO sessions by: attending each session, actively participating in the discussion, presenting relevant cases for group feedback, and sharing comments and questions.
- When presenting a case during a teleECHO session, I am expected to provide the slides to NCI three days in advance of the session, using the provided case presentation slide template.
- I will complete the relevant inter-session assignments and final project documentation to move forward progress on my project in policy and advocacy, including contributing to online discussions via the KSBC Basecamp portal, and development of a final policy brief that demonstrates that the project is need-based, evidence-based, feasible, and achievable.
- During the final teleECHO session I am expected to share information about priority actions I am planning for moving policy and advocacy efforts forward in my country, including those as a result of participating in the KSBC ECHO.
- I am expected to complete the program evaluation survey(s) to help NCI understand how to improve the ECHO program and to evaluate its impact.

Name	Organization	Role/Title	Country	Phone	Email
Popy Yuniar	University of Indonesia	Lecturer/Researcher	Indonesia.	+62 812 861 5001	popyyuniar@gmail.com

Thank you! We look forward to collaborating with you!

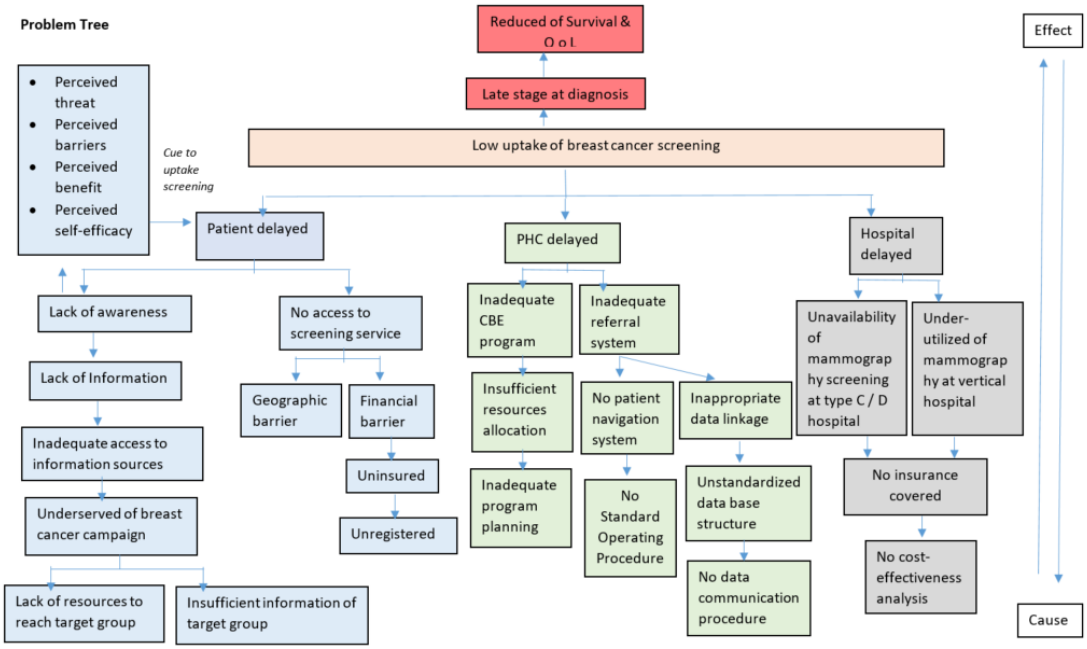
Appendix E: The working group discussions guideline and completed working sheets

Preplanning (Worksheet 1)
Objective:

- To recognize when a change is needed (policy/program does not or outdated or not evidence based.
- To recognize how to identify data needs/source.
- To identify key leadership and stakeholder

Questions and discussion

1. **Is your proposed program/project needed, based on what criteria?**
   - *Yes*
   - *Issue/gap to address:*
     - *Early detection program with clinical breast examination (SADANIS) has already launched for 10 years and no clear result of the program*
     - *Low uptake of screening, low compliance of recall procedure, late stage at diagnosis, un-integrated patient pathway of screening, diagnostic and treatment services*
     - *The need to establish an integrated services to increase screening uptake and referral system to diagnostic and treatment*
     - *The proposed program/project will be aligned with the national policy in promoting breast cancer early detection (SADANIS)*
   - *Analyse the existing situation – brainstorming for problem analysis*



2. **What data source have you identified in support of your project**

   - *Regulation related to the breast cancer early detection program in Indonesia*

Regulations list by type of documentation

No	Name	Type of documentation	Year	Source
1	Cervical and Breast Cancer Prevention (CECAP) Project in partnership with JHPIEGO and the Ford Foundation	Published article – evaluation of a 5-year project implementation	2007-2011	(Kim et al., 2013)
2	The Indonesian Cancer Control Program (ICCPs)	Government regulation (following Minister of Health Decree no HK.03.01/160/I2010 about strategic planning of Ministry of Health	2010-2014	Ministry of Health Republic of Indonesia, 2010
3	Country priority action to improve national cancer control planning – The Asia Pacific Leadership forum	Published article	2014	(Singh et al., 2017)
4	The Minister of Health decree No 34 about The Prevention of Breast Cancer and Cervical Cervix	Government regulation	2015	(Ministry of Health Republic of Indonesia, 2015)
5	The Minister of Health decree No 29 about the amendment of The Minister of Health decree No 34 about The Prevention of Breast Cancer and Cervical Cervix	Government regulation	2017	Ministry of Health Republic of Indonesia, 2017

