MARKOV DECISION PROCESS APPROACH TO STRATEGIZE NATIONAL BREAST CANCER SCREENING POLICY IN DATA-LIMITED SETTINGS

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MARKOV DECISION PROCESS APPROACH TO STRATEGIZE NATIONAL BREAST CANCER SCREENING POLICY IN DATA-LIMITED SETTINGS

A Thesis presented

by

VIJETA DESHPANDE

Submitted to the Graduate School of the University of Massachusetts Amherst, in the partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE IN INDUSTRIAL ENGINEERING AND OPERATIONS RESEARCH

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Department of Mechanical and Industrial Engineering
MARKOV DECISION PROCESS APPROACH TO STRATEGIZE NATIONAL BREAST CANCER SCREENING POLICY IN DATA-LIMITED SETTINGS

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DEDICATION

This thesis is dedicated to Prof. Chaitra and memories of my Aai.
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First and foremost, I offer my sincerest gratitude to my supervisor, Prof. Chaitra Gopalappa, who has supported me throughout my thesis with her patience and knowledge. I attribute the level of my Master’s degree to her encouragement and effort and without her this thesis would not have been completed or written. One simply could not wish for a better or more well-wishing supervisor. I would also like to thank World Health Organization and Pan American Health Organization for all of the support in the form of funding and expert advice on model development necessary for completion of this thesis. I would like to thank my committee members Professor Hari Balasubramanian and Professor Ana Muriel for their sincere interest in my work. Finally, I would like to acknowledge my family and friends who supported me during my time here. First all, I would like to thank my parents, sister and brother in law for their constant and unconditional love and support, without which completion of graduate studies would not have been possible. Kushal Sahare, Rajiv Nair, Ravi Agrawal, Anuj Shanbag and Buyan Munkhbat made my time here at UMass a lot more fun.
ABSTRACT

MARKOV DECISION PROCESS APPROACH TO STRATEGIZE NATIONAL BREAST CANCER SCREENING POLICY IN DATA-LIMITED SETTINGS

SEPTEMBER 2019

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Rising rates of cancer incidence and mortalities in low and middle-income countries (LMICs) are burdening the already strained health care systems in LMICs. As cancer rates are expected to continue to rise, to better cope with this rapidly changing landscape, countries are working on incorporating cancer control programs, including early detection, as part of their national strategic planning. In the absence of control programs, cancers mostly get diagnosed in the advanced stages when they become symptomatic. While treatment in early stages of cancer are mostly effective, treatment in advanced stages is complex, expensive and mostly ineffective. Therefore, early diagnosis is a promising strategy to reduce premature mortalities and for optimal use of resources. But the absence of mathematical models specific to the data settings in LMIC’s impedes the construction of economic analysis necessary for decision-makers in the development of cancer control programs. This thesis presents a new methodology for parameterizing the natural history model of breast cancer based on data availabilities in low and middle income countries,
and formulation of a control optimization problem to find the optimal screening schedule for mammography screening, solved using dynamic programming. As harms and benefits are known to increase with the increase in the number of lifetime screens, the trade-off was modeled by formulating the immediate reward as a function of false positives and life-years saved. The method presented in thesis will provide optimal screening schedules for multiple scenarios of Willingness to Pay (numeric value assigned for each life-year lived), including the resulting total number of lifetime screens per person, which can help decision-makers evaluate current resource availabilities or plan future resource needs for implementation.
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CHAPTER 1
INTRODUCTION AND BACKGROUND

1.1 Cancer trends and burden in low and middle-income countries

Twenty years ago, communicable diseases such as HIV, malaria and tuberculosis were the primary concerns for low and middle-income countries (LMICs) and non-communicable diseases (NCDs) such as chronic heart and respiratory diseases, diabetes, and cancers, had negligible if any spotlight in overall disease burden in LMICs (1). But from 1990 to 2010, cancer fatality in LMICs increased to 7.98 million in 2010, compared to the previous decade, is was a 38% increase in cancer-related deaths in LMIC, which constituted a 15.1% portion of all global deaths in 2010 (1). Also, newly reported cancer cases in LMICs increased from 15% in 1970 to 56% in 2008, and such incremental trends are expected to continue to an estimated 70% by 2030 (1) (2). These increases are generating tremendous burdens on health care systems. Also, more than 60% of cancer related deaths occurred in LMIC and only 5% of global health resources for cancer are spent there (1) (2) (3). Hence, it is essential than ever to develop cost effective cancer control strategies specific to LMIC.

The general recommended approach to cancer control, based on cost-effectiveness estimates, is to first prevent the cancers which can be prevented, second, to treat the cancers which can be cured and third, to palliate the cancer when the first two approaches fail (1). Prevention programs have high potential to reduce the incidence of cancer by 33-50% (1). For several cancers, life can be considerably extended with low-cost drug treatment, e.g. pancreatic and lung cancer. When treatment is not always a feasible option, palliation
through reduction in pain and suffering is deliverable in low cost (3). But many cancers out of all those which are responsible for the most burden on LMIC health system are amenable to treatment e.g. colorectal cancer, cervical cancer and breast cancer (2).

Among all cancers, the highest disease burden in women is from breast cancer (4). Global breast cancer incidence in 2012 (43.3 per 100,000) was estimated to be 3 times that of the next most common cancers in women, namely, colorectal cancer, lung cancer, and cervical cancer with 14.3, 13.6, and 14.0 cases, respectively, per 100,000 persons (4). East and Central Asia reported the highest proportion of global breast cancer burden, about 36.3% and 41.5% of recorded incidence and deaths, respectively (4). Latin America and the Caribbean experienced 9.1% cases and 8.3% deaths of the global count (4).

The population attributable factor (PAF), defined as the contribution of a risk factor to a disease or a death, of breast cancer is 27% for high-income countries and 18% for low-middle-income countries (5). Solin et. al. (6), present results on selective screening (according to risk factors such as previous breast biopsy and family history of breast cancer) for breast cancer. In the simulation of screening of 17,543 women, more than 50% of the cases would not have been detected if it was a selective screening. Madigan et.al. (7) and De Waard et.al. (8) present evidence for the fact that only small proportion of the total breast cancer cases are related to the known risk parameters for breast cancer. Evidence collected from above mentioned studies argues that the sub-setting of women population based on the known risk-factors of breast cancer will not successfully identify the target group for mammography screening. On the other hand, cancer control largely depends on early detection due to the morbid, expensive and often ineffective nature of treatment in advanced stages of cancer (9). Hence, given that there are less known attributable risk
factors for breast cancer, the next best strategy for breast cancer control is conducting mammography screening programs with age-based invitation (4).

1.2 Screening programs and practices in high-income countries and low and middle-income countries

Screening programs can either be organized or opportunistic. Organized screening programs are those which do have clear invitation protocol to a well-defined target population, systematic call and recall for screening, investigation of results, follow-up treatments, quality tracking and program database (4). Dissemination of tracking and investigating team is also a trait of organized screening programs. Opportunistic programs do not target any subset of population but work with recommendations from regular health check-ups, therefore dependent on primary health care providers. Organized programs are generally evident in high income countries and opportunistic programs in low income countries.

Most of the organized programs for breast cancer approximately target the population in age group 40-74 years with biennial frequency of screening (4) (10). But this screening schedule greatly depend on the demographics and the epidemics specific to the population. Some high-income countries recommend populations in the younger age-group than 50 years of age for screening while others do not. While screening in age group 50-69 is strongly recommended for high-income countries by WHO recommendations, invitation to women in age-group 40-49 for mammography screening is conditional (11). For low-middle income countries, WHO recommends not to screen women in age group 40-49 and screening in age group 50-69 is conditional upon the scale and scope of the healthcare systems.
The next sub sections will briefly discuss the practices in different high and low-middle income countries and will point towards the observed positive outcomes of screening programs in high-income countries and the discrepancies between the WHO recommended guidelines and the current practices in low-middle income countries.

1.2.1 Practices in high-income countries and outcomes

Countries such as United States, United Kingdom, Finland, Netherland, Canada have achieved established (approximately 25 years old) organized breast cancer screening programs. In 2007, 26 of the 27 members of states in European Union (former) had an active breast cancer screening program, out of which 22 were organized. Seventy nine percent of the eligible population in these 26 countries were covered under regular screening (mammography) programs, most of the screened population was covered with no or little cost for women undergoing screening. All of the countries in EU recommend screening for women in age group 50 to 59 years, some countries additionally recommend 40 to 49 and/or up to 74 years of age. The frequency of screening is biennial for all the countries but UK and Malta, while in Austria, yearly screenings are also evident (4). In the case of Canada, all provinces have organized screening programs but Nunavut. British Columbia started the program in 1988 while Northwest territories started their program in 2003. Opportunistic screenings are available in those facilities which are not included in the organized screening program. All provinces and territories in Canada recommend women in age-group 50-69 for biennial screening and similar to EU selective screening for women under 50 years of age and over 70 is also available on basis of recommendations from practitioners (4). In the USA, promotion of mammography screening started in late 1980s and early 1990s. Since 1991, biennial screening was recommended and covered in
Medicare insurance plan. Private insurances covered mammography screening costs fully. The proportion of population not covered in Medicare and private insurance plans faced financial barrier for screening, but most of the issues, not all, in these barriers were resolved by the introduction of the Affordable Care Act (ACA) (4).

