Optimal Breast Cancer Screening Policies

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Abstract

Breast cancer is the most common non-preventable cancer among women. Although it has been demonstrated in randomized trials that mammography screening reduces the breast cancer mortality rate, the optimal screening policy is not known. When screening should start and stop, and the optimal interval between screening sessions are controversial issues. In this thesis, we present dynamic programming algorithms that find optimal variable-interval screening policies that can either minimize lifetime cancer mortality risk or maximize life expectancy. We evaluate these policies using a simulation based on the MISCAN-Fadia breast cancer model. By applying the optimal policies, we can typically either increase life expectancy by 4.0 days or reduce the lifetime cancer mortality risk by 0.16%, which is equivalent to saving 3200 women annually from breast cancer death, compared to the standard constant-interval screening guidelines, without increasing the number of screenings. We also find that increasing life expectancy and decreasing cancer mortality risk can be contradictory goals. We demonstrate that variable screening intervals can increase the effectiveness of screening. We show that the benefits of optimizing screenings policies vary according to the cancer incidence risk of the women; but also that optimizing policies over each risk subgroups does not give promising results.
Chapter 1

Introduction

Breast cancer is the most common non-preventable cancer among women, with over 200,000 new cases in the United States in 2012 [4]. It is the second most frequently diagnosed cancer in women (after skin cancer) and ranks second as a cause of cancer death in women (after lung cancer) [4]. The results of randomized controlled trials demonstrate that early detection can reduce the mortality due to breast cancer, and that mammography screening is one of the most effective methods for the early detection of breast cancer [12, 18].

Although it has been demonstrated by randomized controlled trials that mammography screening reduces breast cancer mortality risk [21, 28], different organizations suggest different screening guidelines. For example, the American Cancer Society suggests yearly mammography starting at age 40 and continuing while a woman is in good health[3]. The National Cancer Institute recommends screening every 1-2 years beginning at age 40[19]. The U.S. Preventive Services Task Force recommends that women should be screened biennially between the ages of 50 and 74[30]. There is no clear consensus about when screening should start and stop, and what the optimal interval between screening sessions should be [20, 16, 15].

Such controversies exist in part because breast cancer exhibits complex dynamics as a function of age. Research has shown that the risk of developing breast cancer increases with age [6, 2]. In addition, breast cancer tumors are more aggressive for younger women [6, 17], and the sensitivity of screenings is lower for younger women [7, 22]. Therefore, if we screen older women more frequently, more tumors will be detected because of the higher incidence and higher sensitivity; however, early detection of breast cancer for older women is not as beneficial because they are more likely to die from other causes in a short time and the tumors detected are less aggressive. On the other hand, if we screen younger women more frequently, we benefit more from each tumor detected because the tumors that are incident at a young age are more aggressive and more likely to eventually cause cancer death; however, the incidence of breast tumors among younger women is lower and the screening sensitivity
is lower, so we may not be able to detect as many tumors. The objective of this thesis is to find optimal breast cancer screening policies that resolve this tradeoff and maximize the overall effectiveness of breast cancer screening.

As mentioned above, guidelines suggested by different organizations have different screening starting and stopping ages. A motivation of this thesis is to systematically find optimal starting and stopping ages for screening. While the intervals between screening sessions suggested by these guidelines also differ, the guidelines all assume a constant screening interval; i.e., they assume that women will be screened between a starting and stopping age with a single constant screening interval. But the age-based dynamics of breast cancer suggest that the breast cancer screening policies with constant screening intervals might not be optimal. In this thesis, we describe a method that finds optimal policies with variable intervals between screening sessions, and demonstrate that such policies can improve the effectiveness of screening.

The risk of developing breast cancer varies in women. Risk factors, including age, race, age at menarche, age at first live birth, number of previous biopsies, and number of first-degree relatives with breast cancer, significantly influence the odds that a woman will develop breast cancer [10, 8]. Therefore, it might be expected that individualized screening policies based on the risk factors might produce more effective policies than the single policy applied for an entire population. Whether individualized screening policies help to improve the effectiveness of screening is also investigated in this thesis.

Two of the possible goals of cancer screening are to minimize lifetime cancer mortality risk and to maximize life expectancy. A policy that is effective for one of the goals might be less effective for the other. In this thesis, we discuss the effectiveness of screening policies in achieving these two goals. We implement a simulation model that is based on a synthetic cohort of women. Tumor incidence and progression is simulated using the MISCAN-Fadia model [29], which describes tumors with continuously growing sizes, captures age-dependent characteristics of incidence, aggression and screening sensitivity of breast cancer. We develop dynamic programming algorithms that either minimize the lifetime cancer mortality risk or maximize life expectancy using data generated by the simulation model, assuming that the number of screenings is fixed during a woman’s life time. We fix the number of screenings because it is associated with the cost of the screening program, and in reality the budget for the program is usually limited. We then evaluate the effectiveness of different policies by applying them to the synthetic cohort of women using the same simulation model.

We evaluate the optimal screening policies by applying them to the same simulation model. We find that by applying the optimal policies, we can typically either increase life expectancy by 4.0 days or reduce the lifetime cancer mortality risk by 0.16%, which is equivalent to saving 3200 women annually from breast cancer death, compared to the
standard constant-interval screening guidelines, without increasing the number of screenings. We demonstrate that variable screening intervals can increase the effectiveness of screening. We show that the benefits of optimizing screenings policies vary according to the cancer incidence risk of the women; but also that optimizing policies over each risk subgroups does not give promising results.

This paper is organized as follow: Chapter 2 presents background information. Chapter 3 contains the method used to find an optimal policy. The results are shown in the Chapter 4. Chapter 5 gives the conclusions.
Chapter 2

Background

2.1 Related work

Randomized trials are the best way to evaluate screening policies; however, it is usually not feasible to conduct such trials [14]. Therefore, researchers apply alternative approaches to find the optimal policies. One of the possible approaches is to analytically investigate the mathematical structure of the optimal screening policy.

Kirch and Klein develop a mathematical model for disease examination schedules and show that an optimal examination schedule that minimizes the expected detection delay is non-periodic, and that the frequency of examinations should be proportional to the square root of the age-specific incidence probability of the disease [13]. Although their model incorporates age-specific disease incidence, they assume stationary disease aggression and perfect screening sensitivity. In addition, they define an optimal policy as one that minimizes the detection delay; however, finding tumors as soon as possible is not always beneficial, because some tumors might never influence the life of a woman during her lifetime.

Zelen determines the optimal schedule of examinations for the early detection of disease by maximizing a weighted utility function and concludes that assuming that disease incidence is independent of time, the optimal intervals are equal if and only if the sensitivity of the examination is unity [32]. If the sojourn time is exponentially distributed, the optimal intervals are equal except for the first and the last intervals. Lee et al. further developed this model to maximize the proportional reduction in mortality using variable-interval screening policies [14]. A threshold that utilizes the probability of being in the preclinical state with undiagnosed disease is chosen to generate the policies. But their result might not be optimal.

Ahern et al. propose a utility function that accounts for the costs associated with screenings and the survival benefits due to them [1]. It is assumed that the breast cancer incidence increases linearly with respect to age. Two different optimization criteria are considered: optimize the number of screenings without a fixed total cost assuming that the screening
CHAPTER 2. BACKGROUND

Intervals are equal, and optimize the ages at which screenings are scheduled with a fixed total cost. It is concluded that with the first optimization criterion, more frequent screenings should be scheduled if the cost for screenings is much smaller relative to the value of life gained due to screenings. With the second optimization criterion, it is found that the intervals between screenings consistently decrease with age. Although the model considers age-dependent cancer incidence, it assumes constant disease aggression, constant screening sensitivity and no non-cancer death. Therefore, the model is not able to reveal the complex age-based dynamics of breast cancer.

The research based on mathematical analysis described above reveal important characteristics of the optimal screening policies. However, because of the nature of the methods, they have to simplify the age-based dynamics. In contrast, some researchers use computer simulation models whose parameters are estimated using data from various sources to overcome these shortcomings.

Shwartz evaluates the life expectancy gain under different constant-interval screening policies using a continuous tumor growth model [24]. The model considers age-specific incidence of preclinical tumors, lymph node involvement for the tumor, recurrence of breast cancer and imperfect screening sensitivity. The paper concludes that with yearly mammography and clinical examinations, life expectancy will be improved such that we can realize about one-half of the possible gain that would be realized if breast cancer mortality were eliminated. Michaelson et al. develop a mathematical model to determine the optimal screening interval for breast cancer detection before distant metastatic spread [18]. The findings based on this model suggest that considerable reduction in the breast cancer mortality risk might be achieved if breast cancer screenings were performed more frequently. Their model simulates continuous tumor growth and metastatic spread, but age-specific incidence of tumor and non-cancer death are not incorporated in it. Neither of the models are able to generate optimal policies and are just used to evaluate constant-interval policies.

Maillart et al. formulate a partially observable Markov model that captures several age-based dynamics of breast cancer [15]. They generate a list of efficient policies that achieve a certain lifetime risk with the fewest expected number of mammograms. This model considers only two-phase policies, i.e., policies in which the screening intervals are changed once from one value to another at a certain age. Although they discuss some variable-interval policies, the model is still not be able to generate optimal policies and is just used to evaluate different policies. Therefore, they are not able to demonstrate whether more complicated policies could further improve the effectiveness of screening.