3. **What assessments have been conducted previously on this issue?**

Breast cancer early detection related data source mapping

Data sources listed by type of data

Data source number	Type of data source	Name	Year	Source
1	Survey	Report on Non-Communicable Disease Research: Breast Tumour (SADANIS positive) and Precancerous cervical lesion	2016	(National Institute of Health Research and Development Ministry of Health Republic of Indonesia, 2016)
2	Survey	Indonesia Demographic and Health Survey	2017	dhsprogram.com/data/dataset/Indonesia
3	Survey	The Indonesian Family Life Survey (IFLS) wave 5	2014/2015	(http://www.rand.org/labor/FLS/IFLS/ifls5.html)
4	Patient level data	Monthly data of SADANIS visit in five districts of Jakarta Province	2017	DKI Jakarta Provincial Health Office – sub directorate of cancer prevention
5	Patient level data	Breast cancer stage at diagnosis based on patient admission from early detection unit – Dharmais Hospital	2010-2012	Cancer registry Dharmais Hospital
6	Preliminary report	Preliminary result of		
7	Journal article	Short report: Limited effectiveness of screening mammography in addition to clinical breast examination by trained nurse	2014	(Kardinah et al., 2014)

8	Journal article	Awareness level about breast cancer risk factors, barriers, attitude and Breast Cancer Screening among Indonesian women	2019	(Solikhah et al., 2019)

4. **Name 3 key stakeholders/leaders to support your project**

- *Wisnu, MD (Jakarta Provincial Health Department)*
- *Aldrin, MD (Head of cancer sub directorate in Ministry of Health)*
- *Ester, MD: Head of health referral services in Ministry of Health*

Planning step 1 (Worksheet 2): Assessing the need and current service
Objective:

- To know how to assess local disease burden.
- How to map current service, stakeholders and partnership.

Questions and discussion

1. What is the current level of need/burden of disease in your community?

Current burden of breast cancer:

- *Based on estimated numbers, breast cancer is the most common cancer among women in Indonesia, accounting for 39.51% of all cancer cases in women (HBCR Data 2015, Dharmais Cancer Hospital-National Cancer Centre)*
- *Breast cancer in Indonesia is the top cancer for both sex and female. The crude incidence rate of breast cancer is 44.0 per 100.000 population. The overall incidence of breast cancer (ASR) is 42.1 per 100,000 population, with TASR (15-64 years) is about 52, 81 per 100.000 population.*
- *For extremely young female (20-34 years old) breast cancer in female still the top with crude rate about 14.1 per 100.000 populations*
- *Breast cancer arises in the younger age group. At 25-29 years old, the incidence is fourth times than age group before and then increase with the peak in 60-64 years old. But, in cumulative, the peak cases is 60-64 years old, (under 50 y.o)*
- *In 2018, estimated 22, 692 women died from breast cancer. The age-standardized mortality rate is 17 / 100,000 (Globocan, 2018)*
- *Cumulative data of stage distribution (based on the HBCR between1993 and 2013) showed that 3.6% of patients were diagnosed at stage I, 17% at stage II and 22% at stage III.*
- *From National Cancer Registry data, almost 62, 7 % cases are diagnosed at late stage (stage 3-4).*
- *Early breast cancer detection as a program not well monitored and evaluated in the province and national level*
- *Referral system for positive clinical breast examination not well developed*

Programmatic needs regarding breast cancer in the community

In term of the programmatic approach, the basic concept is to optimize the existing program with the development of technical guidance. As per the discussion in the first session, our team will focus on three programmatic objectives toward downstage acceleration as follow:

- *Strengthen referral system for those who have apositive result of CBE.*
- *Formulate risk factors criteria of breast cancer as the basis of the targeted screening program*
- *Designing an optimal opportunistic targeted screening to accommodate women with negative CBE result and women aged over 40 with a positive risk factor.*

2. What current services exist (detection, diagnosis, treatment) and by whom are they led?

- *Opportunistic of Clinical Breast Examination Program at primary health care.*
- *Opportunistic mammogram screening*
- *Outreach (annual) mobile mammography (only in Jakarta area)*
- *Diagnosis, and treatment currently performed by the hospital (secondary and tertiary level)*
- *Public awareness mostly conducted by NGO, collaborate with MOH and society*

