CHEMO PREVENTION TREATMENT FOR WOMEN WITH HIGH RISK TO DEVELOP

BREAST CANCER

A thesis presented

By

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Abstract

Recent studies and clinical trials, such as the Breast Cancer Prevention Trial (BCPT), have shown a great reduction in the risk of developing invasive breast cancer among high-risk women by taking specific drugs, like tamoxifen and raloxifene. Despite the significant reduction in breast cancer risk, which is approximately the same risk reduction as seen with bilateral prophylactic mastectomies, many women are not currently opting to take the anti-estrogen medication for breast cancer prevention.

The most common reasons why patients are not opting to take the preventive therapy are that patients are more likely to accept preventive services if recommended by their physician, but that doesn’t happen since they are not sufficiently trained in risk/benefit analysis. Patients also can experience fear and an overestimation of the side effects. A common perception also afflicting patients is that preventive therapy will not substantially reduce risk of developing breast cancer. Finally, the risk of breast cancer is not associated with a clinical sign or symptom. Therefore, the goal of this project is to simulate and compare the intake of both medicines and then compare with placebo, when no medicine is taken. The result will be in terms of Quality Adjusted Life Years (QALY), a generic measure of disease burden, including both the quality and the quantity of life lived.

In the future, studies like this can support the development of an online decision making tool for patients’ own evaluation on whether to take or not to take the medicine. It is expected that more knowledge and studies will eventually
increase the awareness among female patients prescribing chemoprevention therapy.
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Chapter 1
Introduction

1.1 Problem being addressed

Breast cancer is the form of cancer with the second highest incident rate in the United States, behind only skin cancer. According to the American Cancer Society, 232,670 women were diagnosed with breast cancer in the United States in 2014, with an estimated 40,000 women dying from the disease during that year (American Cancer Society, 2014). Studies found that 13.2% of all women in the population group considered high risk (typically determined by a five-year probability of developing invasive breast cancer greater than 1.67%) would develop the disease in the next 5 years.

For women considered at high risk to develop breast cancer, there are two ways to lower the chances of getting breast cancer. The first one would be preventive mastectomy. This means that a surgeon removes entire or part of the breast in order to prevent breast cancer. The second one would be taking certain preventive medications.

There are several consistent studies, such as Project P1 Trial (Fisher B, 1998) and Project STAR P2 Trial (Vogel VG, 2006). These studies demonstrate that tamoxifen and raloxifene, two nonsteroidal hormones that act as an antiestrogen agent in breast tissue, reduce the risk of breast cancer for women in a high risk demographic. These drugs work as an estrogen receptor positive for tumors (ER+); it means that they would take the place of estrogen, due to their similar shape, and would prevent the growth of tumor cells. However, the acceptability by doctors and patients of these preventive drugs often rests on their efficacy as
well as their adverse-effect profiles.

In 1998, the United States Food and Drug Administration (FDA) approved the use of tamoxifen for primary prevention in both premenopausal and postmenopausal women at high risk. In 2007, the FDA approved raloxifene, earlier used to prevent osteoporosis, for primary breast cancer chemoprevention in postmenopausal women (Waters EA, 2010). Both can decrease the risk of invasive breast cancer by up to 48%, but there exists a risk of serious side effects including endometrial cancer, stroke, pulmonary embolism, and cataracts.

The risk reduction demonstrated by tamoxifen and raloxifene is approximately the same as with bilateral prophylactic mastectomies. However, despite the significant reduction in breast cancer risk, many women are not currently opting to take the anti-estrogen medication for breast cancer prevention. There is a potential to prevent 125,000 invasive breast cancer per year in the United States with the chemoprevention (Freedman AN, 2003).

National estimates indicate that less than 1% of eligible women use tamoxifen for prevention and based on that, the American Society of Clinical Oncology (ASCO) updated its clinical practice guidelines on the use of tamoxifen or raloxifene for risk reduction in 2013 (Waters EA, 2010).
There is still a need to show patients the benefits of chemoprevention therapies. Therefore, we discuss in this thesis a simulation study where three different age groups take both medicines, reported in terms of Quality Adjusted Life Years (QALY). We then compare the results between the two simulation along with a placebo group and analyze the results.