In these high-income countries, incidence of breast cancer sharply increased from 1980 to 2000 and mortality rates decreased consistently between 1990 to 2010 (12). Both the outcomes are majorly related to increasing prevalence of mammography screening from 1980 to 2005 (12). An estimated 28% to 65% reduction in mortality rates is expected to have occurred because of early detection and the rest proportion due to the systematic treatment (13). (Variability in the estimates of different models is associated with the difference in the modeling approach and assumptions.)

1.2.2 Practices in low and middle-income countries

Unlike in high-income countries, screening programs in low and middle-income countries have not yet reached to the scale where it can be considered as an organized program. Some countries in Asia, such as China and Indonesia, have local community-based screening programs (4). In the case of India, screening programs are restricted to controlled study purposes only, but educational/awareness programs are promoted (not specific to breast cancer) widely (4). Except South Africa, none of the countries in the Sub-Saharan African region have developed any screening guidelines for the population. Participation in screening programs of breast cancer in South Africa is also very low, approximately 15% of women reported having at least one mammogram in lifetime (4). In Central and West Asia and North Africa, most of the countries are categorized as low and middle income, in
these countries resource allocated to healthcare is limited and screening is rarely available (4).

Latin American countries have increased awareness towards the changing epidemiology of cancer and most of the countries where breast cancer is the leading cause of death, have developed screening guidelines for population. Most of the countries recommend self and clinical breast examination along with mammography for screening (4). Screening recommendations in most Latin American countries is for age-group 50-70, along with self or clinical examination for the younger age-groups. In few Latin-American countries, screening recommendation for women in age-groups 40-49 years is conditioned on breast cancer history while for few others, it is unconditioned(4) (14). But the opportunistic or regional organized screening programs inspired from such recommendation in Latin-American countries have not produced the similar reduction in the mortality rates as observed in high-income countries (9).

WHO Position Paper on Mammography Screening (11), recommends screening only for those lower-middle income countries which does have strong health systems, i.e. health systems having capacity to gradually develop and sustain an organized screening program. Recommended guidelines suggest conditional screening for age-group 50-69 and guidelines strongly recommends against screening the age-group 40-49 (11). However, certain countries such as Peru, a lower middle-income country, has developed legislative framework for early diagnosis, treatment and follow-up in 2008 which includes screening for women aged 40 years and older (15). The current evidence-based recommendations and practices of screening in low-middle income settings greatly vary. Majority of the evidence provided for development of the guidelines are either synthesized from the data
from randomized control trials conducted in high-income countries or extrapolation of the modeling studies conducted for high-income countries (11).

Therefore, it is essential to inform the development of the screening programs with evidence collected from studies which extensively and exclusively consider all aspects of the low-middle income settings.

1.3 Global action plan for non-communicable diseases (NCDs)

In 2008, 63% of the global deaths occurred due to NCDs out of which 38% were premature (before the age 70) and 90% of the premature deaths occurred in low and middle-income countries. Considering the changing trends and shifting burden of NCDs towards low and middle-income settings, the 66th World Health Assembly endorsed the global action plan proposed by World Health Organization for prevention and control of NCDs. The goal of the Global Action Plan is to reduce the burden in the form of morbidity, mortality and disability due to non-communicable diseases, through collaboration at regional, national and global level, so that populations will reach the highest attainable levels of health and productivity, ensuring the socioeconomic growth. The global action plan offers a paradigm shift by providing a road map and a menu of policy options for UN Member States, WHO, other UN organizations and intergovernmental organizations, NGOs and the private sector which, when implemented collectively between 2013 and 2020, will attain 9 voluntary global targets, including a 25% relative reduction in premature mortality from NCDs by 2025 (16).

1.4 Intrinsic challenges in mammography screening
As stated before, screening programs have resulted in reduction of mortality rates in high-income countries. When a screening program is organized, even though asymptomatic patients benefit from it, a large proportion of the screened population do not experience any benefit from screening, which encourages the questions of resource (screening resource with auxiliary support staff) management, utilization improvement and target group selection. In the case of breast cancer, as it is difficult to determine target group with currently known risk factors (5), resource management is a challenging task.

When a large proportion of screened population is not benefitting from the screening, ideally, they also should not experience any harms from it. In fact, screened population might be exposed to addition health risks or even death as a result of screening (17). Some health risks are embarked upon screened person with the false positive result of the test, which are followed up with more clinical procedures and also causes short term psychological distress (4). Other health risks are due to diagnosis of cancer which never would have caused death or any degradation of quality of life (17). There is sufficient evidence that women in age group 50-69 are diagnosed with cancer which never would have been diagnosed or caused any harms if the women had not been screened (4). In other words, when woman undergoes screening she reduces the risk of death due to cancer but also accepts the risk of over diagnosis and overtreatment, hence, assessment of risks and benefits is of significance. There is sufficient evidence that mammography screening is cost effective in the 50-69 age group in the population with high incidence but, importantly, there is limited evidence available for cost-effectiveness of the mammography screening in low and middle-income settings, as the incidence of cancer in such settings is relatively low (4).
Considering the fact that mammography screening does have risks along with benefits and the necessity of strengthening and orientating health systems towards NCDs, it is required to test the validity of mammography in low and middle-income settings and produce enough evidence for development of policy menu from which guidelines can be adopted to achieve goals mentioned in Global Action Plan. Critically analyzing the balance of benefits and risks for producing an age-based invitation policy is a complex decision problem, but operations research tools have been successful in developing solutions with required cost-benefit balance. Next section will discuss the literature addressing the screening decision problems with different operations research tools in different perspectives.
CHAPTER 2
LITERATURE REVIEW

In introduction section we discussed the broader challenges faced healthcare systems in low and middle-income settings, i.e. changing trends of cancer and lack of resources to address increasing incidence and mortality of cancer. In addition to the broader challenges, intervention strategies might also have intrinsic complexities in terms of application or health risks; e.g. mammography can lead to overdiagnosis and overtreatment. Operations Research tools have been successful in performing cost-effective and cost-benefit analysis of different intervention strategies for cancer prevention and control.

2.1 Simulation methods

Simulation models have proven to be an effective tool in testing and/or comparing cost-effectiveness of different strategies available for decision maker. While simulations models can be classified on numerous categories, one important distinction for the models is whether the model is empirically based shallow model or biologically based deep model (18). Stage shift model, an example of shallow model, simulate the diagnosis events in process of comparing the cost-effectiveness of different strategies, e.g. in comparison to no screening a specific screening strategy can result into diagnosis in less advance stage or early diagnosis in the same stage. But stage shift models do not delineate the trajectory followed in result of any specific event, therefore cannot be inclusive of the small details, e.g. if diagnosis is a case of overdiagnosis then the resulting life years saved should not be considered in the benefits of the strategy, but stage shift cannot incorporate such details (18). Opposed to shallow models, deep models are biologically inspired models where the
underlying process of leading to results is considered, e.g. the natural progression of tumor. As deep models are generally much more detailed than a shallow model, time required for their development and data required to tune the parameters is higher than shallow models. The comprehensive nature of the deep models also makes them adaptable to the changes and therefore can address broader policy question (18).

Stout et. al. (19), presents a model which evaluates lifetime cost and number of QALY for women aged 40 years or older, in the period of 1990 to 2000, for different breast cancer screening scenarios. Datum scenario was a one with no screening and other 65 scenarios were compared with datum. Out of 65 other scenarios, 64 were designed with different variations of starting age, ending age and frequency of screening, and one scenario was screening which actually took place from 1990 to 2000 in the USA. Authors found 11 strategies on the efficient frontier and the annual screening strategy from 40 to 70 years of age (closely resembling with the contemporary practices) was one of them with the highest cost. Therefore, this study with use of deep model presents alternative strategies which can be adopted with lower costs.

Study report from U.S. Preventive Services Task Force (20), also presents comparative analysis of 20 different screening schedules based on benefits (life years gained), resource usage (number of mammograms) and harms (false positive rate, unnecessary biopsies and overdiagnosis). Results from 6 independently developed models; deep models, developed with common input data on incidence, mortality, treatment algorithm and few model specific data variables; were compared on the metrics mentioned above. Population considered in the models is the cohort of women born in 1960 and tracked from age 25 years for their whole life. Results indicated that the policies which suggested screening in
age group 40-49 had relatively higher harms than the policies which did not include this specific age group. In resulting 8 non-dominant strategies out of the total 20 screening schedules, 6 schedules started from age 50 and all but one schedule was biennial. Hence, this study also presented cost-effectiveness analysis which provided a quantitative comparison of different screening policies with help of deep model.