3. How have previous assessments been conducted? Who was involved? What have you learned from them?

Area of assessment	Method / source	Stakeholder involved	Key information / Lesson learned
CBE uptake	Desk review on secondary data (routine reporting of CBE)	- Ministry of Health - Provincial Health Officer – subdivision NCD/cancer	• Low coverage of SADANIS (CBE) program across 32 provinces in Indonesia • We assumed the low rate of coverage was caused by insufficient resources of an early detection program. However, we have not found the detail information yet regarding the Service Availability Mapping for this issue
Community-based assessment	Household national survey (Indonesian Family Life Survey)	- Ministry of Health, - RAND (a research organization)	- Early detection practice (mammography, self-breast examination) among eligible women - Breast cancer in the family history - SES - Further analysis can be conducted to explore more about the characteristics of the respondent who had or had not practiced mammography or self-breast examination.
Cancer control program evaluation	Indonesia health profile	Ministry of Health	Epidemiology indicators Program's Key Performance Indicator
Dharmais Research	Report of research	Ministry of Health, Provincial Health Officer – subdivision NCD/cancer	Breast cancer quality data improvement

4. What collaborations or partnerships exist already to address this issue?

Collaboration among NGO, Hospital, University and provincial health department (Jakarta) area already develop e.g:

- *Pilot screening mammography in West Jakarta: National Cancer Center /Dharmais Cancer Hospital-Indonesian Breast Cancer Foundation – Public Health Faculty University of Indonesia – Jakarta Provincial Health Departement*
- *2.Pilot screening in Sardjito Hospital Jogyakarta :Sardjito Hospital – Public Health Faculty University of GadjahMada*
- *Training of trainer in Clinical Breast Examination: Subdirectorate of Cancer Ministry of Health – Society*
- *The recording and reporting CBE in Jakarta were using IACR's standards so they can be compiled with hospital-based cancer registry*

Planning step 1 (Worksheet 3): Assessing access and barriers
Objective:
3. To know how to assess barriers to access (structural, sociocultural, personal and financial);
4. To know how to identify bottlenecks and gaps in service

Questions and discussion

4. What barriers to accessing breast health services exist in your community?

Indonesia has already had National Health Insurance since 2014 for breast cancer early detection (SADANIS). However, there are still barriers to accessing breast health services e.g: (as illustrate in logical framework)

- *Sociocultural situation about traditional and alternative medicine as the first choice if they were diagnosed as cancer. Therefore, they seek medical treatment in advanced stage.*
- *Afraid of pain when examine by mammography devices as a follow up after CBE*
- *Afraid of knowing that they have breast cancer*
- *The high proportion of late-stage presentation may indicate that there was a delay in accessing breast health services in the community. Inadequate access to information on breast health, geographic barriers and financial barriers could be the reason of the patient delayed accessing breast health services*

5. What services exist to facilitate access to breast health service in your community?

- *Health personnel in primary health care such as GP, midwives have already trained to performed CBE and how to refer patient to secondary level hospital. Breast cancer early detection program integrated in community level with other non-communicable diseases.*
- *Since 2007 up to 2014 the SADANIS have been implemented in 1,986 PHCs throughout 304 districts/municipals in 34 provinces in Indonesia. The total number of trainers were 430, they consisted of gynaecologists, surgeon, general practitioners (GPs) and midwives. These certified trainers had given the training to 2,671 midwives and 1,456 GPs at the PHC level. It was expected that the target of the CBE program will reach 50% after five years of implementation (Wahidin et al., 2012)*
- *There is a referral system of National Health Insurance from primary care to hospital*
- *There is a decree from Minister of Health and the head of province health department about early detection program and their follow up system with their report form.*

6. What other health services exist that could be leveraged to improve access to breast healthcare?
- *Primary Health Care Outreach program*
- *Several NGO help women to have access in breast health such as mobile mammography and breast ultrasound but not as program, these activities only in sporadic schedule.*
- *Several departments of government or private do the mammography screening during special events, such as the Breast Cancer Day*

7. How have previously identified barriers to access (via assessment if available) been addressed? What can be learned from that?
- *From published article*
- *Lesson learned:*

There are socioeconomic disparities in cancer screening awareness and participation among

Indonesian women. Our findings may help inform targeted health promotion and screening for cancer in the

presence of limited resources(Anwar et al., 2018).There are socioeconomic disparities in cancer screening awareness and participation among Indonesian women. Our findings may help inform targeted health promotion and screening for cancer in the presence of limited resources (Solikhah et al., 2019)

Planning step 1 (Worksheet 4): Assessing health system capacity
Objective:
4. To know how to assess health system capacity to accurately/efficiently detect/diagnose/treat/manage breast cancer (including human resources capacity, knowledge.
5. To know how to assess availability/ affordability/acceptability of services.