There are several Markov models that have been formulated to generate optimal policies. Rauner et al. develop a risk-group oriented partially observable Markov model for chronic diseases [23]. The model applies Pareto ant colony optimization paradigm to find
Pareto-optimal or efficient screening strategies that maximize the quality-adjusted life years (QALYs) and minimize total costs simultaneously considering budget constraints. The model is applied to breast cancer as an illustrative example. The women are divided into two risk groups, younger women aged 30-49 and older women aged 50-70. The model finds that mammographic screenings should be focused on the older women. However, the model fails to demonstrate the complex age-based dynamics of breast cancer since it divides the women into only two age groups. Ayer et al. formulates a partially observable Markov decision process (POMDP) model for the mammography screening problem [5]. Optimal screening policies that maximize the total expected QALYs for the patient are generated by solving the POMDP. Instead of considering screening recommendations for the whole population, the policies are developed for individuals given their prior screening history and personal cancer risk factors. The results show that the proposed personalized screening policies increase the QALYs for the patients while decreasing the number of mammograms and false-positive results. The model does not consider the financial costs associated with the screenings. In addition, the optimal policies generated by the model are very sensitive to the disutility associated with mammography results, which is chosen relatively arbitrarily.

Hanin and Pavlova develop an approach that minimizes the probability that a tumor has metastasized when it is detected [11]. The approach is based on a continuous tumor growth model that simulates tumor latency, tumor growth, spontaneous and screening-base tumor detection, and cancer metastasis. The optimal policies are found using Monte Carlo simulations. It is concluded that the screening schedules with constant intervals are not necessarily optimal and an optimal screening policy tends to screen older women more frequently given their higher cancer incidence rate and greater screening sensitivity. In this model, it is assumed that screening is not scheduled for women younger than 50 or older than 80 years old. It does not consider the higher non-cancer mortality risk of the older women. In addition, preventing metastasis may not always be beneficial, because metastasized tumors may not cause cancer death, especially for the old women.

In summary, our approach differs from these approaches in one or more critical ways. First, the majority of previous approaches optimize for a utility function or the QALYs of the patients that requires assumptions about the estimation of the value of life and disease, which is subjective. In contrast, we optimize for the cancer mortality risk and life expectancy, which are objective measures, while fixing the number of lifetime screening, which is equivalent to fixing the cost. Second, most computer simulation approaches either are not able to generate optimal policies or are based on a Markov model, which assumes that the patient is in a certain discrete healthy or disease state. In contrast, we propose an approach based on a continuous tumor growth model. To the best of our knowledge, our approach is the first one applied to generate optimal policies using a continuous tumor growth model and considering
CHAPTER 2. BACKGROUND

all the age-based dynamics of breast cancer including cancer incidence, tumor progression, imperfect screening sensitivity and non-cancer mortality risk. Third, we allow screenings to be scheduled in any quarter during the lifetime of women without additional restrictions. This allows us to reveal the fine-grained pattern of the optimal screening policies. Finally, we analyze how screening policies influence the cancer mortality risk and life expectancy for women at different ages. With this analysis, policy makers are able to determine the relationship between the effectiveness of a screening policy within certain age intervals and the overall performance of the policy.

2.2 Simulation model

Our model simulates the lifetimes of a cohort of synthetic women. When the simulation starts, all the women in the cohort are initialized to be 15 years old. Time in the simulation increases by one quarter year (one quarter) in each round. The simulation continues until all the women in the cohort are dead. Women may die of either breast cancer or from other causes. Cancer death is simulated according to the MISCAN-Fadia model [29]. The age-specific probability of non-cancer death is taken from the Social Security Actuarial Tables [25].

In the model, we only consider invasive tumors, i.e., we do not model in situ tumors. The tumor incidence rate is taken from the age-specific invasive breast cancer incidence rate in the MISCAN-Fadia model. A tumor’s progression after its incidence is simulated according to the MISCAN-Fadia model. The parameters for the model is described in Figure 2.1.

Tumors start at a size of 0.1mm. Each tumor is assigned a constant growth rate \( r \), and the tumor’s diameter is assumed to grow exponentially with respect to time \( t \), i.e., the diameter after time \( t \) is \( (1 + r)^t \). A fatal tumor is a tumor that is larger than a certain fixed size and can no longer be cured. Each tumor is assigned a fatal diameters. When a tumor is larger than its fatal diameter, it becomes fatal. I.e., if the woman does not die of other causes, the tumor will eventually cause cancer death. We assign each tumor a survival duration equal to the amount of time it takes a fatal tumor to cause cancer death in the absence of death from other causes. A tumor’s survival duration is correlated with its growth rate because tumors that grow faster tend to cause death more quickly.

The clinical diagnosis of tumors is simulated by assigning each tumor a clinical diagnosis diameter. We assume that each tumor is diagnosed as soon as it becomes larger than this size because of signs or symptoms caused by it. The cohort will be screened according to a specified screening policy. We assume that all women in the cohort follow the given policy. We simulate the age-dependent screening sensitivity of screening by assigning each tumor a series of screening detection diameters. Each of these values represents the screening
FIGURE 2.1: The parameters for the tumors in the MISCAN-Fadia model. Note that the relative relation in size among clinical diagnosis diameter, fatal diameter and screening detection diameter might differ across different tumors.

detection diameter at age 45, 55, 65 and 75 respectively. We assume that the screening detection diameter is always decreasing with respect to ages, and apply linear interpolation to estimate the values at ages that are different from these ages. A tumor is detectable for a woman at a certain age by screening if and only if it is larger than the screening detection diameter at the specified age. All non-fatal tumors detected either by clinical diagnosis or screening are removed and do not cause cancer death. Fatal tumors that are detected still cause cancer death eventually if the woman does not die of other causes first.

Following the MISCAN-Fadia model, the fatal diameter and the screening detection diameter are assumed to follow a Weibull distribution [31], and the growth rate, survival duration, and clinical diagnosis diameter are assumed to follow a correlated log-normal distribution. We use parameters, described in Table 2.1 and 2.2, that were estimated using maximum likelihood estimation [29] based on data from the Swedish Two County Study [27].
CHAPTER 2. BACKGROUND

Distribution for each variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Distribution</th>
<th>Mean</th>
<th>SD</th>
<th>10%</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth rate (1/y)</td>
<td>Log-normal(0.062,0.87)</td>
<td>1.6</td>
<td>1.6</td>
<td>0.3</td>
<td>1.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Fatal diameter (cm)</td>
<td>Weibull(4.0,0.95)</td>
<td>4.1</td>
<td>4.3</td>
<td>0.4</td>
<td>2.8</td>
<td>9.7</td>
</tr>
<tr>
<td>Survival duration (y)</td>
<td>Log-normal(2.4,1.1)</td>
<td>21</td>
<td>35</td>
<td>3</td>
<td>11</td>
<td>48</td>
</tr>
<tr>
<td>Clinical diagnosis diameter (cm)</td>
<td>Log-normal(1.0,0.6)</td>
<td>3.2</td>
<td>2.2</td>
<td>1.2</td>
<td>2.6</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Correlation between variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>ρ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth rate - Survival duration</td>
<td>-0.90</td>
</tr>
<tr>
<td>Growth rate - Clinical diagnosis diameter</td>
<td>+0.41</td>
</tr>
<tr>
<td>Survival duration - Clinical diagnosis diameter</td>
<td>-0.43</td>
</tr>
</tbody>
</table>

\(^a\) mean and standard deviation for log-normal distribution.

\(^b\) scale and shape parameters for Weibull distribution.

All the parameters are taken from Table 1 and 5 in [29].

Table 2.1: Tumor’s progression parameters in MISCAN-Fadia model [29].

<table>
<thead>
<tr>
<th>Ages (y)</th>
<th>Distribution</th>
<th>Mean</th>
<th>SD</th>
<th>10%</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>Weibull(1.5,3.0) (^a)</td>
<td>1.3</td>
<td>0.5</td>
<td>0.7</td>
<td>1.3</td>
<td>2.0</td>
</tr>
<tr>
<td>55</td>
<td>Weibull(1.1,3.0) (^a)</td>
<td>1.0</td>
<td>0.4</td>
<td>0.5</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>65</td>
<td>Weibull(0.9,3.0) (^a)</td>
<td>0.8</td>
<td>0.3</td>
<td>0.4</td>
<td>0.8</td>
<td>1.2</td>
</tr>
<tr>
<td>75</td>
<td>Weibull(0.6,3.0) (^a)</td>
<td>0.5</td>
<td>0.2</td>
<td>0.3</td>
<td>0.5</td>
<td>0.8</td>
</tr>
</tbody>
</table>

\(^a\) scale and shape parameters for Weibull distribution.

All the parameters are taken from Table 10 in [29].

Table 2.2: Screening detection diameters at different ages (cm).
Chapter 3

Computation

A breast cancer screening policy is a schedule describing the ages at which breast cancer screening should take place. We assume that all women follow the same screening policy, and that the policy is fixed in advance. In this thesis, dynamic programming is used to compute optimal breast cancer screening policies. The input to the algorithm is data generated by our simulation model. The effectiveness of the optimal policies is also evaluated using the same simulation model. The method is summarized in Figure 3.1.

We first use the simulation model to generate tables that give the probability that a tumor exists and becomes fatal during a particular quarter, given the quarter at which the most recent screening took place. We then use dynamic programming to find an optimal policy that either minimizes the lifetime cancer mortality risk or maximizes the life expectancy.

In this chapter, we denote a woman’s age as an integer $a$, representing the instant when she is exactly $a$ quarters (i.e. quarter years) old. We denote the quarter between ages $a-1$ and $a$ as the $a^{th}$ quarter of the woman’s life. We define a woman’s life expectancy at age $a$ to be the expected number of quarters of life remaining at a given age $a$. If a woman has a non-fatal tumor at age $a-1$ and the tumor becomes fatal at age $a$, we say that a fatal tumor developed during the $a^{th}$ quarter.