2.2 Markov Decision Process

Özekici and Pliska (21), by assuming the disease risk and test properties are stationary, develop an infinite horizon MDP model minimizing the cost of inspection, false positives, treatment and death. They present a policy to screen, for a person whose terminal medical care costs and dollar value assigned to each loss of life is higher than 55000 USD. Maillart et. al. (22), considering age specific risk and imperfect tests (false-positive/negative), they present POMDP model maximizing the probability of survival to investigate screening frequency of breast cancer for premenopausal and postmenopausal women. Ayer et. al. (23), formulate a finite-horizon POMDP model maximizing the QALY lived during a lifespan. They have considered age-dependent disease progression, test accuracies and probability of self-detection and show that the individualized personal screening schedules resulted into higher QALY than the screening guidelines, simultaneously decreasing the total number of mammograms.

Kong and Mondschein (24), develop a stochastic dynamic programming approach in finite planning horizon, minimizing the total expected lifetime cost they determine individualized mammography guidelines which will enable dynamic tracking of patient’s risk factor. As the optimal policy generated by their model is very aggressive for low-risk
patient while is very conservative for high-risk patients, they also suggest segmenting the population according to the breast cancer risk for better tracking of risk factors and better policy results. Kong et. al. (25) used the same model to present and analyze mammography screening policy for Chilean population.
CHAPTER 3
MOTIVATION

Although randomized control trials provide evidence regarding efficacy of the screening methods, the stringent barriers on timeline of the study, population under consideration and type of screening technology being evaluated in the trial makes usability of the evidence limited (18). Trials cannot determine whether the evidence collected with the current cohort will also hold for another (18). Also, the screening and follow-up schedule which have been followed throughout the trial also needs to be compared with multiple other schedules for testing the effectiveness and finding the non-dominant strategies (18). Lastly, the decision regarding development of the screening guidelines cannot wait until the completion of any specific trial (18). Modeling techniques can leverage findings from trials and generate more comprehensive cost-benefit analysis of the screening schedule which are of interest to decision maker but are not covered in randomized trials. Furthermore, given the current developments in screening technologies, treatment and understanding of the disease, finding optimal screening strategy for any population is a moving target problem (18), which motivates the development of more flexible models acceptable to the current developments and are designed specifically for different population settings.

Developed models till now are suited to the data availability in high-income countries (HIC), while data availability and data quality in LMICs are low, even today. General approach used to address LMIC conditions was to extrapolate evidence from models developed for HIC. The models which were developed for LMICs, lacked technical depth (26) (17). Hence, it is utmost important to develop mathematical models encapsulating
epidemics and demographics specific to LMICs while considering the constraints on data availability, data quality and healthcare-resources to address the worsening incidence and mortality of cancer.
CHAPTER 4

RESEARCH QUESTION

In the background section we discussed how cancer is imparting incremental burden on health systems in low-middle income countries due increasing incidence and mortality of cancer. We also discussed the different aspects of the cancer control problem, to summarize,

1. In spite of the drastic increase in the incidence and mortality, healthcare system’s spending and orientation of control policies towards cancer has not increased in low-middle income countries.

2. Out of all the cancer, burden is mostly imparted due to cancers amenable to treatment, i.e. breast cancer, colorectal cancer and cervical cancer. As treatment of cancer is morbid, expensive and often ineffective in advanced stages, cancer control hinge on early diagnosis.

3. Moreover, breast cancer incidence in women is thrice the incidence of next most common cancers.

4. Due to low Population Attributable Factor (PAF), breast cancer cannot be effectively prevented and population sub-setting for better utilization of screening resource is also not possible. Therefore, age-based screening becomes next best strategy for breast cancer control.

5. Guidelines by WHO and practices observed in low-middle income countries do not show consensus on schedules of age-based mammography screening.
6. Evidence of effectiveness of mammography screening specific to population in low-middle income setting is absent and decision making in such setting greatly depend upon data from trials conducted in high-income countries or modeling studies done specific to high-income setting population.

Considering all the challenges mentioned above, in this thesis we have considered the case of breast cancer in lower-middle income population setting. Following this selection of problem, we will present a methodology to address the question of cost-effective age-based breast cancer screening schedule for a lower-middle income country for different values of willingness to pay of service provider (USD amount assigned to each life year lived), i.e., “What is cost-effective mammography screening schedules specific to a population for different values of willingness to pay?”

Development of mathematical model will provide necessary evidence required by decision makers in development of the screening guidelines for breast cancer in the country under consideration. The model we present is developed for breast cancer but has potential to produce evidence on cervical cancer and colorectal cancer with respective changes. Addressing issues in screening schedule development and reinforcing the decisions with evidence on breast cancer, colorectal cancer and cervical cancer (these three cancers being responsible for major proportion of burden) will significant help low and middle-income countries in managing the increasing burden due to cancer.

Next section will discuss the developed method in detail followed by discussion and conclusion.
CHAPTER 5
METODOLOGY

5.1 Approach

The developed model has three main components, first is parameterization of the natural
history of breast cancer, second is finite horizon Markov decision process model for
computing optimal mammography schedules and finally a compartmental simulation
model for simulating the screening schedules either computed from MDP model or the
suggested screening guidelines from previous literature. These three models are arranged
in series as shown in Figure 1, where second and the third model take input from the
previous model and literature. Parametrization model, the first one, takes data input from
GLOBOCAN 2012 database for age-specific incidence and mortality of breast cancer,
literature and demographic projection software ‘Spectrum’. The literature input for the

Figure 1: Model structure
parameterization model includes distribution of diagnosed cases over cancer stages, observed specifically in a country. For the optimization model, literature input includes cost and test specific parameters for mammography screening. Lastly, for the simulation model for outcomes and economic analysis, the literature input contains set of different policies observed in practice or mentioned in WHO guidelines.

Following sections will discuss each block of the mathematical model, from parameterization to simulation model, in detail.

5.2 Method

5.2.1 Overview of breast cancer disease progression

We assumed that breast cancer initiated first as carcinoma in-situ (CIS), i.e. women could transition from healthy to CIS. In the absence of diagnosis, the disease naturally progresses through the invasive carcinoma preclinical stages local, regional, and distant, that we refer to as system states. From any of these preclinical disease states persons could transition to clinical states through diagnosis based on symptoms or through screening. Upon transition to a clinical state through diagnosis, persons remain in the state at diagnosis and face a certain rate of death based on treatment efficacy at the cancer stage at diagnosis. For persons who were diagnosed, we did not explicitly model recurrence of disease, we only applied an average stage-specific rate of survival. We present the flow diagram in Figure 2.
We assumed that onset rates, i.e., the rate of transition from healthy to CIS, and diagnostic rates, i.e., the rates of transition from preclinical to clinical states, are dependent on the population under consideration and developed a two-step Markov process methodology for estimation of these rates. We assumed rates of natural progression through cancer stages,
i.e., from preclinical CIS to local, to regional, and to distant, do not vary by geographical region and used pre-estimated rates from the literature. We present the data estimates taken from published literature in Appendix A.1.

5.2.2 Two-Step Markov Process (TSMP) methodology for parametrization of the natural onset and progression of cancer

The TSMP divides the estimation of population-specific onset rates of disease and diagnostic rates into two Markov process models, each defined over different state spaces. In the first step, we define the disease onset and progression as a discrete-time Markov process,

\[ X = \{X_t; t \geq 0, \Omega, \mathbb{P}\} \]

with a collapsed state space,

\[ \Omega = \{[H_a], [U_a], [D_a]\} \]

Where,

\( a = age \), and

health states \( H_a = \) Healthy, \( U_a = \) Undiagnosed, and \( D_a = \) Diagnosed,

(see Figure 3 for a flow diagram, and Table 1: Overview of notations for the two-step Markov process parameterization methodology for a list of notations).

Figure 3: Flow diagram for the collapsed states space in the first step of the Markov process parameterization
Table 1: Overview of notations for the two-step Markov process parameterization methodology

<table>
<thead>
<tr>
<th>Notation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_a$</td>
<td>Incidence of cancer at age $a$, from GLOBOCAN</td>
</tr>
<tr>
<td>$\bar{I}_a$</td>
<td>Incidence of cancer at age $a$, from simulation model</td>
</tr>
<tr>
<td>$\Delta t$</td>
<td>time step in the simulation model</td>
</tr>
<tr>
<td>$\rho_t$</td>
<td>steady state population in the state space $Z$ (equation), from the simulation model,</td>
</tr>
<tr>
<td>$d_{i,a}$</td>
<td>diagnostic rate of cancer in stage $i$ and age $a$,</td>
</tr>
<tr>
<td>$s_j$</td>
<td>percentage of diagnosed cases of cancer in the stage ‘j’</td>
</tr>
<tr>
<td>$p_{i,a}$</td>
<td>prevalence in pre-clinical state $i$ at age $a$</td>
</tr>
<tr>
<td>$\lambda_i$</td>
<td>dwell rate for cancer stage $i$</td>
</tr>
<tr>
<td>$I_{i,a}$</td>
<td>Incidence of cancer stage $i$ at age $a$ from GLOBOCAN data</td>
</tr>
<tr>
<td>$\bar{I}_{i,a}$</td>
<td>Incidence of cancer stage $i$ at age $a$ from simulation model</td>
</tr>
</tbody>
</table>

clustering together all micro-states of the disease; and $\mathbb{P}$ is the transition probability matrix.