In the future, studies like this can support the creation of a robust database tool that can simulate the possible outcomes for patients if they take the chemoprevention drugs. The possible outcomes would be in terms of chances of getting side effects and quality of life gained. The tool would aid a patients' own decision process about whether or not to take the medication. The patients would use their personal data as an input, like their age and then compare the expected results using graphics and probabilities. We expect that more information regarding the outcomes of chemoprevention drug use, supplemented with new analytics tools will increase the awareness among female patients being prescribed chemoprevention therapy.
1.2 Motivation

Cancer is the second leading cause of death in the United States. Breast cancer has high incidence and mortality rates, what makes the disease critical and subject to study and search to find better treatments and prevention therapies. This work applies industrial engineering tools, like simulation and Markov analysis, to create a strong model and predict the possible outcomes of taking breast cancer’s chemoprevention drugs. The model can be part of a future decision making tool built to support patients and physicians on whether to take or not patients take the drugs. This will enable patients to make decisions with a knowledge of different possible outcomes and side effects, and hopefully with more information and knowledge more patients will start the treatment with chemoprevention drugs decreasing the higher rates of incidence of breast cancer in the United States and globally.

1.3 Approach

There are many simulation methods available in the literature and after doing some research about each one, we decided that the problem that we have is formulated as a discrete event model. It means that each event occurs at a particular instant in time and marks a change of state in the system. Between consecutive events, no change in the system is assumed to occur; thus, the simulation can directly jump in time from one event to the next (Robinson, 2004).

The model attempts to approximate the real situation, but it may require substantial information about the patient’s family history, such as history of
hysterectomy, history of previous cancer and breast cancer predicted risk. Due to the limited data, most of the data used on this work was obtained as probabilities distributions for certain patient groups. Therefore, the discrete event simulation replaces agent-based modeling. The treatment of the patients will follow specified time sequences and will take place as events.

In the model, patients are divided into subgroups according to their age, once the incidence rate of breast cancer and the death rate are affected by it. Age will be considered as an attribute in this model where we are considering groups of age of 35, 50 and 60 years old. Patients with different ages may have different reactions to the same type of treatment, in this case tamoxifen or raloxifene.

A computer simulation is adopted in this thesis for modeling. Among all the industrial engineering tools, simulation is frequently used to build models to understand the target system behavior, and to evaluate different strategies of operation without actually building a real system. This simulation model is built using the Java programming language, which allows an interface with external functions as well as, objects written in the Java language.

In this simulation, a Markov model is applied to track the progression of the patients’ relapse. Patients receive different chemoprevention treatments in different types of relapses or no treatment, being considered placebo. The results are in terms of life years gained.

### 1.4 Overview of thesis

Chapter 2
The second chapter is the literature review. Research about the most important topics involved on this thesis was done, so we could decide which one was
applicable to our objective. Breast cancer, modeling methods and state transition modeling are explained on this chapter.

It is important to understand the nature of the disease to understand the problem better. In the first section the disease and the different types of occurrence are explained. Data from the American Cancer Society and other regulated institutions are used to explain the patterns of occurrences in the United States population. Then some information about risk factors, which can be modifiable or not, to develop the disease are discussed. Furthermore, research about different treatments and prevention are discussed.

In chapter 2, research regarding simulation and modeling methods is presented. What are the recent methods used in the literature and which one would be better applicable to our problem. Finding out that state transition modeling would be the best one, some was necessary to do some research about this topic in the context of healthcare.

Chapter 3
Chapter 3 is dedicated to reviewing the Markov chain modeling method used in this work. The method that we chose was based on the research done previously about available modeling methods. The one that satisfied our objectives because of its characteristics is the Markov method.

In this chapter it is explained in detail, the states considered on the present study, the cycle length, the transition probabilities used and how they were gotten and the assumptions to build the model.

Chapter 4
Chapter 4 brings the results of the model developed and some discussions about
Chapter 2
Literature Review

2.1 Breast cancer

2.1.1 What is breast cancer?

Cancer is the name of a group of diseases where abnormal cells start to grow out of control. Normal cells grow, divide to make new cells and die in an orderly way. In a healthy adult new cells are made only if the old ones die or to repair an injury. However, when you have cancer, sick cells start to grow quickly even if the old ones do not die.

Many cancers form solid tumors, which are masses of tissue. Tumors can be divided into benign or malignant classes. Cancerous tumor are malignant and they can spread to other tissues, which is unlikely to happen if the tumor is benign ones (American Cancer Society, 2014).