3.1 Probability of cancer death and life expectancy for women with a fatal tumor

We assume that if a woman eventually dies of cancer, then her death is caused by the fatal tumor that developed first. We let $P_{DC|F}(a_1, a_2|a_F)$ be the probability that an arbitrary woman in the cohort eventually dies of cancer between ages $a_1$ and $a_2$ given that she develops a fatal tumor during the $a_F^{th}$ quarter. The definitions of $P_{DC|F}(a_1, a_2|a_F)$ is demonstrated in Figure ??\footnote{Note that the probability is independent of the screening policy. We also assume...}.
CHAPTER 3. COMPUTATION

Figure 3.1: Dynamic programming is used to compute optimized breast cancer screening policies. The input to the algorithm is data generated by our simulation model. The effectiveness of the optimized policies is also evaluated using the same simulation model.

Figure 3.2: Definition of $P_{DC|F}(a_1, a_2|a_F)$.

that a fatal tumor does not cause cancer death during the quarter in which it developed, i.e., it takes at least one quarter for a fatal tumor causes cancer death. In addition, because only fatal tumors cause cancer death,

$$P_{DC|F}(a_1, a_2|a_F) = 0, \text{ for any } a_1 < a_2 \leq a_F$$  \hspace{1cm} (3.1)

We let $P_{AL|F}(a_1, a_2|a_F)$ be the probability that an arbitrary woman in the cohort is alive at age $a_2$, given that she was alive at an earlier age $a_1$ and developed a fatal tumor during the $a_F^{th}$ quarter. We estimate $P_{DC|F}(a_1, a_2|a_F)$ as

$$P_{DC|F}(a_1, a_2|a_F) = \sum_{A=a_1}^{a_2-1} P_{AL|F}(a_1, A|a_F)P_{DC|F}(A, A+1|a_F)$$  \hspace{1cm} (3.2)
CHAPTER 3. COMPUTATION

From the property of conditional probability,

\[ P_{AL|F}(a_1, a_2|a_F) = P_{AL|F}(a_1, a_2 - 1|a_F) \cdot P_{AL|F}(a_2 - 1, a_2|a_F), \quad \text{if } a_1 < a_2 \]  

(3.3)

We let \( P_{DNC}(a, a + 1) \) be the probability that an arbitrary woman dies from non-cancer causes between \( a \) and \( a + 1 \). We denote the age-specific death rate when a woman is \( y \) years old in the Social Security Actuarial Tables [25] as \( DR(y) \) and estimate \( P_{DNC}(a, a + 1) \) for any \( a \) as

\[ P_{DNC}(a, a + 1) = 1 - \left[ 1 - DR(\text{round}(\frac{y}{4})) \right]^{\frac{1}{a}} \]  

(3.4)

Then we compute \( P_{AL|F}(a, a + 1|a_F) \) as

\[ P_{AL|F}(a, a + 1|a_F) = 1 - \{ P_{DC|F}(a, a + 1|a_F) + [1 - P_{DC|F}(a, a + 1|a_F)] \cdot P_{DNC}(a, a + 1) \} \]  

(3.5)

Note that fatal tumors in younger women must have grown to the fatal diameter in a relatively short time. Therefore, fatal tumors in younger women are more likely to have higher growth rates. Since a tumor’s survival duration is correlated with its growth rate, as described in Section 2.2, fatal tumors in younger women are also more likely to have shorter survival durations. In contrast, fatal tumors in older women include both slow-growing tumors with longer survival durations and fast-growing tumors with shorter survival durations. Let \( P_{SD|F}(l|a_F) \) denote the probability that the survival duration of an arbitrary tumor equals \( l \), given that the tumor becomes fatal during the \( a_F^{th} \) quarter of a woman’s life. We estimate the values of \( P_{SD|F}(l|a_F) \) for any \( l \) and \( a_F \) by running the simulation described in Section 2.2 and observing the survival duration of the tumors that becomes fatal during the \( a_F^{th} \) quarter.

By definition of the survival duration, if a woman does not die from non-cancer causes, she will die after \( l \) quarters after the tumor become fatal. I.e.,

\[ P_{DC|F}(a, a + 1|a_F) = P_{SD|F}(a - a_F|a_F) \cdot \prod_{A=a_F}^{a-1} [1 - P_{DNC}(A, A + 1)] \]  

(3.6)

From Equation (3.5) and (3.6), we can compute \( P_{AL|F}(a_1, a_1 + 1|a_F) \) for any \( a_F \leq a_1 \). Since Equation (3.3) is a recursive function, and we already computed the boundary condition \( P_{AL|F}(a_1, a_1 + 1|a_F) \), we can compute \( P_{AL|F}(a_1, a_2|a_F) \) for any \( a_F \leq a_1 < a_2 \). Then we compute \( P_{DC|F}(a_1, a_2|a_F) \) for any \( a_F \leq a_1 < a_2 \) using Equation (3.2).

The life expectancy at age \( a \) for an arbitrary woman in the cohort who develops her first
fatal tumor at an earlier age $a_F$ is

$$e_F(a|a_F) = \sum_{t=1}^{\infty} t \cdot P_{AL|F}(a, a + t|a_F) \cdot [1 - P_{AL|F}(a + t, a + t + 1|a_F)]$$  \hspace{1cm} (3.7)$$

The definition of $e_F(a|a_F)$ is demonstrated in Figure 3.3.

### 3.2 Probability of developing a fatal tumor

We assume that each woman in the cohort is screened no more than $n$ times through her lifetime, with the $i^{th}$ screening scheduled at age $T_i$. A screening policy is represented by a vector $T = \{T_1, T_2, \ldots, T_n\}$, where $T_{i-1} < T_i$ for all $2 \leq i \leq n$.

The probability that a woman develops a fatal tumor during the $a^{th}$ quarter depends on the screening policy. Given a screening policy, we define $P_F(a; T_1, \ldots, T_n)$ to be the probability that an arbitrary woman develops her first fatal tumor during the $a^{th}$ quarter of her life.

Let the $k^{th}$ screening be the last screening at or before age $a$, i.e. $T_1 < \ldots < T_k \leq a < T_{k+1} < \ldots < T_n$. Because screenings after the $(k + 1)^{th}$ screening are scheduled after age $a$, they will not influence the probability of developing fatal tumors. Among the screenings scheduled before age $a$, we assume that only the most recent screening influences the probability of developing fatal tumors during the $a^{th}$ quarter and the earlier screenings have no effect on the probability. That is, we assume

$$P_F(a; T_1, \ldots, T_n) = P_F(a; T_k),$$  \hspace{1cm} (3.8)$$

The relationship between the age $a$ and the most recent screening is described in Figure 3.4. This assumption is true because we assume that the tumor is growing and the screening detection threshold decreases with respect to age. Therefore, a tumor that is not detectable
Figure 3.4: Only the most recent screening influences the probability of developing fatal tumors during the \( a^{th} \) quarter.

by the most recent screening is also not detectable by earlier screenings since the tumor was smaller and screening detection threshold is larger then. In contrast, a tumor detected by the most recent screening might be detected and removed in earlier screenings, if we change the previous screening schedules. But this does not influence the probability of developing a fatal tumor at age \( a \), because as long as the tumor is removed before age \( a \), whether it is detected in the most recent screening or the previous screenings does not matter.

If we fix \( T_k \), we can estimate \( P_F(a; T_k) \) by running the simulation described in Section 2.2 with the most recent screening at \( T_k \), and counting number of women in the cohort who develop a fatal tumor during the \( a^{th} \) quarter. We repeat this process across all possible combinations of \( T_k \) and \( a \).

### 3.3 Minimizing lifetime cancer mortality risk

Given a screening policy, we let \( P_{DC|NF}(a_1, a_2 | a_{NF}; T_1, \ldots, T_n) \) denote the probability that an arbitrary woman in the cohort dies of breast cancer between ages \( a_1 \) and \( a_2 \), under the condition that she has not developed a fatal tumor at age \( a_{NF} \), where \( a_{NF} \leq a_1 < a_2 \). Because there are no fatal tumors, the woman cannot die of cancer between \( a_{NF} \) and \( a_{NF} + 1 \). However, she might develop a fatal tumor between age \( a_{NF} \) and \( a_{NF} + 1 \), and eventually dies of cancer because of it, or she might die from fatal tumors developed later than \( a_{NF} + 1 \). We consider \( a_{NF} = a_1 = a \) and \( a_2 = \infty \) for some arbitrary \( a \), from the property of conditional probability,

\[
P_{DC|NF}(a, \infty | a; T_1, \ldots, T_n) = [1 - P_{DNC}(a, a + 1)] \cdot [P_F(a + 1; T_1, \ldots, T_n) \cdot P_{DC|F}(a + 1, \infty | a + 1) \\
+ (1 - P_F(a + 1; T_1, \ldots, T_n)) \cdot P_{DC|NF}(a + 1, \infty; a + 1 | T_1, \ldots, T_n)]
\]  

(3.9)

Let the \( k^{th} \) screening be the last screening at or before age \( a \), i.e. \( T_1 < \ldots < T_k \leq a < \)
Figure 3.5: $P_{DC|NF}(a; T_1, \ldots, T_n)$ can be expressed using $P_{DC|NF}(a + l; T_1, \ldots, T_n)$.