We estimate age-specific onset rates using an iterative analytical model derived using the Markov chain $X$. The technical details and proofs leading to the analytical model are presented in (27), here we only summarize the outline of the algorithm in

Table 2: Algorithm for computing age-specific onset rate of cancer.

Table 2: Algorithm for computing age-specific onset rate of cancer

Initializes $\pi_{H_0} = A_0; \pi_{U_0} = 0; and \mathbb{P}_{H_0,U_0} = 0$; Set $a = 1$, the youngest age-group of cancer onset (we assumed age 15 for breast cancer).
Step 1: Calculate in-situ onset rate

\[
P_{H_a U_a} = I_{D_a} c_a - \sum_{k=0}^{a-1} \left( \pi_{H_k} P_{H_k U_k} \left[ \sum_i s_i \left( 1 - e^{-(a-k)\lambda_i} \right) - \sum_i s_i \left( 1 - e^{-(a-1-k)\lambda_i} \right) \right] \right) \frac{A_a \left[ \sum_i s_i \left( 1 - e^{-\lambda_i} \right) \right] \left( e^{-\mu_a} \right) - I_{D_a} c_a}{A_a \left[ \sum_i s_i \left( 1 - e^{-\lambda_i} \right) \right] \left( e^{-\mu_a} \right)}
\]

Where,

\[
\frac{1}{\lambda_i} = \sum_{j=0}^{i} \frac{1}{p_j}; \text{ if } p_j \text{ are a function of age at disease onset then } \frac{1}{\lambda_{i,a}} = \sum_{j=0}^{i} \frac{1}{p_{j,a}}
\]

Then, disease onset rate at age \( a \) is estimated as

\[
\theta_a = -\ln \left( 1 - P_{H_a U_a} \right)
\]

Step 2: Calculate prevalence of healthy state:

\[
\pi_{H_a} = A_a - \sum_{k=0}^{a-1} \left( \pi_{H_k} P_{H_k U_k} P(\mathcal{T} \geq a - k) P(S \geq a - k) \right) \frac{1 + P_{H_a U_a}}{1 + P_{H_a U_a}}
\]

\[
P(\mathcal{T} \geq a - k) P(S \geq a - k) = \sum_i s_i \left( 1 - e^{-(a-1-k)\lambda_i} \right) \prod_{j=k:a} e^{-\mu_j}
\]

Where,

\[
\frac{1}{\lambda_i} = \sum_{j=0}^{i} \frac{1}{p_j}; \text{ if } p_j \text{ are a function of age at disease onset then } \frac{1}{\lambda_{i,a}} = \sum_{j=0}^{i} \frac{1}{p_{j,a}}
\]

Step 3: Increment \( a \) by 1; if \( a \) is less than the maximum age go to step 1, else stop.

In the second step, we estimated diagnostic rates in each stage of cancer, i.e., transition rates from preclinical to clinical states \((d_{i,a})\), by using a simulation-based optimization method. In this method we simulate the Markov process \( \mathbf{Y} = \{Y_t; t \geq\)
0, Z, Q}, where state space is \( Z = \{[H_a], [U_{i,a}], [D_{i,a}]\} \), and rate matrix \( Q \), which corresponds to the to the flow diagram in Figure 2.

The objective of the simulation-based optimization model is to minimize the sum of square errors between the simulated cancer incidence \( \overline{I_a} \) and the GLOBOCAN predicted incidence \( I_a \) (28). For completeness, we first present this earlier version of the model formulation before discussing the modifications specific to a data-limited setting that has partial screening programs. The objective function was formulated as

\[
\text{Minimize}_{d_{i,a}} \sum_a (\overline{I_a} - I_a)^2, \quad d_{i,a} \geq 0, \forall i, a
\]

(2)

As the analytical form of \( \overline{I_a} \) are unknown, but the value of the objective function can be evaluated at different points of the decision parameters \( d_{i,a} \geq 0, \forall i, a \), with simulation. Here, for any specific \( d_{i,a} \) values, we simulated the Markov Process \( Y \) over time \( t \) using

\[
\rho_{t+1} = \rho_t + \rho_t Q \Delta t \quad \text{until it reached state steady, i.e.,}
\]

\[
\rho = \rho + \rho Q \Delta t
\]

(3)

where \( \rho \) is a vector of state distribution at steady state and \( Q \) is the rate matrix.

We estimated \( \overline{I_a} \) using following equation,

\[
\overline{I_a} = \sum_i \rho_{U_{i,a}} d_{i,a},
\]
where $\rho_{U_{i,a}}$ is the steady state value for state $U_{i,a}$ (denoting the prevalence in pre-clinical cancer stage $i$ at age $a$), which can be estimated by expansion of equation (3) as

$$\rho_{U_{i,a}} = \rho_{U_{i,a}} + \rho_{U_{i-1,a-1}} \lambda_{i-1,a} - \rho_{U_{i,a-1}} (\lambda_{i,a} + d_{i,a} + \mu_{i,a})$$

In the previously presented TSMP model in (27), because of the assumption that diagnosis is only symptomatic and that the probability of showing symptoms are higher in advanced disease stages, i.e., $d_{i,a} > d_{i-1,a}$, the distribution of the stage at diagnosis was a good approximation for the ratio of stage-specific diagnostic rates. That is, $\frac{d_{i,a}}{d_{3,a}} = \sum_{j=0}^{i} s_j$, where $s_j$ is the proportion diagnosed in stage $j$, and $d_{i,a}$ is the diagnostic rate at state $i$ and age $a$. Therefore, for the terms in the objective function in equation (2) we could write

$$(I_a - l_a)^2 = \left(\sum_i \rho_{U_{i,a}} d_{i,a} - l_a\right)^2 = \left(\sum_i \rho_{U_{i,a}} (d_{3,a} \sum_{j=0}^{i} s_j) - l_a\right)^2 \approx f(d_{3,a})$$

Therefore, the only unknown values in the objective function in equation (2) were the diagnostic rates in the last stage of cancer ($d_{3,a}$), as the steady state values in the pre-clinical states, $\rho_{U_{i,a}}$, are estimated numerically from the simulation of the Markov model in equation (3) as discussed above. The resulting objective function was

$$\text{Minimize}_{d_{3,a}} \sum_a \left(\sum_i \rho_{U_{i,a}} (d_{3,a} \sum_{j=0}^{i} s_j) - l_a\right)^2$$

and the decision variables $d_{3,a}$ $\forall a$ were solved iteratively for each $a$. However, in the case of countries such as Peru, certain populations have undergone screening based on recommendations and regional programs help in country prior to 2012 (the latest incidence
data available at the time of this work was for year 2012), and thus, the assumption \( d_{i,a} > d_{i-1,a} \) does not hold. Therefore, we modified the objective function in equation (5) to

\[
\text{Minimize}_{d_{i,a} \forall i,a} \sum_{i,a} \left( \rho_{U_{i,a}} (d_{i,a}) - l_a \right)^2, \quad d_{i,a} \geq 0 \forall i, a
\]

(6)

Thus, the number of decision variables (the unknown values) now increase to include diagnostic rates in all stages \( i \) and ages \( a \), i.e., \( d_{i,a} \forall i, a \). This creates a large number of decision variables. As the number of decision variables increases, ascertaining the convergence of a solution algorithm to the global optima becomes more challenging. We address this by showing below that the optimization problem in equation (6) is separable both on \( i \) and \( a \) and thus equation (6) can be converted to \( ia \) number of sub-problems. Each sub-problem can then be solved separately but iteratively for \( d_{i,a} \), iterating over each \( i \) and \( a \) (see below). We further test for the convexity of each sub-problem (see Appendix A.2).

**Remark 1:** We can rewrite equation (6) as,

\[
\text{Minimize}_{d_{i,a}} \left( \rho_{U_{i,a}} (d_{i,a}) - l_a \right)^2, \quad d_{i,a} \geq 0
\]

(7)

for each combination of \( i, a \) pair thus generating \( ia \) number of sub-problems. Each function can then be solved separately for \( d_{i,a} \) but iteratively over age \( a \) starting from the youngest age and, within each age, iteratively over cancer state \( i \) starting with the earliest disease state.