Questions and discussion

1. **To what extent is the health system capable of providing accurate/effective breast cancer services?**

   - *Our health system is not well distributing across nationwide in providing early detection of breast cancer. If a patient come directly to tertiary level hospital, she could perform diagnostic and treatment according to the guidelines (staging conventional/PET-CT staging, molecular pathology, surgery with reconstruction, radiotherapy, chemotherapy, targeted therapy).*
   - *Patient with national health insurance should come first to the primary health care then for those who diagnosed with abnormalities will be referred to first tier level of referral hospital and continued according to next referral tier. The services available in first tier hospital are breast ultrasound, basic pathology and mastectomy while in the second-tier hospital services include breast ultrasound and mammography, molecular pathology (not in every hospital), mastectomy, chemotherapy and radiation therapy (not in every hospital). However, the coordination between first, second and third tier hospital was not adequate in terms of follow-up. For example, the second-tier hospitals were not able to track patients who were referred by the primary health care for further diagnostic test and vice versa, although according to the guideline, the secondary hospital should make notification to the primary health care if the referred patient had received the test.*

2. **To what extent are these services accessible/ affordable/acceptable?**

   - *Since 2014, National Health Insurance covers 171.9 million citizen, therefore if a patient has already member of national insurance, access to diagnostic and treatment for breast cancer are possible. The routine program to early detection at primary health is free of charge, the test is covered by national insurance program.*
   - *Although mammography has proved to be an effective test for breast cancer screening, this modality was not chosen as the national program setting in Indonesia due to the high cost of purchasing units, continued quality control and maintaining a screening register. Other issues include the fragmented of the health system and the fact that many provinces have uneven or limited capacity. However, the regional program in Jakarta province had been organized mammography screening through a mobile mammography program. Over a decade the program had been reached 11,170 women in selected areas (Indonesian Breast Cancer Association, 2017)*

3. **What bottlenecks and gaps in service exist in your community?**
   - *Even though our government has already opened the access for diagnostic and treatment, patient still reluctant go to hospital for small breast lump further treatment. Therefore, most patient come to hospital in advance stage. The potential barriers of taking mammography or routine check-up were related to lack of information where to go to the test as well as the cost, and fear.*

Present state:

- *Screening registry – cohort patient database not available – high-risk group cannot be well identified and follow-up*
- *Those who were referred for the further diagnostic test cannot be traced – unlink information between health services at a primary and secondary/tertiary level*
- *There is no follow-up mechanism to navigate patient to the further diagnostic test it may lead to the high number of lost- to follow-up*

Desire state:

- *To establish screening registry system in order to deliver systematic and targeted opportunistic screening program*
- *Create technical guideline to ensure the link information between health services*

Planning step 2 (Worksheet 5): Defining target population and partnership
Objective:

1. To know how to define the appropriate target population
2. To know how to engage stakeholders and key decision-makers and build community and health-system partnerships.

Questions and discussion

4. What is the target population for your project?

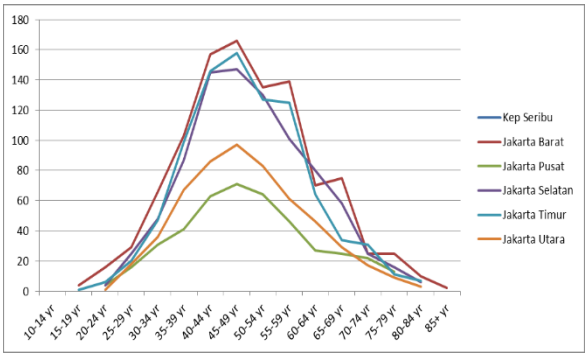
- *Our pilot project will be in West Jakarta district with female population approximately 1.122.833 and estimated new cases about 472 yearly.*
- *Dharmais Cancer Hospital is in West Jakarta and has responsibility by the decree Jakarta Province Health Office to supervise cancer registry in this region.*
- *Therefore, implementation of referral system in West Jakarta could be developed and evaluated.*

Breast malignancy incidence in Jakarta Province (source: National Cancer Registry, Dharmais NCC)

Incidens	Kep Seribu	Jakarta Barat	Jakarta Pusat	Jakarta Selatan	Satuan
Crude Rate	1.93	18.29	19.26	17.14	per 100,000
ASR (W) =	**3.60**	**22.58**	**19.36**	19.06	per 100,000
TASR (25-74) =	**7.21**	**41.83**	**35.40**	**36.36**	per 100,000
cumulative rate (0-74) =	**450.45**	**2,473.93**	**2,053.95**	**2,119.33**	per 100,000
cumulative rate (0-74) =	**0.45**	2.47	2.05	2.12	%
cumulative risk (0-74) =	**0.45**	2.44	2.03	2.10	%

Incidens	Jakarta Timur	Jakarta Utara	Jakarta	
Crude Rate	13.26	13.47	15.86	per 100,000
ASR (W) =	14.99	16.44	18.29	per 100,000
TASR (25-74) =	**28.60**	**31.36**	**34.38**	per 100,000
cumulative rate (0-74) =	**1,680.09**	**1,832.38**	**2,017.81**	per 100,000
cumulative rate (0-74) =	1.68	1.83	2.02	%
cumulative risk (0-74) =	1.67	1.82	2.00	%

Breast Cancer Distribution among Female Population by age group in Jakarta (source: National Cancer Registry, Dharmais NCC)