Breast cancer begins in the breast tissue that is made up of glands for milk production, called lobules, and the ducts that connect the lobules to the nipple. The remainder of the breast is made up of fatty, connective, and lymphatic tissues. Generally, breast cancer is detected during screening examination or
when a woman feels a lump. When there is suspicion whether it is benign or malignant additional exams are needed for an definitive diagnosis.

If breast cancer is found it can be classified into one of two types according to the American Cancer Society: In Situ or Invasive. In situ happens when the abnormal cells have not grown beyond the layer of cells where they originated. The most common are Ductal carcinoma in situ (DCIS) and Lobular carcinoma in situ (LCIS). This last one is an indicator of increased risk for developing invasive cancer. Invasive breast cancer happens when abnormal cells grown into the surrounding breast tissue.

2.1.2 Breast cancer occurrence

In 2016, an estimated 246,660 new cases of invasive breast cancer are expected to be diagnosed in women in the United States, along with 61,000 new cases of non-invasive (in situ) breast cancer (breastcancer.org, 2016). There are some patterns observed in the occurrence and mortality of breast cancer regards of sex, age and race/ethnicity. Men are generally at lower risk for developing breast cancer. The incidence is higher in non hispanic white women and usually increases with age.

When considering age, the chances of getting breast cancer generally increase as a woman gets older. Approximately 79% of new cases of the disease and 88% of deaths linked to breast cancer occurred in women at least 50 years old or older, as demonstrated in the figure below. The incidence is also higher in non hispanic white women. However, african american women have a higher incidence rate before age 40 and are more likely to die from breast cancer at every age (Figure 2).
2.1.3 Breast cancer risk factors

In 2016, there are more than 2.8 million women with a history of breast cancer in the United States. This includes women currently being treated and women who have finished treatment. Many known risk factors increase the chances to get the disease, some of them are modifiable and some of them do not. The main unmodifiable risk factors are:

- Sex, age and race: As presented in the topic above, being a white American, woman and getting older
- Personal and family history: A woman’s risk of breast cancer
approximately doubles if she has a first-degree relative (mother, sister, and daughter) who has been diagnosed with breast cancer. Compared to women without a family history, risk of breast cancer is 1.8 times higher for women with one first-degree female relative who has been diagnosed

- Genetic predisposition: About 5-10% of breast cancers can be linked to gene mutations (abnormal changes) inherited from parents

- Personal history of breast cancer: Women who have had breast cancer before, especially at younger ages are more susceptible to have a second breast cancer

- Lobular carcinoma in situ (LCIS): This uncommon condition is the result of abnormal cells forming in the lobules or milk-producing glands of the breast. Although LCIS seldom becomes invasive cancer, women with LCIS are 7 to 12 times more likely to develop invasive cancer in either breast than women without LCIS (Kilbride KE)

- Early menarche and late menopause: Women that have more menstrual cycles starting early and having the menopause late have higher risk to develop breast cancer due to longer lifetime exposure to reproductive hormones

There are also some lifestyle-related factors that influence the risk of getting breast cancer. These are considered modifiable risk factors that increase the chances to develop breast cancer:

- Use of postmenopausal hormone

- Obesity and weight gain

- Alcohol consumption
• Tobacco smoking
• Use of oral contraceptive

Some other factors that decreases the chance to develop the disease are:
• Regular physical activity
• Healthy diet

2.1.4 Breast cancer treatment

The treatment regimen for breast cancer depends on the stage of the disease and the preferences of the physician and the patient. To decide the optimal solution for each person they need to evaluate the benefits, side effects and the chances of being cured of the treatments. Most of the treatments involves some kind of surgery combined with other treatments, like chemotherapy, radiotherapy or hormone therapy.

Surgeries are done to remove the cancer from the tissue and to evaluate the stage of the disease. They can be partial surgeries, such as breast conserving therapy, or they can remove the entire breast, such as mastectomy.

Radiation therapy is the use of high-energy beams or particles to kill cancer cells remaining after surgeries. Radiation therapy may be administered internally, externally or a combination of both depending on the type, stage, and location of the tumor, as well as doctor and patient preferences.