**Proof:**
Using the expression for $\rho_{U_{i,a}}$, from the expansion of the Markov process in equation (3) discussed above, and multiplying by $d_{i,a}$ we can write

$$
\rho_{U_{i,a}} d_{i,a} = \left[ \rho_{U_{i,a}} + \rho_{U_{i-1,a-1}} \lambda_{i-1,a} - \rho_{U_{i,a-1}} \left( \lambda_{i,a} + d_{i,a} + \mu_{i,a} \right) \right] d_{i,a} \quad (8)
$$

In equation (8), for $i = 0$ (the in-situ stage) $\lambda_{i-1,a-1} = \theta_{a-1}$ the cancer onset rate, and for all other values of $i$ (i.e., local, regional, and distant stages) $\lambda_{i-1,a-1}$ are the progression rates (see Figure 2); and $\mu_{i,a-1}$ are the mortality rates. Values for $\lambda_{i-1,a-1}$ and $\mu_{i,a-1}$ are known. When $i = 0$ (the in-situ stage) $\rho_{U_{i-1,a-1}} = \rho_{H_{a-1}}$ denoting the steady state value in healthy (i.e., prevalence of healthy stage), and under all other values of $i$, $\rho_{U_{i-1,a-1}}$ are the steady state values in the pre-clinical states (i.e., prevalence of pre-clinical cancer stages).

For any given $i, a$ pair, from Remark 2 and its proof below, the steady state values for $\rho_{U_{i,a}}$ and $\rho_{U_{i-1,a-1}}$, and solution to $d_{i,a-1}$ are known. Therefore, for any value of $d_{i,a}$, the steady state value for $\rho_{U_{i,a}}$ can be calculated through simulation of the Markov process in equation (3). As such, the only unknown value in equation (8) will then be $d_{i,a}$ which can be solved by applying a non-linear solver to the optimization problem in equation (7). To identify convergence of the algorithm to global optima, we test for the convexity of equation (7), which we discuss in Appendix A.2.

This completes the proof.

Remark 2: If we iteratively solve for $d_{i,a}$ using equation (8) by iterating over $a$ and, within each $a$, iterate over $i$, then, for any given $i, a$ pair, the steady state values for $\rho_{U_{i,a}}$ and
\( \rho_{u_{i-1,a-1}} \), and the solution to \( d_{i,a-1} \) are known. Thus, the only unknown term in equation (8) is \( d_{i,a} \)

**Proof:**

We prove this by applying mathematical induction on equation (8)

For \( i = 0, a = 1 \),

\[
\rho_{u_{0,1}} d_{0,1} = \left[ \rho_{u_{0,1}} + \rho_{H_0} \theta_1 - \rho_{u_{0,0}} \left( \lambda_{0,a} + d_{0,a} + \mu_{H,a} \right) \right] d_{0,1}
\]

Then, the only unknown value is \( d_{0,1} \) because \( \rho_{u_{0,0}} = 0 \) and \( \rho_{H_0} \) is the actual prevalence of healthy persons in age 0 (obtained from population demographics) as the first age for disease risk is 1, and all other parameters are known as discussed in proof of Remark 1.

Assuming the proof holds for \( i = m, a = 1 \),

for \( m + 1, a = 1 \)

\[
\rho_{u_{m+1,1}} d_{m+1,1} = \left[ \rho_{u_{m+1,1}} + \rho_{u_{m,0}} \lambda_{m,1} - \rho_{u_{m+1,0}} \left( \lambda_{m+1,1} + d_{m+1,1} + \mu_{m+1,1} \right) \right] d_{m+1,1}
\]

Then, the only unknown parameter is \( d_{m+1,1} \) as \( \rho_{u_{m,0}} = 0 \) and \( \rho_{u_{m+1,0}} = 0 \) as the first age of disease risk is 1.

For \( 0, a = 2 \)
\[ \rho u_{0,2} d_{0,2} = \left[ \rho u_{0,2} + \rho_{H_1} \theta_2 - \rho u_{0,1} (\lambda_{i,2} + d_{i,2} + \mu_{i,2}) \right] d_{0,2} \]

Then, the only unknown parameter is \( d_{0,2} \) because \( \rho_{H_1} = \rho_{H_1} - \rho_{H_0} (\theta_1 + \mu_{H,1}) \) can be estimated through steady state simulation of equation (3) and \( \rho_{U,0,1} \) was estimated previously under \( a = 0 \), \( a = 1 \).

Assuming the proof holds for \( i = m \), \( a = 2 \),

for \( m + 1 \), \( a = 2 \)

\[ \rho u_{m+1,2} d_{m+1,2} = \left[ \rho u_{m+1,2} + \rho_{U,m,1} \lambda_{m,2} - \rho u_{m+1,1} (\lambda_{m+1,2} + d_{m+1,2} + \mu_{m+1,2}) \right] d_{m+1,2} \]

Then, the only unknown parameter is \( d_{m+1,2} \) as \( \rho u_{m,1} \) and \( \rho u_{m+1,1} \) were estimated above under \( m \), \( a = 1 \) and \( i = m + 1 \), \( a = 1 \), respectively.

Finally, assuming the proof holds for any \( i \) and \( a = k \),

for any \( i \), and \( a = k + 1 \)

\[ \rho u_{i,k+1} d_{i,k+1} = \left[ \rho u_{i,k+1} + \rho_{U_{i-1,k}} \lambda_{i-1,k+1} - \rho u_{i,k} (\lambda_{i,k+1} + d_{i,k+1} + \mu_{i,k+1}) \right] d_{i,k+1} \]

Then, the only unknown parameter is \( d_{i,k+1} \) as \( \rho u_{i-1,k} \) and \( \rho u_{i,k} \) were estimated above under any \( i \) and \( a = k \).

This completes the proof.
Therefore, in this way we are first making the objective function fit for the setting of countries such as in Latin America, where diagnosis is not entirely symptomatic, i.e. changing the objective function from equation (5) to equation (6). By doing so, we are increasing the size of the problem as equation (6) does have 4 times more decision variables \((d_{i,a}, number\ of\ decision\ variables = 400)\) than the equation (5) \((d_{4,a}, number\ of\ decision\ variables = 100)\). Proving the separability of the objective function coverts the larger problem into 400 sub-problems, each having only one decision variable, if solved iteratively from earliest disease state and age. Figure 4, gives a visual representation of the optimization process, starting from earliest cancer state and age.
5.2.3 A Markov decision process (MDP) to identify optimal screening intervals for mammography

We formulated the problem of identifying an optimal screening strategy, specifically, what ages to screen, as a finite horizon MDP defined as \( \{X_s, D_s; Z, A, \mathbb{P}_a, R_a\} \) (see Table 3: Overview of the notations used in the Markov decision process model for notations).

Table 3: Overview of the notations used in the Markov decision process model

<table>
<thead>
<tr>
<th>Notation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mathbb{P} )</td>
<td>Transition probability matrix</td>
</tr>
<tr>
<td>( A )</td>
<td>Action space</td>
</tr>
</tbody>
</table>
\( Z \) | \([\{H_a\}, \{U_{i,a}\}, \{D_{i,a}\}]\)  \\
\( k \) | \([\{H_a\}, \{U_{i,a}\}]\)  \\
\( V(i', s, a) \) | value function of the Bellman equation for state \( i' \), at stage \( s \), if action \( a \) is taken  \\
\( \pi_{i'} \) | steady state distribution for state \( i' \in k \)  \\
\( r(i', s, a) \) | expected reward in state \( i' \) and stage \( s \), under action \( a \)  \\
\( p(i', s, a, j) \) | probability of transition from \( i' \) to \( j \), at stage \( s \), under action \( a \), where \( j \in Z \)  \\
\( a^*(k, s) \) | optimal action in state \( k \) at stage \( s \)  \\

Where,

\( s = 1 \) to 100 are the decision making stages, here representing individual ages,

\( X_s \in Z \) is the disease state at stage \( s \), defined over state space \( Z = \{[H_a], [U_{i,a}], [D_{i,a}], M\} \), where \( [H_a], [U_{i,a}], [D_{i,a}] \) are healthy, preclinical, and clinical states as in the Markov process model, and \( M \) denotes a mortality state,

\( A \) is the action space which is a set of possible decisions at stage \( s \), \( A_i = \{\text{Screen}(1), \text{Do not Screen}(0)\} \ \forall i' \in k = \{[H_a], [U_{i,a}]\}, A_i = \{\text{Do nothing}\} \ \forall i \in [D_{i,a}], M\)
$D_s \epsilon A$ is the decision taken at stage $s$ (choosing from set $A$, a set of possible decision choices),

$P_a$ is the transition probability matrix for action $a$, with each element $p(i', s, a, j)$ representing the probability of transitioning from state $i'$ to state $j$ if the system is in stage $s$ and action $a$ is taken (expressions for transition probabilities are mentioned in Appendix A.4), and $R_a$ is the immediate reward for action $a$, with $r(i', s, a, j)$ representing each element of the matrix.