5. How will you engage key stakeholders, decision makers?

- *As National Cancer Center and Tertiary Referral Hospital, our hospital directly subordinate by Ministry Of Health. We have already collaborated with Jakarta Province Health Office and Sub Health Office West Jakarta.*
- *We have been collaborated for breast cancer early detection and develop pilot project. The result of pilot project will be submitted to Ministry of Health and Jakarta Province Health Office as a model for early detection program, especially to integrate referral system from primary health care to hospital (according to referral hospital stratification)*
- *We will report and discuss the result with National Health Insurance Office to establish early detection program in future.*

6. How will you build community and health-systems partnership to support your project?

- *We also have been collaborated with Indonesian Breast Cancer Foundation to develop pilot project screening with mobile mammography. To establish better program, we will develop follow up system by empowering cadres in the region.*
- *Meanwhile public health care in Jakarta province had trained them in every sub village. There is also breast cancer survivors volunteer to educate people in the region.*

Planning step 2 (Worksheet 6): Identifying gaps and barriers to implementation
Objective:

1. To know how to identify barriers to program implementation

Questions and discussion

3. What are the gaps and barriers to implementation of your proposed program?

- *There is no integrated care pathway to handle women with positive clinical breast examination. Thus, there is no mechanism to monitor presentation delay to referral hospital.*
- *Local regulation focus on awareness and increasing CBE coverage, and there is no technical details for referring women with CBE positive.*

4. How will communicate the need for action

- *We will begin with pilot project in West Jakarta to decrease presentation delay of women with positive CBE.*
- *Therefore, we will collaborate with Jakarta Province Health office to collect the data of women with positive CBE and monitoring when those women come to referral hospital to have further diagnostic process.*

5. How will you communicate the need for action/gain political support?

- *First from beginning of this project we have already collaborate with Jakarta Province Health Office and MoH, Cancer Sub Directorate therefore our pilot project will be closely monitored by them.*
- *The result will be reported to Jakarta Province Health Office and MoH Cancer Sub Directorate.*

Planning step 3 (Worksheet 7): Establishing partnerships, financing
Objective:

1. To know how to engage decision-makers and staff.
2. To know how to establish financial support and partnership
3. To know how to match investments to resource-appropriate interventions

Questions and discussion

1. **Which stakeholders (advocates, patients, providers across disciplines) are you engaging, and which partnerships are you establishing (local institutions, other cancer centres, NGO, industry, etc.) and how?**

- *Our project stakeholders are Referral hospital under MOH, Provincial Health Department (including Primary Health Care and Secondary Referral Hospital) under Jakarta Province Governor, NGO (Indonesian Breast Cancer Foundation) , National Health Insurance and University of Indonesia (Public Health Faculty) , which have already had MOU with our hospital.*
- *Some previous project had involved those stakeholders but not for policy changes. Hopefully this initial project will be an evidence-based recommendation for early detection policy in Indonesia*

2. **What are the financial requirements? How will financial support be established? Consider the resources needed both for program implementation AND for services. What are the existing or possible financing policies or models (e.g., conditional cash payments, prepayment, or insurance) to ensure access? Is the intervention resource-appropriate? Do your proposed investment match with resource-appropriate interventions?**
   - *Our project will be submitted under hospital budget and for services will be covered by national health insurance.*
   - *Currently all citizens in Indonesia should have national health insurance card. We will propose also to national health insurance that early breast cancer findings during the project could directly refer to our hospital in case secondary referral hospital could not give services according to the standards.*

3. **How are you engaging key decision-makers and securing political commitment?**
   - *This project will be reported to MOH and Provincial Health Office because our hospital is directly under MOH. We will share this project to 14 National Referral Hospitals and recommend implementing early detection program and improving referral system in their provinces.*

Planning step 3 (Worksheet 8): Establishing partnerships, financing
Objective:
1. To know how to engage decision-makers and staff.
2. To know how to establish financial support and partnership
3. To know how to match investments to resource-appropriate interventions

Questions and discussion

1. **Which stakeholders (advocates, patients, providers across disciplines) are you engaging, and which partnerships are you establishing (local institutions, other cancer centres, NGO, industry, etc.) and how?**

   - *Our project stakeholders are Referral hospital under MOH, Provincial Health Department (including Primary Health Care and Secondary Referral Hospital) under Jakarta Province Governor, NGO (Indonesian Breast Cancer Foundation) , National Health Insurance and University of Indonesia (Public Health Faculty) , which have already had MOU with our hospital.*
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3. **How are you engaging key decision-makers and securing political commitment?**
   - *This project will be reported to MOH and Provincial Health Office because our hospital is directly under MOH. We will share this project to 14 National Referral Hospitals and recommend to implement early detection program and improving referral system in their provinces.*

Planning step 3 (Worksheet 10): Implement and Evaluate
Objective:

1. To understand how to implement quality assurance measures in project design
2. To understand key concepts in monitoring and evaluation