Systemic therapies are treatments administered in the bloodstream and affecting all parts of the body, not only the cancer cells. These include chemotherapy, hormone therapy, and targeted therapy. If a therapy is administered before surgery, to try to shrink tumors, it is called neoadjuvant, and if it is given after surgery, to kill any undetected tumor cells that were left behind or had migrated...
to other parts of the body, it is called adjuvant.

2.1.5 Breast cancer prevention

There are mainly three ways to prevent breast cancer and lower the risk of getting the disease according to American Cancer Institute. Each one has their own risk and benefits and together, patients and doctors, must decide the better thinking about each one of them carefully.

The first one involves eat well, have healthy habits, regular mammograms and avoid every one of the beforehand mentioned factors that could increase your risk to develop the disease.

The second one is with preventive mastectomy. In this case, doctors remove with surgery the breast of women considered at high risk before that they are diagnosed with cancer. This option sounds radical for some women, but it dramatically reduces the chance of getting breast cancer.

In addition, the third one is chemoprevention, taking some medications. As of now, two medicines have been found to prevent the chances to develop the disease: they are tamoxifen and raloxifene pills. Both are known as selective estrogen receptor modulator (SERMs). Estrogen is a hormone that helps normal cells to grow and many breast cancers to grow. The medicine works by attaching to receptor cells that are meant only for estrogen. Therefore, breast cancer cells will have a hard time finding estrogen and without it, they cannot grow.

Tamoxifen has been used for over 20 years by women who already had breast cancer to stop the cancer from coming back after treatment. Within the last 10 years, several studies found that tamoxifen can also prevent breast cancer from occurring a first time. Raloxifene was first used to prevent osteoporosis since
Large studies found that women who took this medicine had a lower incidence of breast cancer compared to a placebo group. A recent study also showed raloxifene to be similar to tamoxifen in preventing breast cancer from occurring for the first time. Figure 3 summarizes the main studies done of breast cancer prevention trials using both medicines.

<table>
<thead>
<tr>
<th>Trial and Year</th>
<th>Comparison</th>
<th>Eligibility Criteria</th>
<th>No. Randomly Assigned</th>
<th>Effect on Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP-P1,1998</td>
<td>Tamoxifen 20 mg per day vs placebo for 5 years</td>
<td>Goal 5-year risk score &gt; 1.66%</td>
<td>13,388</td>
<td>Reduced invasive, non-invasive breast cancer (HR, 0.61) Effect on ER+ but not ER− cancers</td>
</tr>
<tr>
<td>IBIS-II,2007</td>
<td>Tamoxifen 20 mg per day vs placebo for 5 years</td>
<td>Relative risk = 2 x general population basis of family history results of previous benign breast biopsy</td>
<td>7,139</td>
<td>Reduced invasive, non-invasive breast cancer (HR, 0.72; 95% CI, 0.58 to 0.91) Effect on ER+ but not ER− cancers</td>
</tr>
<tr>
<td>Marsden,1996,2007</td>
<td>Tamoxifen 20 mg per day vs placebo for 11 years</td>
<td>Family history of breast cancer</td>
<td>2.4/1</td>
<td>Non-significantly lower invasive breast cancer (HR, 0.78; 95% CI, 0.66 to 1.04) Effect on ER+ but not ER− cancers</td>
</tr>
<tr>
<td>Vergnenesi et al.1997,2007</td>
<td>Tamoxifen 20 mg per day vs placebo for 5 years</td>
<td>Average breast cancer risk, prior hysterectomy</td>
<td>5,408</td>
<td>Non-significantly lower invasive, non-invasive breast cancer (HR, 0.84; 95% CI, 0.60 to 1.17) Significantly reduced breast cancer in high-risk women (HR, 0.24; 95% CI, 0.10 to 0.60) Significantly reduced breast cancer in women receiving estrogen replacement (HR, 0.42; 95% CI, 0.20 to 0.94)</td>
</tr>
<tr>
<td>NSABP (STAR), 2000, 2010</td>
<td>Raloxifene 60 mg per day vs tamoxifen 20 mg per day for 5 years</td>
<td>Goal 5-year risk score &gt; 1.66% (postmenopausal)</td>
<td>19,747</td>
<td>Comparable invasive breast cancer risk at 47 months (HR, 1.03; 95% CI, 0.82 to 1.29) More invasive breast cancers with raloxifene at 61 months (HR, 1.24; 95% CI, 1.05 to 1.47) More non-invasive breast cancers with raloxifene</td>
</tr>
<tr>
<td>MAP.3,2011</td>
<td>Exemestane 25 mg per day vs placebo for 5 years (analysis at 36 months median follow-up)</td>
<td>Goal 5-year risk score &gt; 1.66% (postmenopausal)</td>
<td>4,600</td>
<td>Reduced invasive breast cancer (HR, 0.36; 95% CI, 0.16 to 0.70) Reduced invasive and non-invasive breast cancer (HR, 0.47; 95% CI, 0.27 to 0.78) Reduced ER+ but not ER− cancers</td>
</tr>
<tr>
<td>IBIS-II,2013</td>
<td>Anastrozole 1 mg per day vs placebo for 5 years</td>
<td>Relative risk = 2 x general population basis of family history, benign breast disease, postmenopausal</td>
<td>3,064</td>
<td>Reduced invasive, non-invasive breast cancer (HR, 0.47; 95% CI, 0.23 to 0.69) Reduced ER+ but not ER− cancers</td>
</tr>
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</table>