$T_{k+1} < \ldots < T_n$. From Assumption (3.8), screenings before or after $T_k$ will not influence the cancer mortality risk at or after age $a$, i.e.

$$
P_{DC|NF}(a, \infty|a; T_1, \ldots, T_n) = P_{DC|NF}(a, \infty|a; T_k, \ldots, T_n)$$

$$= [1 - P_{DNC}(a, a + 1)] \cdot \{P_F(a + 1; T_k) \cdot P_{DC|F}(a + 1, \infty|a + 1)$$

$$+ [1 - P_F(a + 1; T_k)] \cdot P_{DC|NF}(a + 1, \infty|a + 1; T_k, \ldots, T_n) \} \quad (3.10)$$

Equation (3.10) is a recursive equation for $P_{DC|NF}(a, \infty|a; T_k, \ldots, T_n)$. It can be expressed as a linear function of $P_{DC|NF}(a + l, \infty|a + l; T_k, \ldots, T_n)$, for any $l \geq 1$. I.e., there exist coefficients $C_{DC1}(a, l; T_k, \ldots, T_{k+i})$ and $C_{DC2}(a, l; T_k, \ldots, T_{k+i})$ such that

$$P_{DC|NF}(a, \infty|a; T_k, \ldots, T_n) = C_{DC1}(a, l; T_k, \ldots, T_{k+i}) \cdot P_{DC|NF}(a + l, \infty|a + l; T_k, \ldots, T_n)$$

$$+ C_{DC2}(a, l; T_k, \ldots, T_{k+i}), \quad (3.11)$$

where we assume that there are $i$ screenings between ages $a$ and $a + l$, i.e. $T_1 < \ldots < T_k \leq a < T_{k+1} < \ldots < T_{k+i} \leq a + l < T_{k+i+1} < \ldots < T_n$. The relationship between $P_{DC|NF}(a, \infty|a; T_k, \ldots, T_n)$ and $P_{DC|NF}(a + l, \infty|a + l; T_k, \ldots, T_n)$ are described in Figure 3.5. The coefficients $C_{DC1}(a, l; T_k, \ldots, T_{k+i})$ and $C_{DC2}(a, l; T_k, \ldots, T_{k+i})$ can be computed by substituting the Equation (3.10) into itself for $l$ times.

Given that an arbitrary woman is screened $m$ times after age $a$, we define $f_{DC|NF}(a, m)$ to be the minimum probability over all screening policies after age $a$ that she dies of breast cancer after age $a$, under the condition that she has not developed a fatal tumor before age
The relationship between function 3.1 and 3.2. Therefore, we can compute
\[ f_{DC|NF}(a, m) \]
\[ = \min_{T_{k+1}, \ldots, T_{k+m}} P_{DC|NF}(a, \infty; T_k, \ldots, T_{k+m}) \]
\[ = \min_{T_{k+1}, \ldots, T_{k+m}} \{ C_{DC1}(a, l; T_k, \ldots, T_{k+i}) \cdot P_{DC|NF}(a + l, \infty; a + l; T_k, \ldots, T_{k+i}) + C_{DC2}(a, l; T_k, \ldots, T_{k+i}) \} \]
\[ \text{(3.12)} \]

where \( l \geq 1, \ T_1 < \ldots < T_k = a < T_{k+1} < \ldots < T_{k+m} \).

Let \( l = T_{k+1} - a \). In this case, \( i = 1 \). Therefore, \( C_{DC1}(a, T_{k+1} - a; a, T_{k+1}) \) and \( C_{DC2}(a, T_{k+1} - a; a, T_{k+1}) \) are functions of \( a \) and \( T_{k+1} \), but are independent of \( T_{k+2}, \ldots, T_{k+m} \). Therefore,
\[ f_{DC|NF}(a, m) \]
\[ = \min_{T_{k+1}} \{ C_{DC1}(a, T_{k+1} - a; a, T_{k+1}) \cdot \min_{T_{k+2}, \ldots, T_{k+m}} \{ P_{DC|NF}(T_{k+1}, \infty; T_k, \ldots, T_{k+m}) \} \}
\[ + C_{DC2}(a, T_{k+1} - a; a, T_{k+1}) \} \]
\[ \text{(3.13)} \]

The most recent screening at or after age \( T_{k+1} \) is scheduled at \( T_{k+1} \). Due to Assumption (3.8), \( P_{DC|NF}(T_{k+1}, \infty; T_k, \ldots, T_{k+m}) = P_{DC|NF}(T_{k+1}, \infty; T_{k+1}, \ldots, T_{k+m}) \). Therefore,
\[ f_{DC|NF}(a, m) \]
\[ = \min_{T_{k+1}} \{ C_{DC1}(a, T_{k+1} - a; a, T_{k+1}) \cdot \min_{T_{k+2}, \ldots, T_{k+m}} \{ P_{DC|NF}(T_{k+1}, \infty; T_{k+1}, \ldots, T_{k+m}) \} \]
\[ + C_{DC2}(a, T_{k+1} - a; a, T_{k+1}) \} \]
\[ = \min_{T_{k+1}} \{ C_{DC1}(a, T_{k+1} - a; a, T_{k+1}) \cdot f_{DC|NF}(T_{k+1}, m - 1) + C_{DC2}(a, T_{k+1} - a; a, T_{k+1}) \} \]
\[ \text{(3.14)} \]

The relationship between \( f_{DC|NF}(a, m) \) and \( f_{DC|NF}(T_{k+1}, m - 1) \) are described in Figure 3.6.

Equation (3.14) is a recursive function. Its boundary condition with \( m = 0 \) is given by
\[ f_{DC|NF}(a, 0) = P_{DC|NF}(a, \infty; a; a) \]
\[ \text{(3.15)} \]

\( P_{DC|NF}(a, \infty; a; a) \) can be computed using the Equation (3.10), where the values for \( P_{DNC}(a, a+1) \), \( P_F(a+1; T_k) \) and \( P_{DC|F}(a+1, \infty; a+1) \) can be computed or estimated according to Section 3.1 and 3.2. Therefore, we can compute \( f_{DC|NF}(a, m) \) for any \( a \) and \( m \) using Equation (3.14).

The minimum lifetime cancer mortality risk assuming that an arbitrary woman in the
cohort is screened no more than \( m \) times through her lifetime is given by

\[
 f_{DC|NF}(0, m), \quad (3.16)
\]

When we use the recursive function (3.14) to estimate the minimum cancer mortality risk, the screening age \( T_{k+1} \) that corresponds to the minimum lifetime cancer mortality risk is recorded across all possible combinations of \( a \) and \( m \) as

\[
g_{DC}(a, m) = \arg \min_{T_{k+1}} \{C_{DC1}(a, T_{k+1} - a; a, T_{k+1}) \cdot f_{DC|NF}(T_{k+1}, m - 1) + C_{DC2}(a, T_{k+1} - a; a, T_{k+1})\} \quad (3.17)
\]

Let \( \{T_1^*, T_2^*, \ldots, T_m^*\} \) denote a policy that minimizes the lifetime cancer mortality risk for an arbitrary woman. Then \( T_i^* \) for any \( 1 < i \leq m \) is given by

\[
 T_i^* = g_{DC}(T_{i-1}^*, m - i + 1), \quad (3.18)
\]

where the boundary condition is given by

\[
 T_1^* = g_{DC}(0, m) \quad (3.19)
\]

### 3.4 Maximizing life expectancy

Given a screening policy, let \( e_{NF}(a|a_{NF}; T_1, \ldots, T_n) \) denote the life expectancy of an arbitrary woman in the cohort at age \( a \), under the condition that no fatal tumor has developed before age \( a_{NF} \), where \( a_{NF} \leq a \). Given the screening policy, let \( P_{AL|NF}(a_1, a_2|a_{NF}; T_1, \ldots, T_n) \) be the probability that an arbitrary woman will be alive at age \( a_2 \), given that she was alive at age \( a_1 \) and she has not developed a fatal tumor before age \( a_{NF} \), where \( a_{NF} \leq a_1 \leq a_2 \). By
CHAPTER 3. COMPUTATION

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definition,

\[ e_{NF}(a|a_{NF}; T_1, \ldots, T_n) = \sum_{t=0}^{\infty} t \cdot P_{AL|NF}(a, a + t|a_{NF}; T_1, \ldots, T_n) \cdot [1 - P_{AL|NF}(a + t, a + t + 1|a_{NF}; T_1, \ldots, T_n)] \]

\[ = \sum_{t=1}^{\infty} t \cdot P_{AL|NF}(a, a + t|a_{NF}; T_1, \ldots, T_n) \cdot [1 - P_{AL|NF}(a + t, a + t + 1|a_{NF}; T_1, \ldots, T_n)] \]

(3.20)

where \([1 - P_{AL|NF}(a + t, a + t + 1|a_{NF}; T_1, \ldots, T_n)]\) denotes the probability that an arbitrary woman in the cohort dies of cancer or non-cancer causes between ages \(a + t\) and \(a + t + 1\).

From the property of conditional probability,

\[ P_{AL|NF}(a_1, a_2|a_{NF}; T_1, \ldots, T_n) = P_{AL|NF}(a_1, a_1 + 1|a_{NF}; T_1, \ldots, T_n) \cdot P_{AL|NF}(a_1 + 1, a_2|a_{NF}; T_1, \ldots, T_n), \] (3.21)

where \(a_{NF} \leq a_1 < a_2\)

Substituting (3.21) into (3.20), we have

\[ e_{NF}(a|a_{NF}; T_1, \ldots, T_n) = \sum_{t=1}^{\infty} t \cdot P_{AL|NF}(a, a + 1|a_{NF}; T_1, \ldots, T_n) \cdot P_{AL|NF}(a + 1, a + t|a_{NF}; T_1, \ldots, T_n) \cdot [1 - P_{AL|NF}(a + t, a + t + 1|a_{NF}; T_1, \ldots, T_n)] \]

\[ = \sum_{t=1}^{\infty} \sum_{q=0}^{t-1} (t - 1)P_{AL|NF}(a + 1, a + t|a_{NF}; T_1, \ldots, T_n) \cdot [1 - P_{AL|NF}(a + t, a + t + 1|a_{NF}; T_1, \ldots, T_n)] \]

\[ + \sum_{t=1}^{\infty} P_{AL|NF}(a + 1, a + t|a_{NF}; T_1, \ldots, T_n)[1 - P_{AL|NF}(a + t, a + t + 1|a_{NF}; T_1, \ldots, T_n)] \]

(3.22)

Let \(q = t - 1\),
\[ e_{NF}(a|a_NF; T_1, \ldots, T_n) \]
\[ = P_{AL|NF}(a, a + 1|a_NF; T_1, \ldots, T_n) \cdot \]
\[ \left( \sum_{q=0}^{\infty} q \cdot P_{AL|NF}(a + 1, a + 1 + q|a_NF; T_1, \ldots, T_n) \cdot \right. \]
\[ \left[ 1 - P_{AL|NF}(a + 1 + q, a + 1 + q + 1|a_NF; T_1, \ldots, T_n) \right] \]
\[ + \sum_{q=0}^{\infty} P_{AL|NF}(a + 1, a + 1 + q|a_NF; T_1, \ldots, T_n) \cdot \]
\[ \left[ 1 - P_{AL|NF}(a + 1 + q, a + 1 + q + 1|a_NF; T_1, \ldots, T_n) \right] \]
\[ = P_{AL|NF}(a, a + 1|a_NF; T_1, \ldots, T_n)[e_{NF}(a + 1|a_NF; T_1, \ldots, T_n) + 1] \quad (3.23) \]

where

\[ \sum_{q=0}^{\infty} P_{AL|NF}(a + 1, a + 1 + q|a_NF; T_1, \ldots, T_n)[1 - P_{AL|NF}(a + 1 + q, a + 1 + q + 1|a_NF; T_1, \ldots, T_n)] = 1 \]

because it represents the probability that a woman will die after the age of \( a + 1 \) given that she is alive at \( a + 1 \).