Questions and discussion

1. What indicators/metrics will you use to assess quality, relevance, effectiveness and impact

Objective	Indicator	Data source
1. **To establish practical guidelines on patient referral and follow-up system**	Written documents of standard operating procedure of: - Referral system and patient pathway of those who have positive result in Clinical Breast Examination (CBE) - Follow-up and navigation system for those who get further diagnostic test and treatment - Standard of radiology and pathology test	The results of working group consensus, best practices, and other references.
2. **To implement the practical guidelines in the pilot area.**	2.1 Number of women performed CBE. 2.2 Number of woman with abnormalities result. 2.3 Number of woman with abnormalities referred for further diagnostic test. 2.4. Number of referred woman get diagnostic test 2.5. Number of women diagnosed with breast cancer	- Recording of CBE at PHC - Patients' admission - Medical records
3. **To increase public awareness regarding risk factors, symptoms and screening behaviors (i.e. BSE, CBE, mammography)**	Input: 3.1 # of PHC / integrated health post equipped with health promotion media on BC 3.2. # of hospital which have routine events of health promotion on breast cancer 3.3. # / list of NGO which have routine events of health promotion 3.4. Types of media used in BC health promotion Process 3.5. Frequencies of BC health promotion (PHC/hospital/NGO) Output 3.6. # of participants attending the event (PHC/hospital/NGO)	3 1. Health promotion unit at PHC 3.2.Health promotion unit at hospital 3.3.Existing partnership database recorded in the hospital, PHC, provincial health office, ministry of health

2. How do you plan to collect and analyse the data (monitor and evaluate)?

Activities	Monitoring and Evaluation Dharmais Cancer Hospital, Health Department and MOH	Indicator

1.Practical Guidelines	Routine Meeting /bi-weekly and dead line for practical guidelines	Manual (hard copy and e-manual)
		Posters for referral positive CBE based on manual
2. Implementation	Routine Meeting/bi-weekly with primary health care	Data evaluation Follow up for CBE positive
	Monthly report	User friendly format – to be developed
3. Breast cancer awareness	MOU with hospitals and NGO to increase awareness activities and disseminate posters for referral guidelines	Number of MOU Number of awareness activities

3. **What is your plan to apply (inform future implementation) and disseminate/communicate the findings of your intervention?**

Activities	**Stake holders**	**Dissemination**
1.Practical Guidelines	Dharmais Cancer Hospital	Webinar – nation wide Short training for 14 Province Referral Hospital
	Health Department Jakarta Province	E-Posters for referral positive CBE based on manual to primary and secondary hospital in Jakarta Province
	MOH	E-Posters for referral positive CBE based on manual to primary and secondary hospital nation wide
2. Implementation	Dharmais Cancer Hospital, Health Department Jakarta Province	Routine meeting/monthly Workshop for primary and secondary care in Jakarta
	MOH	National Guidelines Revised and disseminated nation wide
3. Breast cancer awareness	All stake holders in Indonesia will be coordinated by MOH	

Planning step 3 (Worksheet 11): SMART Objective

SMART Goal/Objectives

1. **Specific – Specify what it is you want to achieve? Why should you achieve this goal? (Who, What, Where, Why) Be specific.**

   - **What are we going to do:**
     - *To establish practical guidelines on the referral and follow-up system in patients who have symptoms of breast abnormalities/breast cancer.*
     - *To implement the practical guideline in the pilot area.*
     - *To increase public awareness regarding risk factors, symptoms and screening behaviours (i.e. BSE, CBE, mammography)*
   - **Why is it important for us**
     - *Given the fact from studies in LMIC (Dey, 2014; Stapleton et al., 2011) and the importance placed by WHO and BHGI that the increase of public awareness of practicing breast screening behaviours leading on to the detection of BC at earlier stage.*

- *To ensure the patient pathways and providing sufficient monitoring system to follow-up patients who have symptoms of breast abnormalities/breast cancer.*
- *To provide evidence on the effectiveness of early detection program which have been implemented in the pilot area.*
- *Breast Cancer is the most cancer incidence in Indonesia (ASR: 42.1/100.000) (3) , 61,9% of breast cancer that came to NCC was diagnosed at late stage (4) .*
- *Time from diagnosed to treatment is about 3-7 months (5)*

- **Where:**
  - *The pilot project will be conducted in Jakarta Province.*
- **Who:**
  - *The pilot project will engage medical specialists, public health specialist, stakeholders from relevant institution such as Ministry of Health, Jakarta Provincial Health Office, Primary Health Center, Indonesian Women Breast Cancer Foundation (NGO),*

2. Measurable – How will you measure progress and know change has occurred? What metrics will you use? Are these metrics available or collectable?