The problem is then to solve for the optimal values of $D_s$. Use of MDP in this context is a well-studied problem (26) so we do not discuss further details of the methodology here. We only show the formulation of the problem in the context of identifying optimal screening guidelines for any country considering costs of screening and willingness to pay per quality-adjusted life-year saved.

The above MDP was solved using dynamic programming. In this method, at every stage $s$ (representing age) the model chooses to do nothing if $i \epsilon \{[D_i, a], M\}$ and if $i' \in k = \{[H_a], [U_i, a]\}$, the model either chooses to screen or to not screen by calculating the ‘value’ of each action choice $V(i', s, a)$, and selecting the action that resulted in the highest values as the optimal action $a^*(i', s)$ for that specific disease state ($i'$) and age ($s$) combination, as follows.
\begin{align*}
V(i', s, a) &= \sum_{i' \in k} \left( \frac{\pi_{i'}}{\sum_{m \in k} \pi_m} \right) \left[ \sum_{j \in Z} p(i', s, a, j) r(i', s, a, j) \right. \\
& \quad + \left. \sum_{j \in Z} p(i', s, a, j) J^*(i', s + 1) \right] \\
\forall a \in A, \forall i' \in k = \{[H_a], [U_{i,a}]\}, \\
a^*(i', s) &= \arg \max_{a \in A} V(i', s, a), \forall i' \in k \\
J^*(i', s) &= r(i', s, a^*(i', s)) + \sum_{j \in Z} p(i', s, a^*(i', s), j) J^*(i', s + 1) \\
\end{align*}

Note that with the above equations all \( i' \in k = \{[H_a], [U_{i,a}]\}, \) will have the same optimal action, as \{[U_{i,a}]\} are unobservable states.

We set,

\[
\begin{aligned}
r(i', a, s = \text{no screening}, j) &= 
\begin{cases}
0, & \text{if } j \text{ is mortality} \\
r_{LY}.q_j + c_d + c_i, & \text{if } i' \in [U_{i,a}] \text{ and } j \in [D_{i,a}], \text{ and} \\
r_{LY}.q_j, & \text{if } i' \in [D_{i,a}] \text{ and } j \in M \\
r_{LY}.q_j, & \text{otherwise}
\end{cases}
\end{aligned}
\]

\[
\begin{aligned}
r(i', a, s = \text{screening}, j) &= 
\begin{cases}
0, & \text{if } j \text{ is mortality} \\
r_{LY}.q_j + c_d + c_i, & \text{if } i' \in [U_{i,a}] \text{ and } j \in \{D_{i,a}\} \\
r_{LY}.q_j + c_t, & \text{if } i' \in [D_{i,a}] \text{ and } j \in M \\
r_{LY}.q_j + c_s, & \text{otherwise}
\end{cases}
\end{aligned}
\]

where,

\[
c_s = - (\zeta_{mammography_a} c_{mammogram} + (1 - \zeta_{mammography_a})(c_{mammogram} + c_{-diagnosis})).
\]
\[ c_d = - (c_{\text{mammogram}} + c_{\text{diagnosis}}), \]

\[ r_{LY} = \text{value-per-QALY lived}, \]

where,

\[ q_j = \text{QALY associated with state } j, q_j = \begin{cases} 
1 & \text{if } j = H_a \\
0 & \text{if } j = M \\
0 < q_j < 1 & \text{otherwise} 
\end{cases}, \]

\( \zeta_{\text{mammography}_a} \) is the specificity of mammography at age \( a \),

\( c_{\text{mammogram}} \) is the unit cost of mammography per person,

\( c_{-\text{diagnosis}} \) is the cost of follow-up diagnostic tests for a false positive (per person)

\( c_{+\text{diagnosis}} \) is the cost of follow-up diagnostic tests for a true positive (per person)

\( c_i \) is the initial treatment cost per person, and

\( c_t \) is terminal treatment cost per person, which was applied at the final year of life for women who die from breast cancer.

Values of the above-mentioned parameters are noted in Appendix A.3.

5.2.4 Simulation Model

5.2.4.1 Pseudocode for simulation

The model described above will consider the cross-sectional data and will compute the optimal screening schedules for given value per QALY. To evaluate performance of such screening schedules or to compute the outcomes of the screening schedules, we have developed a simulation model. This simulation model is a compartmental simulation model.
and it computes outcomes collected over 100 years of span screening schedule. Pseudocode for the simulation model is as follows,

\textit{Initialize }\rho\textit{ and }l

\begin{align*}
\rho & \leftarrow \text{zeros}(|Z|, s_{max}) \\
l & \leftarrow \text{zeros}(|Z|, 1) \\
\text{for } a = 1: s_{max} \\
\quad \rho_s & \leftarrow \pi_s A_s \\
\text{for } t = 1: t_{max} \\
\quad \text{for } s = s_{max}: 2 \\
\quad \quad \rho_s & \leftarrow \rho_{s-1} P(., s - 1, ., a, ., s) \\
\quad \rho_{1,1} & \leftarrow \text{births} \\
\quad l & \leftarrow l + \sum_s \rho_s
\end{align*}

Where,

\(\rho\) is matrix of population in each state, i.e. total \(|Z|\), and each age/stage, i.e. \(s_{max}\).

\(s_{max}\) is maximum value of age/stage, i.e. 100,

\(t_{max}\) is horizon over which policy outcomes are calculated, i.e. 100

\(l\) is life years lived in each state, i.e. \(Z = \{[H_a], [U_{i,a}], [D_{i,a}]\}\),

\(\pi_s\) is stationary distribution over the state space \(Z\), when age/stage is ‘\(s\)’,

\(A_s\) is population distribution over ages

\(P(., s - 1, ., a, ., s)\) is transition probability matrix at stage/age ‘\(s - 1\)’ under action ‘\(a\)’
5.2.4.2 Impact Metrics

To measure the outcomes of screening schedules identified by our model, we consider two impact metrics, life-years-saved per 1000 women and false positives per 1000 women, defined as follows.

\[
\text{Life years saved per 1000 women} = \frac{10^3 (L_{policy} - L_{basecase})}{L_{basecase} / t_{avg}}
\]

\[
\text{False positives per 1000 women} = \frac{10^3 N_{FP}}{L_{basecase} / t_{avg}}
\]

Where,

\[L_{policy} = \text{Life years lived in the intervention scenario (optimal screening strategy) over a 100 year period,}\]

\[L_{basecase} = \text{Life years lived in the base-case (no screening) over a 100 year period,}\]

\[t_{avg} = \text{average life expectancy in the country, thus, } \frac{L_{policy}}{t_{avg}} \text{ is an approximation used for estimating the average number of women in the simulation.}\]

\[N_{FP} \text{ is the total number of false positives over a 100-year period,}\]

The values used in this application are summarized in Appendix A.3.

5.2.5 Model validation

To validate the model results, we generated additional scenarios of biennial screening under multiple age groups to compare with results presented in the literature (Figure 3).
Our model estimations for life years saved per 1000 women under these different screening schedules compared well with results presented in (29) (see Figure 5: Model validation: Life years saved per 1000 women compared to current screening levels).
Figure 5: Model validation: Life years saved per 1000 women compared to current screening levels

(Model group abbreviations: D = Dana-Farber Cancer Institute; E = Erasmus Medical Center; G = Georgetown University; M = M.D. Anderson Cancer Center; S = Stanford University; W = University of Wisconsin)

The results in (29), from six independent models, were based on simulations of screening in women born in 1960 in the United States representative of a screening naïve US population. Model inputs for parameterization, including pre-screening incidence and stage at diagnosis distribution, and mammography screen specificity, sensitivity, and costs were based on (29) and are presented in Appendix A.5.
CHAPTER 6
DISCUSSION AND CONCLUSIONS

In summary, this thesis presents a new methodology for parameterization of cancer natural onset and progression for data limited settings such as in low and middle income countries, and an application of MDP model for estimating optimal number of screens and ages to screen under different constraints of WTP (numeric value assigned for each life year lived) or number of possible lifetime screens. Though the literature presents multiple Markov processes-based parameterization methodologies and MDP models for identifying screening options, most of these have been applied to or derived from application to populations in high income countries (HICs). As noted by other researchers in systematic reviews of economic evidence for informing breast cancer strategies for low and middle-income countries (LMICs), the quality of studies specific to LMICs are poor due to lack of data availabilities. (30) Countries thus adopt to extrapolating strategies or impacts of strategies from high-income countries, which can be challenging as clinical practices, health systems, infrastructure availabilities, and culture differ across countries.

We believe the natural progression parameterization methodology presented here, that was specific to data availabilities in LMIC settings, addresses this key gap. This enables development of economic analysis that are more tailored to the country, by considering the population’s disease risk, resource availabilities, and preferences.

Further, current WHO guidelines recommend prioritizing screening ages 50-69 and strongly recommends against screening for ages 40-49 in low resource settings even if health systems are relatively strong. The latter is mainly because of the increased number
of false positives, and increment in the risk of over treatment and over diagnosis due to false positives in ages 40-49, which require careful monitoring and evaluation that are usually not available in low resource settings.