Because a woman will either develop a fatal tumor during the \((a_NF + 1)^{th}\) quarter or not, from the property of conditional probability,

\[ e_{NF}(a + 1|a_NF; T_1, \ldots, T_n) = P_F(a_NF + 1; T_1, \ldots, T_n) \cdot e_F(a + 1|a_NF + 1) \]
\[ + [1 - P_F(a_NF + 1; T_1, \ldots, T_n)] \cdot e_{NF}(a + 1|a_NF + 1; T_1, \ldots, T_n) \]

\[ (3.24) \]

Let \( a_NF = a \). Then \( P_{AL|NF}(a, a + 1|a; T_1, \ldots, T_n) = 1 - P_{DNC}(a, a + 1) \) because given that no fatal tumor has developed at age \( a \), a woman cannot die of cancer between ages \( a \) and \( a + 1 \). Substituting Equation (3.24) into (3.23), we have

\[ e_{NF}(a|a; T_1, \ldots, T_n) = [1 - P_{DNC}(a, a + 1)] \cdot \left\{ \left[ P_F(a + 1; T_1, \ldots, T_n) \cdot e_F(a + 1|a + 1) \right. \right. \]
\[ + (1 - P_F(a + 1; T_1, \ldots, T_n)) \cdot e_{NF}(a + 1|a + 1; T_1, \ldots, T_n) \left. \right\} + 1 \}

\[ (3.25) \]

Let the \( k^{th} \) screening be the last screening at or before age \( a \), i.e., \( T_1 < \ldots < T_k \leq a < T_{k+1} < \ldots < T_n \). From Assumption (3.8), screenings before \( T_k \) will not influence the probability of developing a fatal tumor at or after age \( a \). Therefore, they have no effect on life expectancy at age \( a \), i.e.,
Figure 3.7: $e_{NF}(a|a; T_k, \ldots, T_n)$ is expressed as a function of $e_{NF}(a + l|a + l; T_k, \ldots, T_n)$.


e_{NF}(a|a; T_1, \ldots, T_n) \\
= e_{NF}(a|a; T_k, \ldots, T_n) \\
= [1 - P_{DNC}(a, a + 1)] \cdot \{[P_F(a + 1; T_k) \cdot e_F(a + 1|a + 1) \\
+ (1 - P_F(a + 1; T_k)) \cdot e_{NF}(a + 1|a + 1; T_k, \ldots, T_n)] + 1\} \\
(3.26)

Equation (3.26) is a recursive function for $e_{NF}(a|a; T_k, \ldots, T_n)$. Since $e_F(a + 1|a + 1)$ is a constant, which is computed in equation (3.7), $e_{NF}(a|a; T_k, \ldots, T_n)$ can be expressed as a linear function of $e_{NF}(a + l|a + l; T_k, \ldots, T_n)$, for any $l \geq 1$; i.e., there exist coefficients $C_{e_1}(a, l; T_k, \ldots, T_{k+i})$ and $C_{e_2}(a, l; T_k, \ldots, T_{k+i})$ such that

$$e_{NF}(a|a; T_k, \ldots, T_n) = C_{e_1}(a, l; T_k, \ldots, T_{k+i}) \cdot e_{NF}(a + l|a + l; T_k, \ldots, T_n) + C_{e_2}(a, l; T_k, \ldots, T_{k+i}),$$

where we assume that there are $i$ screenings between ages $a$ and $a + l$, i.e. $T_1 < \ldots < T_k \leq a < T_{k+1} < \ldots < T_{k+i} \leq a + l < T_{k+i+1} < \ldots < T_n$. The relationship between $e_{NF}(a|a; T_k, \ldots, T_n)$ and $e_{NF}(a + l|a + l; T_k, \ldots, T_n)$ are described in Figure 3.7. These coefficients $C_{e_1}(a, l; T_k, \ldots, T_{k+i})$ and $C_{e_2}(a, l; T_k, \ldots, T_{k+i})$ are functions of $a, l$ and the ages at which the screenings are scheduled between ages $a$ and $a + l$. They can be computed by substituting the Equation (3.26) into itself $l$ times.

Given that an arbitrary woman is screened $m$ times after age $a$, we define $f_{e_{NF}}(a, m)$ to be the maximum life expectancy at age $a$ over all screening policies after age $a$, under the condition that she has not developed a fatal tumor at age $a$, and the most recent screening at or before $a$ is scheduled at $T_k = a$. By definition,
The relationship between $C_f$ and $3.2$. Therefore, we can compute

\[
= \max_{T_{k+1}, \ldots, T_{k+m}} e_{NF}(a|a; T_k, \ldots, T_{k+m})
\]

\[
= \max_{T_{k+1}, \ldots, T_{k+m}} \{C_{e1}(a, l; T_k, \ldots, T_{k+i}) \cdot e_{NF}(a + l|a + l; T_k, \ldots, T_{k+m}) + C_{e2}(a, l; T_k, \ldots, T_{k+i})\},
\]

where $l \geq 1$, and $T_1 < \ldots < T_k = a < T_{k+1} < \ldots < T_{k+i} \leq a + l < T_{k+i+1} < \ldots < T_{k+m}

Let $l = T_{k+1} - a$. In this case, $i = 1$ and therefore, $C_{e1}(a, T_{k+1} - a; a, T_{k+1})$ and $C_{e2}(a, T_{k+1} - a; a, T_{k+1})$ are functions of $a$ and $T_{k+1}$, but are independent of $T_{k+2}, \ldots, T_{k+m}$.

Therefore,

\[
f_{e|NF}(a, m) = \max_{T_{k+1}} \{C_{e1}(a, T_{k+1} - a; a, T_{k+1}) \cdot \max_{T_{k+1}, \ldots, T_{k+m}} \{e_{NF}(T_{k+1}|T_{k+1}; T_k, \ldots, T_{k+m}) + C_{e2}(a, T_{k+1} - a; a, T_{k+1})\}\}
\]

\[
= \max_{T_{k+1}} \{C_{e1}(a, T_{k+1} - a; a, T_{k+1}) \cdot \max_{T_{k+1}, \ldots, T_{k+m}} \{e_{NF}(T_{k+1}|T_{k+1}; T_k, \ldots, T_{k+m}) + C_{e2}(a, T_{k+1} - a; a, T_{k+1})\}\}
\]

\[
= \max_{T_{k+1}} \{C_{e1}(a, T_{k+1} - a; a, T_{k+1}) \cdot f_{e|NF}(T_{k+1}, m - 1) + C_{e2}(a, T_{k+1} - a; a, T_{k+1})\}
\]

The most recent screening at or before age $T_{k+1}$ is scheduled at $T_{k+1}$. Due to Assumption (3.8), $e_{NF}(T_{k+1}|T_{k+1}; T_k, \ldots, T_{k+m}) = e_{NF}(T_{k+1}|T_{k+1}; T_{k+1}, \ldots, T_{k+m})$.

Therefore,

\[
f_{e|NF}(a, m)
\]

\[
= \max_{T_{k+1}} \{C_{e1}(a, T_{k+1} - a; a, T_{k+1}) \cdot \max_{T_{k+1}, \ldots, T_{k+m}} \{e_{NF}(T_{k+1}|T_{k+1}; T_k, \ldots, T_{k+m}) + C_{e2}(a, T_{k+1} - a; a, T_{k+1})\}\}
\]

\[
= \max_{T_{k+1}} \{C_{e1}(a, T_{k+1} - a; a, T_{k+1}) \cdot f_{e|NF}(T_{k+1}, m - 1) + C_{e2}(a, T_{k+1} - a; a, T_{k+1})\}
\]

The relationship between $f_{e|NF}(a, m)$ and $f_{e|NF}(T_{k+1}, m - 1)$ is described in Figure 3.8.

Equation (3.30) is a recursive function. Its boundary condition with $m = 0$ is given by

\[
f_{e|NF}(a, 0) = e_{NF}(a|a; a),
\]

$e_{NF}(a|a; a)$ can be computed using Equation (3.26), where the values for $P_{DNC}(a, a + 1)$, $P_F(a + 1; T_k)$ and $e_F(a + 1|a + 1)$ can be computed or estimated according to Section 3.1 and 3.2. Therefore, we can compute $f_{e|NF}(a, m)$ for any $a, m$ using Equations (3.30).