Objective	Indicator	Data source
1. **To establish practical guidelines on patient referral and follow-up system**	Document of practical guidelines on: - Referral system and patient pathway of those who have positive result in Clinical Breast Examination (CBE) - Follow-up and navigation system for those who get further diagnostic test and treatment - Standard of radiology and pathology test	The results of working group consensus, best practices, and other references.
2. **To implement the practical guidelines in the pilot area.**	2.1 Number of women performed CBE. 2.1 Number of women with abnormalities result. 2.1 Number of women with abnormalities referred for further diagnostic test. 2.1 Number of referred woman get diagnostic test 2.1 Number of women diagnosed with breast cancer	- Recording of CBE at PHC - Patients' admission - Medical records
3. **To increase public awareness regarding risk factors, symptoms and screening behaviors (i.e. BSE, CBE, mammography)**	Input: 3.1 # of PHC / integrated health post equipped with health promotion media on BC 3.2. # Of hospital which have routine events of health promotion on breast cancer 3.3. # / list of NGOs which have routine events of health promotion 3.4. Types of media used in BC health promotion Process 3.5. Frequencies of BC health promotion (PHC/hospital/NGO) Output 3.6. # of participants attending the event (PHC/hospital/NGO)	3.1. Health promotion unit at PHC 3.2. Health promotion unit at hospital 3.3. Existing partnership database recorded in the hospital, PHC, provincial health office, ministry of health 3.4. See point 3.1,3.2 3.5. See point3.1, 3.2

3. **Attainable – Is the goal you set achievable and attainable with the resources available? Are they within your scope? YES, Who is responsible?**

Activities	PIC
CBE/SADANIS program	Ministry of Health, provincial health officers and district health officers (sub-directorate cancer), PHC, Indonesian Women Breast Cancer Foundation (for mobile mammography)
Navigation and Follow-up	PHC, referral hospital network, national health insurance office (BPJS), outreach facilitator (KPLDH program)
Diagnostic test	Secondary Referral Hospital
Health promotion	Ministry of Health, provincial health officers and district health officers, PHC (health promotion division), NGO
Data management system	PHC, district health office, provincial office (recording and reporting unit), cancer registry unit, medical record unit

4. **Relevant -- Is it in alignment with your own work as well as the broader public health and cancer agenda and best practices? What is the impact?**

   - *Yes. The evidence from the pilot implementation will make policy implication of BC early detection program. The impact of improving the referral and follow-up system may result to the down staging of BC in Indonesia*

5. **Time-bound – When do you want to achieve this goal?**

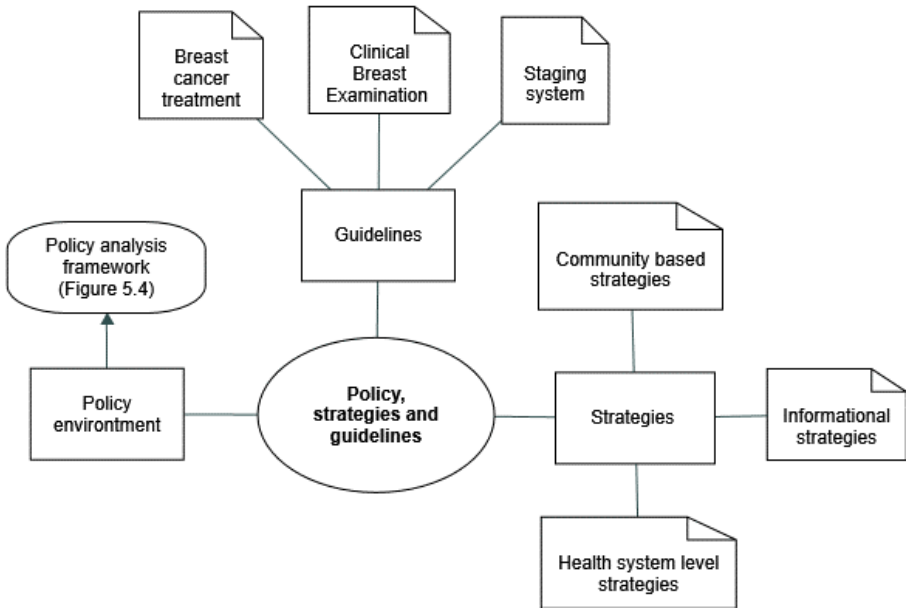
#	Goal/Objectives	Time-bound
1	To establish practical guidelines on the referral and follow-up system in patients who have symptoms of breast abnormalities/breast cancer.	Short-term goal: 3 months
2	To implement the practical guideline in the pilot area.	Short-term goal: 3 months (after the guidelines finalized)
3	To increase public awareness regarding risk factors, symptoms and screening behaviours (i.e. BSE, CBE, mammography)	Long-term goal (6-12 months). This objective will be embedded with health promotion program at Ministry of Health, PHO, DHO and PHC

6. **SMART GOAL To [achieve this goal], [you, your team,] will [complete this action] by [due date].**

#	Goal/Objectives	Starting – End date
1	Meeting with all resources, prepare the formerly data, prepare the proposal and ethical letter, revise practical guidelines	June-July 2019
2	Implementation	August – October 2019
3	Data management and analysis	November 2019
4	December 2019 – May 2020	Reporting and Publication