The above guidelines were based on RCTs and observational studies conducted in high income countries and supported by modeling studies. Conducting RCTs in every country is economically and practically infeasible. We believe, the method presented in this thesis, that integrates disease burden specific to a country into the modeling, can help evaluate evidence necessary to understand the risks and benefits of screening women under alternative strategies.

To test and validate our model, we generated results for United States pre-screening incidence data and compared with previously presented results (29) (Appendix A.5). Results consisted of two outcome metrics, first life-years saved and false-positives, both of which are well matched with the results presented in Mandelblatt et.al. (29).

Further, the optimal screening schedules and its impacts under multiple WTP assumptions or lifetime screen choices could help countries in planning current screening programs and their expansion in the future. For example, as the number of lifetime screenings can be related to infrastructural and resource needs, the scenario to adopt could be based on current or future resource/infrastructure capacities.

The model is subject to limitations. We only considered heterogeneity by age for incidence and did not consider any other population characteristics or differences across countries. Causal factors for differences across countries in the risk of disease could be multiple, including diet, alcohol and tobacco consumption, competing diseases, or genetic. For
persons who were diagnosed, we did not explicitly model recurrence of disease, we only applied an average stage-and age specific rate of survival. We assumed that for persons with the disease, progression rates in preclinical stages do not vary by populations. The transition parameters were based on cancer stage, but we did not model heterogeneity in the cancer subtypes between different populations, or the family history of cancer. We did not model over-diagnosis of cancers, we only modeled age-specific false positives of mammography which were incorporated as costs in the MDP model.

Despite these limitations, we believe the methodologies presented for breast cancer from this study, when applied to a low or middle income country, can have an impactful contribution to cancer control. We believe, our approach to analysis, of identifying optimal screening ages and intervals under alternate choices of number of lifetime screens, can help countries evaluate what options are feasible based on current screening capacities, and adopt the most cost-effective scenario from among the feasible choices. Further, as countries are developing an ‘investment case’ to scale-up infrastructure and strengthen health systems to achieve the goals of mortality reductions from NCDs, pledged under the Sustainable Development Goals and the WHO Global Action Plan, the method presented here could help decision-makers determine future infrastructure needs. We believe, the methodology presented here can be expanded to evaluate interventions in combination or interventions for other types of cancers, which can further help in the development of the broader investment case for the prevention of non-communicable diseases.
APPENDIX A
DATA ASSUMPTIONS FOR PARAMETERIZATION OF CANCER ONSET AND PROGRESSION

Table 4: Region specific input data for parameterization

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>General progression parameters</td>
<td></td>
<td>(32) (33) (34)</td>
</tr>
<tr>
<td>Progression rates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-situ to Local ($\lambda_{0,a}$)</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Local to Regional ($\lambda_{1,a}$)</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Regional to Distant ($\lambda_{2,a}$)</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Annual mortality rate (per person year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>without treatment by stage at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-situ</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Regional</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Distant</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Annual mortality rate (per person year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with treatment by stage at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-situ ($\mu_1$)</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>
Local ($\mu_2$) 0.02
Regional ($\mu_3$) 0.08
Distant ($\mu_4$) 0.27

REGION-SPECIFIC DATA

Pre-screening incidence per 1000 persons per year

<table>
<thead>
<tr>
<th>Age group</th>
<th>US</th>
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<tbody>
<tr>
<td>0-14</td>
<td>0.00</td>
</tr>
<tr>
<td>15-39</td>
<td>0.06</td>
</tr>
<tr>
<td>40-44</td>
<td>1.09</td>
</tr>
<tr>
<td>45-49</td>
<td>1.72</td>
</tr>
<tr>
<td>50-54</td>
<td>1.97</td>
</tr>
<tr>
<td>55-59</td>
<td>2.21</td>
</tr>
<tr>
<td>60-64</td>
<td>2.60</td>
</tr>
<tr>
<td>65-69</td>
<td>2.84</td>
</tr>
<tr>
<td>70-74</td>
<td>3.06</td>
</tr>
<tr>
<td>75-100</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Distribution of stage at diagnosis in base-case

<table>
<thead>
<tr>
<th>Stage</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-Situ</td>
<td>4.70%</td>
</tr>
<tr>
<td>Region</td>
<td>Percentage</td>
</tr>
<tr>
<td>----------</td>
<td>------------</td>
</tr>
<tr>
<td>Local</td>
<td>48.30%</td>
</tr>
<tr>
<td>Regional</td>
<td>39.50%</td>
</tr>
<tr>
<td>Distant</td>
<td>7.50%</td>
</tr>
</tbody>
</table>
APPENDIX B
TEST FOR CONVEXITY OF THE OPTIMIZATION MODEL FOR ESTIMATION OF DIAGNOSTIC RATES

In the main paper, diagnostic rates were estimated by solving for the optimization models

\[ \text{Minimize}_{d_{i,a}} \left( \tilde{I}_{i,a} - I_{i,a} \right)^2, \quad d_{i,a} \geq 0 \]

for each combination of cancer stage \((i)\) and age \((a)\) pair, where \(\tilde{I}_{i,a}\) and \(I_{i,a}\) are the simulated and actual cancer incidence in stage \(i\) and age \(a\), thus solving \(ia\) number of optimization models. To check for the convergence of the solution to global optima we test for the convexity of the objective functions.

Specifically, we test for the commonly used convexity test, a function \(f(x)\) that is twice differentiable on \(x\) is convex if it is positive semi-definite, i.e., the second derivative \(f''(x) \geq 0\) at all points of \(x\). However, we do not know the analytical form of \(\tilde{I}_{i,a}\) to calculate the second derivative of the objective function \((\tilde{I}_{i,a} - I_{i,a})^2\). Therefore, for each combination of cancer stage \((i)\) and age \((a)\) pair, we empirically generated the function for \(\tilde{I}_{i,a}\) by estimation at multiple points of \(d_{i,a}\). See Figure 1 and Figure 2 for results on In-situ and Local stages of cancer and at multiple age groups.
From the above empirical results, for any given cancer stage and age, the simulated incidence $\bar{I}_{l,a}$ is approximately a linear or a logarithmic function of diagnostic rates $d_{l,a}$, i.e.,

$$\bar{I}_{l,a} \sim c \ln(d_{l,a}) + b \quad \text{or} \quad \bar{I}_{l,a} \sim cd_{l,a} + b$$

for some constants $c$ and $b$. 

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Figure 6: Incidence vs diagnostic rate for specific age-group and In-situ stage of cancer

Figure 7: Incidence vs diagnostic rate for specific age-group and local stage of cancer
Writing $x = d_{i,a}$,

If $\bar{I}_{i,a} \sim c \ln(x) + b$, the second derivative of the objective function $(\bar{I}_{i,a} - l_{i,a})^2$ on $x$ is

$$f''(x) = \frac{d^2}{dx^2} \left( c \ln(x) + b - l_{i,a} \right)^2 = \frac{2(l_{i,a} - b - c \ln(x) + c)}{x^2} > 0 \text{ as } l_{i,a} > b$$

And if $\bar{I}_{i,a} \sim cx + b$, the second derivative of the objective function $(\bar{I}_{i,a} - l_{i,a})^2$ on $x$ is

$$f''(x) = \frac{d^2}{dx^2} \left( cx + b - l_{i,a} \right)^2 = 2c(c) > 0$$

thus, proving that the objective function $(\bar{I}_{i,a} - l_{i,a})^2$ is convex.
### Table 5: Parameters specific to mammography

<table>
<thead>
<tr>
<th>Parameter name</th>
<th>Assumption¹ (40) (11) (41) (42)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ζ_{mammography} (Specificity of mammogram) for US</strong></td>
<td>Age</td>
</tr>
<tr>
<td>&lt;49</td>
<td>0.85356</td>
</tr>
<tr>
<td>50–59</td>
<td>0.85576</td>
</tr>
<tr>
<td>60–69</td>
<td>0.86576</td>
</tr>
<tr>
<td>70–79</td>
<td>0.88384</td>
</tr>
<tr>
<td><strong>η_{mammography} (Sensitivity of mammogram) for US</strong></td>
<td>Age</td>
</tr>
<tr>
<td>&lt;49</td>
<td>0.87158</td>
</tr>
<tr>
<td>50–59</td>
<td>0.88126</td>
</tr>
<tr>
<td>60–69</td>
<td>0.90754</td>
</tr>
<tr>
<td>70–79</td>
<td>0.92611</td>
</tr>
<tr>
<td><strong>C_screen (Screening cost) for US</strong></td>
<td>81.35 USD</td>
</tr>
<tr>
<td><strong>C_diagnosis (Cost of follow-up tests if diagnosed) for US</strong></td>
<td>Age group</td>
</tr>
<tr>
<td>40–49</td>
<td>2187.89</td>
</tr>
<tr>
<td>50–64</td>
<td>2053.74</td>
</tr>
<tr>
<td>65–74</td>
<td>2065.13</td>
</tr>
<tr>
<td>≥75</td>
<td>1741.3</td>
</tr>
<tr>
<td><strong>C_treatment (Cost of treatment by stage at diagnosis) for US</strong></td>
<td>Stage</td>
</tr>
<tr>
<td>In situ</td>
<td>13055</td>
</tr>
<tr>
<td>Localized</td>
<td>13055</td>
</tr>
<tr>
<td>Regional</td>
<td>24682</td>
</tr>
<tr>
<td>Distant</td>
<td>38119</td>
</tr>
</tbody>
</table>