The maximum life expectancy when an arbitrary woman is born assuming that she is
screened no more than $m$ times during her lifetime is given by

$$f_{e|NF}(0, m)$$  \hspace{1cm} (3.32)

When we use the recursive function (3.30) to compute the maximum life expectancy, the screening age $T_{k+1}$ that corresponds to the maximum life expectancy is recorded across all possible combinations of $a, m$ as

$$g_e(a, m) = \arg \max_{T_{k+1}} \{C_{e1}(a, T_{k+1} - a; a, T_{k+1}) \cdot f_{e|NF}(T_{k+1}, m - 1) + C_{e2}(a, T_{k+1} - a; a, T_{k+1})\}$$  \hspace{1cm} (3.33)

Let $\{T^*_1, T^*_2, \ldots, T^*_m\}$ denote a policy that maximizes the life expectancy of an arbitrary woman at age 0. Then $T^*_i$ for any $1 < i \leq m$ is given by

$$T^*_i = g_e(T^*_{i-1}, m - i + 1),$$  \hspace{1cm} (3.34)

where the boundary condition is given by

$$T^*_1 = g_e(0, m).$$  \hspace{1cm} (3.35)
Chapter 4

Results

4.1 Methodology

We run simulations, as described in Section 2.2, with a synthetic cohort of 50 million women to estimate the probability of developing a fatal tumor at age $a$, given the age of the most recent screening at age $T_k$, denoted by $P_F(a; T_k)$, and the probability that the survival duration of fatal tumors equals to $l$ given that the tumor become fatal at age $a_F$, denoted by $P_{SD|F}(l|a_F)$. Based on these values, we use dynamic programming to generate screening policies with different numbers of screenings scheduled during a woman’s lifetime, as described in Chapter 3. We compare the effectiveness of the optimal policies generated with some standard constant-interval screening guidelines, assuming that the number of screenings is the same. The chosen reference standard constant-interval screening guidelines are described in Table 4.1.

To estimate the effectiveness of different policies, we generate a synthetic cohort of 50 million women and run simulations on the synthetic cohort using the model described in Section 2.2. We collect the information about the longevity of each woman assuming she does not die of cancer, and all tumor parameters described in Section 2.2 if there are tumor incidences during a woman’s life time. We then apply different screening policies to the same synthetic cohort with the same tumors to estimate the effectiveness of the policies. We compare the lifetime cancer mortality risk and the life expectancy of the cohort across the policies.

4.2 Optimal policies

The standard guidelines and the optimal policies are described in Figure 4.1. Each vertical line in this figure represents the age at which a screening is scheduled. The intervals between
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<table>
<thead>
<tr>
<th>Start age (year)</th>
<th>Stop age (year)</th>
<th>Frequency</th>
<th>Number of screening scheduled</th>
<th>Descriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>74</td>
<td>Biennially</td>
<td>13</td>
<td>The U.S. Preventive Services Task Force recommends that women be screened biennially between the ages of 50 and 74 [30].</td>
</tr>
<tr>
<td>40</td>
<td>79</td>
<td>Biennially</td>
<td>20</td>
<td>The National Cancer Institute recommends screening every 1-2 years beginning at age 40 [19].</td>
</tr>
<tr>
<td>40</td>
<td>79</td>
<td>Annually</td>
<td>40</td>
<td>The American Cancer Society suggests yearly mammography starting at age 40 and continuing while a woman is in good health [3].</td>
</tr>
</tbody>
</table>

Table 4.1: Screening guidelines.

Figure 4.1: The optimized policies for the whole population. Each vertical line represents the age at which a screening is scheduled.

The average screening ages and average screening intervals are shown in Table 4.2. We observe from the tables that when the number of lifetime screenings increases from 13 to 40, the average screening ages of the policies optimized for cancer mortality risk reduces from 68.46 years to 65.0 years and the average screening ages of the policies optimized for life expectancy increases from 74.5 years to 76.5 years.
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(a) Standard guideline (13 screenings)

(b) Standard guideline (20 screenings)

(c) Standard guideline (40 screenings)

(d) Optimized for cancer mortality risk (13 screenings)

(e) Optimized for cancer mortality risk (20 screenings)

(f) Optimized for cancer mortality risk (40 screenings)

(g) Optimized for life expectancy (13 screenings)

(h) Optimized for life expectancy (20 screenings)

(i) Optimized for life expectancy (40 screenings)

Figure 4.2: The screening intervals at different screening ages. The circles represent the screening intervals for a screening at a given age. The smooth curve shows the results of the second-order polynomial regression.
CHAPTER 4. RESULTS

<table>
<thead>
<tr>
<th>Policy Description</th>
<th>Average Screening Age</th>
<th>Average Screening interval (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Guideline</td>
<td>62.0</td>
<td>2.00</td>
</tr>
<tr>
<td>13 Screenings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimized for cancer mortality risk</td>
<td>68.4</td>
<td>2.17</td>
</tr>
<tr>
<td>Optimized for life expectancy</td>
<td>62.3</td>
<td>2.08</td>
</tr>
<tr>
<td>20 Screenings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimized for cancer mortality risk</td>
<td>67.0</td>
<td>1.71</td>
</tr>
<tr>
<td>Optimized for life expectancy</td>
<td>61.0</td>
<td>1.64</td>
</tr>
<tr>
<td>40 Screenings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimized for cancer mortality risk</td>
<td>65.0</td>
<td>1.04</td>
</tr>
<tr>
<td>Optimized for life expectancy</td>
<td>59.1</td>
<td>1.08</td>
</tr>
</tbody>
</table>

Table 4.2: Statistics of policies.

expectancy reduces from 62.34 years to 59.1 years. For each screening criterion, the average screening ages of the optimal policies decreases when the number of screening increase. This suggests that with fewer screenings, it is more effective to concentrate screenings on relatively older women. If there are more screenings, we should also screen relatively younger women.

We also observe from the table that when the number of lifetime screenings increases from 13 to 40, the average screening interval of the policies optimized for cancer mortality risk reduces from 2.17 years to 1.04 years and the average screening interval of the policies optimized for life expectancy reduces from 2.08 years to 1.08 years. This implies that with more screenings, we should concentrate screenings on a relatively narrow age intervals rather than spread the screenings to a wider range.

We also observe from the Table 4.2 that with the same number of screenings, the policies optimized for life expectancy always have a significant smaller average screening age than the policies optimized for cancer mortality risk. This suggests that if we are interested in improving the life expectancy, we should screen younger women more frequently. This makes sense because screening older women may help reduce the cancer mortality risk due to the higher incidence and higher screening sensitivity, but it will not improve the life expectancy significantly, because the tumors for older women are less aggressive and older women are more likely to die from non-cancer causes in a short time.
CHAPTER 4. RESULTS

(a) Cancer mortality risk

(b) Life expectancy at age 15

Figure 4.3: The life expectancy and the cancer mortality risk when different policies are applied to the whole population.

4.3 Simulation results

We estimate the cancer mortality risk and life expectancy when the policies are applied to a group of synthetic women using the simulation model and the results are summarized in Figure 4.3. We may observe from the table that compared to the standard guidelines, the policies optimized for life expectancy increase life expectancy, but may lead to a higher cancer mortality risk; The policies optimized for cancer mortality risk decrease the cancer mortality risk, but may lead to a lower life expectancy. The result indicates that the optimized policies do give improved results, but also that increasing life expectancy and decreasing cancer mortality risk might be contradictory goals. We may not be able to achieve the highest life expectancy and lowest cancer mortality risk at the same time.

In Table 4.3 and 4.4, we compare the following screening policies: no screening, frequent screening, guideline screening and optimal screening. Guideline and optimal screening are indexed by the number of lifetime screenings.

In Table 4.3, policies are optimized for cancer mortality risk. The table includes the cancer mortality risk, the absolute reduction in cancer mortality risk over no screening and the guidelines, the percentage of maximum cancer mortality risk reduction realized, and the expected reduction in annual cancer deaths. We assume that 2 million girls are born every year. From this table, we observe that if we apply policies optimized for cancer mortality risk instead of the guidelines, we can reduce the lifetime cancer mortality risk by 0.09% - 0.12%. This is equivalent to saving 1800-3200 women annually from breast cancer death, or improving the effectiveness of screening by about 3% - 6%. With 40 screenings, optimal screening reduces the lifetime cancer mortality risk by 0.12%, from 2.13% to 2.02%, corresponding to a reduction of 2430 annual cancer deaths. This optimal policy achieves 78.7% of the maximum reduction in cancer mortality risk, compared with 73.2% achieved by the guidelines. The highest reduction in cancer mortality risk due to the optimal policy...
is achieved with 20 screenings. We can reduce the lifetime cancer mortality risks by 0.16%, which is equivalent to achieving 56.3% of the maximum reduction in cancer mortality risk, compared with 49.0% achieved by the guidelines.