Appendix F: Illustration of the extracted qualitative data (thematic map and excerpt table)

The thematic map of the document analysis grouped into domain 2 – Policy, strategies and guideline

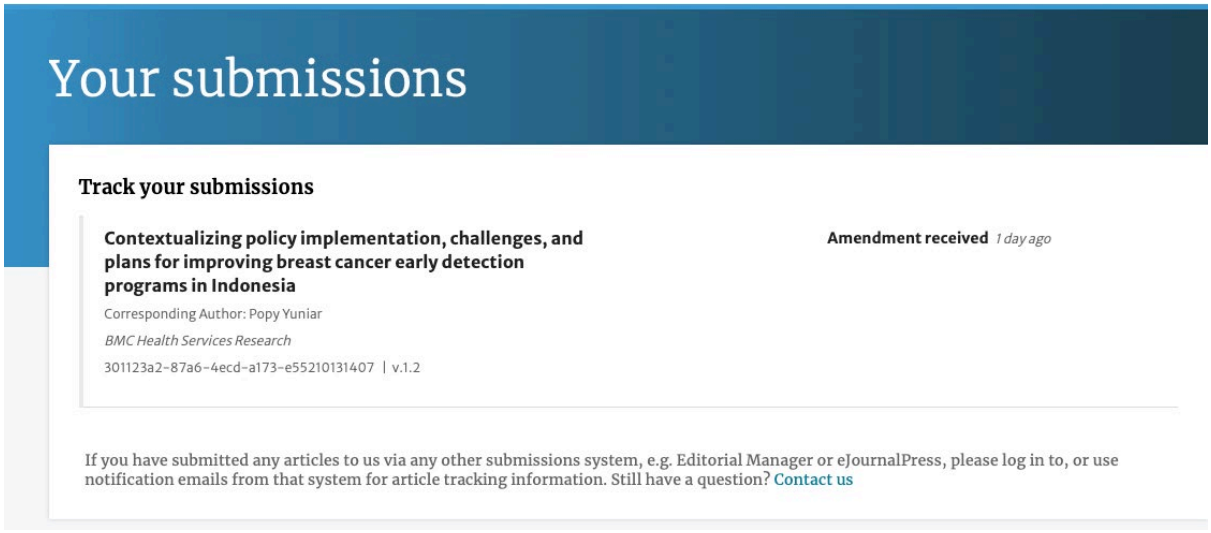


Document analysis of policy context

Excerpt No	Text meaning unit	Concept	Dimension
1	*The decentralization reform in 1999 resulted in decentralization of responsibility for planning and managing service delivery from the Ministry of Health to local governments* ***(D2-OD#9)***	Political structure	Decentralization reform
2	*The providers and financial sources of health system in Indonesia are a mixture of public and private contributors. Public system is administered in line with the decentralized government system in Indonesia, with central, provincial and district government responsibilities.* ***(D2-OD#9)***	Structural health care system	The role and responsibility in managing service delivery

3	*Regulation and legislation in Indonesia are extensive and detailed but lacks common vision and supervised implementation and enforcement.* ***(D2-OD#9)***	Supervision of policy implementation	Quality assurance, Law/regulation enforcement
4	*The MoH has overall responsibility for organizing and developing public health services in Indonesia, particularly for disease surveillance and preventive activities. Delivery is shared with provincial and district health authorities, and provided through specialized programmes and individual health facilities, including Primary Health Centre and their networks at the local level.* ***(D2-OD#9)***	Delegation of authority	Authority and responsibility in delivering public health service
5	*Indonesia's health system approach to NCDs is still very much on an individual basis but it has been shown that a public health approach with a programmatic structure, systematic follow-up, and monitoring of quality of care and routine outcome reporting is much more beneficial in such settings* ***(D2-SW#23)***	Health system approach	Individual approach versus programmatic / systematic approach in NCD program
6	*Fiji, Indonesia, Malaysia, Myanmar, Papua New Guinea, the Philippines, Thailand and Vietnam participated in the Asia-Pacific Phase II Leadership forum…Indonesia highlighted cancer registry strengthening as a priority area in their action plan* ***(D2-SW#23)***	Global networking Action plan	Priority action area identified: - Implement a population-based cancer registry starting with Jakarta and Jogjakarta - Improve; implementation of comprehensive cancer service guideline
7	*In response to the increased of breast cancer incidence and mortality, the Ministry of Health (MoH) launched the Cervical and Breast Cancer Prevention (CECAP) project in January 2007…The CECAP project was implemented on a pilot basis in Karawang District, which is located approximately 1.5 h east of Jakarta* ***(D2-SW#17)***	Pilot scale of implementation	- Design implementation - Lesson learned

Appendix G: Abstract of manuscript



Your submissions

Track your submissions

Contextualizing policy implementation, challenges, and plans for improving breast cancer early detection programs in Indonesia

Corresponding Author: Popy Yuniar

BMC Health Services Research

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