¹: Assumptions for cost parameters are taken from working paper
APPENDIX D
TRANSITION PROBABILITY MATRICES

Table 6: Notation used in transition probability matrix

<table>
<thead>
<tr>
<th>Notation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta_{i,a}$</td>
<td>Onset rate of breast cancer</td>
</tr>
<tr>
<td>$\lambda_{i,a}$</td>
<td>Dwell rate for cancer stage $i$ and age $a$</td>
</tr>
<tr>
<td>$d_{i,a}$</td>
<td>Diagnostic rate of cancer in stage $i$ and age $a$</td>
</tr>
<tr>
<td>$\mu_a$</td>
<td>Natural mortality rate at age $a$</td>
</tr>
<tr>
<td>$\mu_{i,a}$</td>
<td>Diseased mortality in cancer stage $i$ and age $a$</td>
</tr>
</tbody>
</table>

Table 7: Transition probability matrix for action = no screening
\[
\begin{bmatrix}
    e^{-\lambda_a} & e^{-\lambda_a} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 - e^{-\lambda_a} \\
    0 & e^{-\lambda_a} & e^{-\lambda_a} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 - e^{-\lambda_a} \\
    0 & 0 & e^{-\lambda_a} & e^{-\lambda_a} & 0 & 0 & 0 & 0 & 0 & 0 & 1 - e^{-\lambda_a} \\
    0 & 0 & 0 & e^{-\lambda_a} & e^{-\lambda_a} & 0 & 0 & 0 & 0 & 0 & 1 - e^{-\lambda_a} \\
    0 & 0 & 0 & 0 & e^{-\lambda_a} & e^{-\lambda_a} & 0 & 0 & 0 & 0 & 1 - e^{-\lambda_a} \\
    0 & 0 & 0 & 0 & 0 & e^{-\lambda_a} & e^{-\lambda_a} & 0 & 0 & 0 & 1 - e^{-\lambda_a} \\
    0 & 0 & 0 & 0 & 0 & 0 & e^{-\lambda_a} & e^{-\lambda_a} & 0 & 0 & 1 - e^{-\lambda_a} \\
    0 & 0 & 0 & 0 & 0 & 0 & 0 & e^{-\lambda_a} & e^{-\lambda_a} & 0 & 1 - e^{-\lambda_a} \\
    0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & e^{-\lambda_a} & e^{-\lambda_a} & 1 - e^{-\lambda_a} \\
    0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & e^{-\lambda_a} & 1 - e^{-\lambda_a} \\
\end{bmatrix}
\]
Table 8: Transition probability matrix for action = screening
$$
\begin{bmatrix}
    e^{-\gamma_0} \left( \frac{1}{\beta_0 + 1} \right) & e^{-\gamma_0} \left( \frac{\beta_1}{\beta_0 + 1} \right) & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 - e^{-\gamma_0} \\
    0 & e^{-\gamma_0} \left( \frac{s}{d_{0a} + \lambda_{0a} + s} \right) & e^{-\gamma_0} \left( \frac{\lambda_{0a}}{d_{0a} + \lambda_{0a} + s} \right) & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 - e^{-\gamma_0} \\
    0 & 0 & e^{-\gamma_0} \left( \frac{s}{d_{1a} + \lambda_{1a} + s} \right) & e^{-\gamma_0} \left( \frac{\lambda_{1a}}{d_{1a} + \lambda_{1a} + s} \right) & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 - e^{-\gamma_0} \\
    0 & 0 & 0 & e^{-\gamma_0} \left( \frac{s}{d_{2a} + \lambda_{2a} + s} \right) & e^{-\gamma_0} \left( \frac{\lambda_{2a}}{d_{2a} + \lambda_{2a} + s} \right) & 0 & 0 & 0 & 0 & 0 & 0 & 1 - e^{-\gamma_0} \\
    0 & 0 & 0 & 0 & e^{-\gamma_0} \left( \frac{s}{d_{3a} + s} \right) & e^{-\gamma_0} \left( \frac{\lambda_{3a}}{d_{3a} + s} \right) & 0 & 0 & 0 & 0 & 0 & 1 - e^{-\gamma_0} \\
    0 & 0 & 0 & 0 & 0 & e^{-\gamma_0} \left( \frac{\lambda_{3a}}{d_{3a} + s} \right) & 0 & 0 & 0 & 0 & 0 & 1 - e^{-\gamma_0} \\
    0 & 0 & 0 & 0 & 0 & 0 & e^{-\gamma_0} \left( \frac{\lambda_{2a}}{d_{2a} + s} \right) & 0 & 0 & 0 & 0 & 1 - e^{-\gamma_0} \\
    0 & 0 & 0 & 0 & 0 & 0 & 0 & e^{-\gamma_0} \left( \frac{\lambda_{1a}}{d_{1a} + s} \right) & 0 & 0 & 0 & 1 - e^{-\gamma_0} \\
    0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & e^{-\gamma_0} \left( \frac{\lambda_{0a}}{d_{0a} + s} \right) & 0 & 0 & 1 - e^{-\gamma_0} \\
    0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & e^{-\gamma_0} \left( \frac{\lambda_{0a}}{d_{0a} + s} \right) & 0 & 1 - e^{-\gamma_0} \\
    0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & e^{-\gamma_0} \left( \frac{\lambda_{0a}}{d_{0a} + s} \right) & 1 - e^{-\gamma_0}
\end{bmatrix}
$$
Where,

\[
\tilde{d}_{i,a} = (1 - \eta_{\text{mammography}})d_{i,a} + \eta_{\text{mammography}} - \eta_{\text{mammography}}(1 - \eta_{\text{mammography}})d_{i,a}
\]

\[
\tilde{\lambda}_{i,a} = (1 - \eta_{\text{mammography}})\lambda_{i,a}
\]

\[
s = (1 - \eta_{\text{mammography}})
\]
APPENDIX E
MODEL VERIFICATION AND VALIDATION ON THE US POPULATIONS

Verifying parameterization of natural history model for the US:

Table 9: Age distribution of the incidence of the onset of preclinical breast cancer

1. Age distribution of the incidence of the onset of preclinical breast cancer (including ductal carcinoma in situ).

<table>
<thead>
<tr>
<th>Age</th>
<th>US Study (43)</th>
<th>Our Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.000</td>
<td>0.001</td>
</tr>
<tr>
<td>25</td>
<td>0.002</td>
<td>0.003</td>
</tr>
<tr>
<td>30</td>
<td>0.005</td>
<td>0.007</td>
</tr>
<tr>
<td>35</td>
<td>0.021</td>
<td>0.019</td>
</tr>
<tr>
<td>40</td>
<td>0.046</td>
<td>0.046</td>
</tr>
<tr>
<td>45</td>
<td>0.105</td>
<td>0.099</td>
</tr>
<tr>
<td>50</td>
<td>0.169</td>
<td>0.172</td>
</tr>
<tr>
<td>55</td>
<td>0.233</td>
<td>0.258</td>
</tr>
<tr>
<td>60</td>
<td>0.328</td>
<td>0.354</td>
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<tr>
<td>65</td>
<td>0.436</td>
<td>0.457</td>
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<td>70</td>
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<td>75</td>
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<td>80</td>
<td>0.852</td>
<td>0.799</td>
</tr>
<tr>
<td>85</td>
<td>1.000</td>
<td>1.000</td>
</tr>
</tbody>
</table>

2. Compare estimated versus actual incidence at stage diagnosis distribution
Figure 8: Comparison of estimated versus actual incidence at stage diagnosis distribution for US

3. Comparison of outcomes
   a. Life-Years saved

![Graph showing Life Years saved per 1,000 women for different screening intervals and model groups.](image)

Figure 9: Comparison of Life years saved for US from our model with that of six models developed within NCI and CISNET

(Model group abbreviations: D = Dana-Farber Cancer Institute; E = Erasmus Medical Center; G = Georgetown University; M = M.D. Anderson Cancer Center; S = Stanford University; W = University of Wisconsin)

   b. False positive rate
Figure 10: Comparison of false positives for US from our model with that of six models developed within NCI and CISNET

(x-axis abbreviations: A = Annual screening schedule in mentioned age-group, B = Biennial screening schedule in mentioned age-group)
REFERENCES