In Table 4.4, policies are optimized for life expectancy. The table includes the life expectancy at age 15, the increase of life expectancy over no screening and the guidelines, the percentage of maximum life expectancy increase realized. From this table, we observe that with 13 screenings, we do not increase the life expectancy with the optimal policy. This seems to be due to that the optimal policy with 13 screenings is almost identical to the standard guideline. With 40 screenings, optimal screening increases the lifetime expectancy by 0.8 days, from 65.211 years to 65.213 years. This optimal policy achieves 74.8% of the maximum increase in life expectancy, compared with 74.1% achieved by the guidelines. The highest increase in life expectancy due to the optimal policy is achieved with 20 screening. We can increase life expectancy by 4.0 days, which is equivalent to achieving 51.3% of the maximum increase in life expectancy, compared with 47.9% achieved by the guidelines.
<table>
<thead>
<tr>
<th>Policy Description</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screening</td>
<td>3.75%</td>
<td>0.00%</td>
<td>0.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screen every quarter</td>
<td>1.54%</td>
<td>2.21%</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 screenings</td>
<td>Guideline 2.90%</td>
<td>0.85%</td>
<td>38.4%</td>
<td></td>
<td></td>
<td>1800</td>
</tr>
<tr>
<td></td>
<td>Optimized 2.82%</td>
<td>0.94%</td>
<td>42.4%</td>
<td>0.09%</td>
<td>3.01%</td>
<td></td>
</tr>
<tr>
<td>20 screenings</td>
<td>Guideline 2.67%</td>
<td>1.08%</td>
<td>49.0%</td>
<td></td>
<td></td>
<td>3200</td>
</tr>
<tr>
<td></td>
<td>Optimized 2.51%</td>
<td>1.24%</td>
<td>56.3%</td>
<td>0.16%</td>
<td>6.07%</td>
<td></td>
</tr>
<tr>
<td>40 screenings</td>
<td>Guideline 2.13%</td>
<td>1.62%</td>
<td>73.2%</td>
<td></td>
<td></td>
<td>2400</td>
</tr>
<tr>
<td></td>
<td>Optimized 2.02%</td>
<td>1.74%</td>
<td>78.7%</td>
<td>0.12%</td>
<td>5.69%</td>
<td></td>
</tr>
</tbody>
</table>

In this table, all the optimal policies are optimized for cancer mortality risk. Column A shows the descriptions for the policies. Column B represents the cancer mortality risk for each specified policy. Column C represents the absolute reduction in cancer mortality risk if we apply some schedule X instead of no screening. The value is computed using the following expression on cancer mortality risks: \( \text{No screening} - \text{Schedule X} \) Column D represents the relative position of the cancer mortality risk for schedule X between the lower bound (achieved by screening every quarter), and the upper bound (achieved by never screening). The value is computed using the following expression on cancer mortality risks: \( \frac{(\text{No screening} - \text{Schedule X})}{(\text{No screening} - \text{Screen every quarter})} \). A value of 100% implies a best possible result, and a value of 0% implies a worst possible result. Column E represents the absolute reduction in cancer mortality risk if we apply the optimal policies instead of the standard guidelines, assuming that the number of screenings is the same. The value is computed using the following expression on cancer mortality risks: \( \text{Guideline schedule} - \text{optimal schedule} \). Column F represents the percentage additional reduction in cancer mortality risk when optimizing screening over the reduction obtained by following the guidelines. The value is computed using the following expression on cancer mortality risks: \( \frac{(\text{Guideline schedule} - \text{optimal schedule})}{(\text{No screening} - \text{Guideline schedule})} \). Column G gives the expected reduction in annual deaths from breast cancer assuming all women have mammograms following the optimal policies instead of the standard guidelines. We assume that 2 million girls are born every year [9] Then the value is given by \( 2 \text{ million} \times \text{Column E} \).

Table 4.3: Improvements for policies optimized for cancer mortality risk.
### CHAPTER 4. RESULTS

<table>
<thead>
<tr>
<th>Policy Description</th>
<th>Life expectancy at age 15 (years)</th>
<th>Life expectancy improvement over no screening (days)</th>
<th>% maximum gain realized</th>
<th>Life expectancy improvement over guidelines (days)</th>
<th>% additional increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screening</td>
<td>64.971</td>
<td>0.00</td>
<td>0.00%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screen every quarter</td>
<td>65.294</td>
<td>117.9</td>
<td>100.00%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 screenings</td>
<td>Guideline 65.091</td>
<td>43.7</td>
<td>37.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Optimized 65.091</td>
<td>43.7</td>
<td>37.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 screenings</td>
<td>Guideline 65.126</td>
<td>56.5</td>
<td>47.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Optimized 65.137</td>
<td>60.5</td>
<td>51.3%</td>
<td>4.0</td>
<td>7.0%</td>
</tr>
<tr>
<td>40 screenings</td>
<td>Guideline 65.211</td>
<td>87.4</td>
<td>74.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Optimized 65.213</td>
<td>88.2</td>
<td>74.8%</td>
<td>0.8</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

In this table all the optimal policies are optimized for life expectancy.

Column A shows the descriptions for the policies.

Column B represents the life expectancy at age 15 for each specified policy.

Column C represents the absolute increase in life expectancy if we apply some schedule \(X\) instead of no screening. The value is computed using the following expression on life expectancies: \(\text{Schedule } X - \text{No screening}\)

Column D represents the relative position of the life expectancy between the upper bound (achieved by screening every quarter), and the lower bound (achieved by never screening). The value is computed using the following expression on life expectancy: \((\text{Schedule } X - \text{No screening})/(\text{Screen every quarter} - \text{No screening})\). A value of 100% implies a best possible result, and a value of 0% implies a worst possible result.

Column E represents the absolute increase in the number of days of life if we apply the optimal policies instead of the standard guidelines, assuming that the number of screenings is the same. The value is computed using the following expression on life expectancies: \((\text{Optimal schedule} - \text{Guideline schedule})\) \(\times 365\).

Column F represents the percentage additional increase in life expectancy when optimizing screening over the increase obtained by following the guidelines. The value is computed using the following expression on life expectancies: \((\text{Optimal schedule} - \text{Guideline schedule})/(\text{Guideline schedule} - \text{No screening})\).

Table 4.4: Improvements for policies optimized for life expectancy.
CHAPTER 4. RESULTS

(a) 13 screenings  
(b) 20 screenings  
(c) 40 screenings

(d) Difference (13 screenings)  
(e) Difference (20 screenings)  
(f) Difference (40 screenings)

Figure 4.4: The cancer mortality risk reduction at different ages. The horizontal axes show the ages of cancer death of the women in the synthetic population if there were no screening. The vertical axes show the cancer mortality risk reduction when the specified screening policies are applied. The first row shows the results when the standard guidelines and the policies optimized for cancer mortality risk are applied. The second row shows the difference of the values between the optimal policies and the standard guidelines.

To analyze the reasons why the optimal policies show improvements, we show the cancer mortality risk reduction in Figure 4.4. The horizontal axes show the ages of cancer death of the women in the synthetic population if there were no screening. The vertical axes show the cancer mortality risk reduction when the specified screening policies are applied, and therefore the area under the curve shows the overall cancer mortality risk reduction for the whole population. The charts in the first row show the results when the standard guidelines and the policies optimized for cancer mortality risk are applied. The second row shows the difference of the values between the optimal policies and the standard guidelines.

From the second row of Figure 4.4, we observe that the cancer mortality reduction is negative before age 60, but it becomes positive after age 70. This suggests that compared to the standard guidelines, the optimal policies start screening later and screen less frequently before age 70, and therefore more women die of cancer before age 40. But because the optimal policies stop screening later and screen more frequently between ages 70 and 85, less women die of cancer after age 70. Overall, the optimal policies outperform the standard guidelines because integrating along the age axis gives a positive value.

In Figure 4.5, the horizontal axes again show the ages of cancer death of the women in the synthetic population if there were no screening. The vertical axes show the life expectancy
CHAPTER 4. RESULTS

(a) 13 screenings  
(b) 20 screenings  
(c) 40 screenings

(d) Difference (13 screenings)  
(e) Difference (20 screenings)  
(f) Difference (40 screenings)

Figure 4.5: The life expectancy increase at different ages. The horizontal axes show the ages of cancer death of the women in the synthetic population if there were no screening. The vertical axes show the life expectancy increase when the specified screening policies are applied. The first row shows the results when the standard guidelines and the policies optimized for life expectancy are applied. The second row shows the difference of the values between the optimal policies and the standard guidelines.

From the second row of Figure 4.5, we observe that with 13 screenings, since the optimal policy is almost identical to the guideline, the value fluctuate around 0. Overall, the optimal policy does not improve the life expectancy. With 20 and 40 screenings, the optimal policies lead to a life expectancy increase between ages 50 to 70, because these policies screen more frequently during these ages. Since the optimal policies screen less frequently before and after these ages, a negative life expectancy increase results. Overall, the optimal policies outperform the standard guidelines because integrating along the age axis gives a positive value.
4.4 Erasmus results

Researchers at the Erasmus Medical Center who developed the MISCAN-Fadia breast cancer model [29], evaluated the optimized policies described in Section 4.2 using their models. The results are summarized in Figure 4.6.

We observe that when applying policies optimized for life expectancy with 13, 20 and 40 screenings, the life expectancy at birth is 78.942 years, 78.973 years and 79.024 years respectively. Comparing to the standard guidelines, the optimal policies do not increase the life expectancy and achieve almost identical results.

If we apply the policies optimized for cancer mortality risk, we observe a mild decrease in cancer mortality rate comparing to the standard policies. With 40 screenings, the optimal policy reduces the cancer mortality risk by 0.059%, from 2.289% to 2.230%, which is equivalent to saving 1180 women annually from breast cancer. With 13 and 20 screenings, the cancer mortality risk is reduced by 0.026% and 0.054% respectively.

We may also observe from the figure that although the policies are identical, the results are different from ours. This is most likely a result of the fact that our implementation of the breast cancer model differs from theirs. Their model has been evolving over time, and it is possible that the current model is not accurately described in the publications.

4.5 Uniform-interval policies

We can observe that the optimal policies differ from the standard guidelines not only by the starting and ending ages, but also by the varying intervals between screenings. For practical reason, we might prefer policies with uniform intervals. To observe how well uniform policies could perform compared to optimal variable-interval policies, we generate the four sets of policies. In each case, the number of lifetime screenings is unchanged, and the resulting
CHAPTER 4. RESULTS

Figure 4.7: We generate 4 sets of policies: 1. We shift the screening guidelines so that the average screening age is the same as the optimal policies, but do not change the screening intervals. 2. We keep the screening starting and stopping ages the same as the optimal policies and schedule the screenings uniformly between the starting and stopping ages. 3. We keep the average screening ages of the screening policies the same as the guidelines, but change the screening intervals to be the same as the average screening intervals of the optimal policies. 4. We generate uniform policies so that both the average screening ages and the average screening intervals are the same as the optimal policies.

The simulation results for the standard guidelines, the optimal policies and the policies generated based on the optimal policies are summarized in Figure 4.7. We observe that optimal variable-interval screening policies outperform all other policies. But the simulation results of the policies with the same starting and stopping ages (i.e. the 2nd generated uniform-interval policy) are consistently similar to results of the optimal policies; while the results for other generated policies are usually worse. This suggests that the optimal policies outperform the standard guidelines mainly because the proper starting and stopping ages are found. The improvements due to varying screening intervals are less significant.
CHAPTER 4. RESULTS

(a) Optimized for cancer mortality risk

(b) Optimized for life expectancy

Figure 4.8: Simulation results for the optimal policies with different number of screenings.

4.6 Number of screenings

In Section 4.2, we show the optimal screening policies, given the number of screenings $n$. But it is not obvious how different values of $n$ increases the effectiveness of screenings. To answer this question, we generate optimal policies with 0 to 50 screenings and evaluate these policies using the simulation model. The results are shown in Figure 4.8.

In Figure 4.8, we observe that the plots for the cancer mortality risk and the life expectancy for the optimal policies are smooth curves. When the number of screenings is larger, the marginal benefit of increasing the number of screenings is smaller. As the number of screenings increases, the curves converge to the value corresponding to screening every quarter. Given a threshold for a minimum acceptable marginal benefit, we could choose an optimal value of $n$. However, it is not clear what value of the threshold would be appropriate, and each woman might make her own choice.

4.7 Over-diagnosis

Over-diagnosis refers to the diagnosis and treatment of a disease that will never cause death during a patient’s lifetime. It is considered a side effect of screening because it leads to unnecessary treatment that is not beneficial and might do harm. We can estimate the over-diagnosis rate for screenings using our simulation model by detecting those synthetic women who do not die of cancer, but have tumors detected by screenings and removed during their lifetime. Since we have all the parameters for the tumors, we are able to determine the age at which cancer death is caused by these detected tumors assuming they are not detected by screenings, according to the growth rate, the fatal diameter and the survival duration of the tumors. If we observe that the estimated cancer-death age is larger than the actual death
age of a woman, we conclude that cancer has been over-diagnosed. We count the number of over-diagnosed tumors and the number of diagnoses for the synthetic women, and estimate the over-diagnosis rate for different policies. The over-diagnosis rate for the guidelines and the optimal policies with different numbers of screenings are shown in Figure 4.9.

We conclude from Figure 4.9 that policies optimized for life expectancy usually have lower over-diagnosis rates, comparing to the policies optimized for lifetime cancer mortality risk. This is a result of the fact that policies optimized for life expectancy schedule more screenings for younger women, and policies optimized for lifetime cancer mortality risk concentrate more on screening older women. Younger women are more likely to die of cancer if a tumor develops and remains undetected, because the tumors are usually more aggressive and the younger women are not likely to die from other reasons. So, if such tumors are detected, they are less likely to be over-diagnosed. On the other hand, older women are more likely to die of other causes even if they have a tumor, and the tumors are less aggressive. Therefore their over-diagnosis rate is usually higher.

We also find that the screening guidelines with 13 and 40 screenings have a lower over-diagnosis rate than the optimal policies. This suggests that although the optimal policies achieve maximum life expectancy or minimum cancer mortality risk, the over-diagnosis rate associated might not be optimal at the same time.
4.8 Optimal policies for risk groups

We are also interested in estimating the effectiveness of individualized screening policies over varying demographic parameters. The parameters that are known to affect breast cancer incidence include race, age at menarche, age at first live birth, number of previous biopsies, and number of first-degree relatives with breast cancer. We select the 4 sets of demographic parameters out of the 144 possible combination of the parameters described in Table 4.5. Within the 144 possible groups, group 1 in the table corresponds to the most common demographic parameters, group 2 corresponds to the least common demographic parameters, group 3 is the subgroup with the lowest lifetime breast cancer incidence risk, and group 4 has the highest breast cancer incidence risk. In the table, the prevalence of each parameter is estimated according to the the Nurses’ Health Study [26]. To estimate the prevalence of the combinations of the parameters, we assume these parameters are mutually independent.

For each group, we generate a collection of women who share the same demographic parameters. We simulate groups of women with specified risk factors using the MISCAN-Fadia model, but estimate the tumor incidence rate according to the Gail 2 model [8]. The tumor incidence rate is expressed as the product of the relative risk and the baseline age-specific incidence rate. The relative risk value is a function of risk factors described in [8], and the baseline incidence rate is taken from the MISCAN-Fadia model.

We use the same optimal policy generation and policies estimation procedure for the whole population, except that the tumor incidence rate of the synthetic women are estimated using the Gail 2 model for the specified groups.

The simulation results for the subgroups with different policies are summarized in Table 4.6 and 4.7. In these tables, we observe that with 40 screenings scheduled for subgroup 1, if we apply the the policy optimized for the whole population, we may reduce the cancer
CHAPTER 4. RESULTS

<table>
<thead>
<tr>
<th>Policy Description</th>
<th>Number of screenings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Standard guideline</td>
<td>2.17%</td>
</tr>
<tr>
<td>Subgroup 1</td>
<td></td>
</tr>
<tr>
<td>Optimized for the whole population</td>
<td>2.10%</td>
</tr>
<tr>
<td>Optimized for the subgroup</td>
<td>2.09%</td>
</tr>
<tr>
<td>Standard guideline</td>
<td>6.07%</td>
</tr>
<tr>
<td>Subgroup 2</td>
<td></td>
</tr>
<tr>
<td>Optimized for the whole population</td>
<td>5.92%</td>
</tr>
<tr>
<td>Optimized for the subgroup</td>
<td>5.91%</td>
</tr>
<tr>
<td>Standard guideline</td>
<td>1.28%</td>
</tr>
<tr>
<td>Subgroup 3</td>
<td></td>
</tr>
<tr>
<td>Optimized for the whole population</td>
<td>1.24%</td>
</tr>
<tr>
<td>Optimized for the subgroup</td>
<td>1.24%</td>
</tr>
<tr>
<td>Standard guideline</td>
<td>11.80%</td>
</tr>
<tr>
<td>Subgroup 4</td>
<td></td>
</tr>
<tr>
<td>Optimized for the whole population</td>
<td>11.74%</td>
</tr>
<tr>
<td>Optimized for the subgroup</td>
<td>11.68%</td>
</tr>
</tbody>
</table>

In this table, all the optimized policies are optimized for cancer mortality risk.

Table 4.6: Cancer mortality risk for the subgroups.

mortality risk to 1.50% or increase the life expectancy to 65.313 years. If we apply the the policy optimized for the subgroup, we may reduce the cancer mortality to 1.49%, which is risk 0.01% lower, and increase the life expectancy to 65.313 years, which is identical. Other entries in these tables also suggest that although the simulation results for the individualized policies are always identical to, or better than the results for the policies optimized for the whole population, the difference between them is not significant. This suggests that using individualized policies does not provide a significant benefit.

We may also find from the tables that for subgroup 3 with 40 screenings, we can reduce the cancer mortality risk by 0.06%, from 0.94% to 0.88%, or increase the life expectancy by 0.4 days from 65.425 years to 65.426 years, comparing to the guidelines. But for subgroup 4, with the same number of screenings, we may reduce the cancer mortality risk by 0.26%, from 8.74% to 8.48%, or increase the life expectancy by 5.1 days from 63.948 years to 63.970 years. Other entries in the tables also suggest that the optimal screening policies can improve the effectiveness more for the high-risk women than for the low-risk women. High-risk women benefit more from the optimal policies.
In this table, all the optimized policies are optimized for life expectancy.

Table 4.7: Life expectancy at age 15 for the subgroups (in years).
Chapter 5

Conclusions

5.1 Summary

In this thesis we introduced a dynamic programming algorithm that finds optimal variable-interval screening policies for breast cancer. The algorithm computes the optimal policies using the data generated by a continuous tumor growth model. We find that the optimal screening policies screen younger and older women less frequently, and middle-aged women more frequently. By applying the optimal policies, we can typically either increase life expectancy by 4.0 days or reduce the lifetime cancer mortality risk by 0.16%, which is equivalent to saving 3200 women annually from breast cancer death, compared to the standard constant-interval screening guidelines, without increasing the number of screenings.

We conclude that increasing life expectancy and decreasing cancer mortality risk can be contradictory goals. We might not be able to simultaneously achieve the largest life expectancy and the smallest cancer mortality risk.

We also find that some uniform-interval policies approximate the performance of the optimal variable-interval policies, but variable screening intervals do increase the effectiveness of screening.

We show that the benefits of optimizing screenings policies vary according to the cancer incidence risk of the women; but also that optimizing policies over each risk subgroups does not give promising results.

5.2 Limitations and future work

Although we are able to find policies optimized for lifetime cancer mortality risk and life expectancy and to observe the over-diagnosis rate, we do not resolve the trade-off between them and do not propose a systematic method to find the optimal value for number of
screenings. We are interested in solving this problem.

We find that with our approach, we could maximize life expectancy or minimize cancer mortality risk. But the over-diagnosis rate associated might not be optimal at the same time. We would like to include the over-diagnosis rate in our optimization goal.

Our work generates optimal policies for women assuming they have never been screened before and they all follow the given screening policy. However, previous screenings might alter the nature of an optimal screening policy, and in practice, not all women always follow the screening policy. We would like to modify our techniques to find optimal policies for women given their screening history assuming that they do not always follow the given policy.

Our model assumes that the disease is static, i.e., the cancer incidence rate, tumor progression and the detection rate of screening do not change as a function of time or geography. However, these values might varying with location or time. We would like to extend our techniques to handle these dynamics.
Bibliography