**Abbreviations:** ER, estrogen receptor; HR, hazard ratio; IBIS-I, International Breast Cancer Intervention Study I; IBIS-II, International Breast Cancer Intervention Study II; MAP.3, Mammary Prevention 3; NSABP-P1, National Surgical Adjuvant Breast and Bowel Project trial P1; STAR, Study of Tamoxifen and Raloxifene.

Figure 3: Randomized Breast Cancer Prevention Trials of Hormone Interventions

### 2.2 Simulation and Modeling methods

There are many simulation techniques present in the literature. The most popular in the recent studies are the discrete event, continuous simulation, system dynamics and Monte Carlo simulation.

A discrete event simulation models events that occur at a particular instant in time and marks a change of state in the system. (Robinson, 2004) Between consecutive events, no change in the system is assumed to occur; thus, the
simulation can directly jump in time from one event to the next. In the healthcare area, there is a potential to apply this method in logistics, patient pathway, design, reengineering, scheduling and queue management, and reduction of waiting times. (Kuljis, Paul, & Stergioulas)

Continuous simulation model continuously tracks system response according to a set of equations typically involving differential equations (Definition of Simulation with reference to "continuous simulation", 2016) and in the healthcare system, it seems to be limited to physical/biological laboratory processes.

System dynamics is an approach to understanding the nonlinear behavior of complex systems over time using stocks, flows, internal feedback loops, and time delays. (MIT System Dynamics in Education Project, 2016) Potential applications to healthcare include resource and asset allocation and patient pathway design and management.

Monte Carlo simulation furnishes the decision-maker with a range of possible outcomes and the probabilities they will occur for any choice of action. Applications to health care may include risk analysis and management, decision making/support under conditions of uncertainty (e.g. in commissioning, procurement, policy making, organizational change etc.).

Carter et al. says that there are three modeling methods, in the context of healthcare, that already associate with a patients' stages of the disease: Markov model, analytic hierarchy process (AHP), and the analytic network process (ANP).

Markov chain models have a long history of use in health service decision-making, including clinical and epidemiological applications. (Michaels JA, 1993)
An AHP model weighs information from both physicians and patients in an interactive way to build a hierarchical tree from the objective level to the detailed elements.

ANP serves the same function as AHP, but the former uses element clusters instead of a strict hierarchical tree.

2.3 State Transition Modeling (STM) in the context of healthcare

The state transition modeling can be applied to many clinical situations. In this kind of method, individuals are assigned to states (conditions) and they can move among such states depending on probabilities associated with these possible transitions. Generally, STM are formed by state, transitions, initial state vector, transition probabilities, cycle length, state values (utility weights), and logical tests that will define the beginning, transition and termination criteria.

STMs can be used to simulate a closed cohort over time or a dynamic population. They may simulate all individuals simultaneously or one at a time.

In healthcare the most common frameworks are cohort, also known as “Markov”, models and individual based models, commonly known as “microsimulation” or “first order Monte Carlo” models (Siebert, 2012). Transitions in both frameworks are allowed to occur only on a specific interval of time and do not capture interactions, since model a single or closed cohort (Medical Decision Making, 2012).

We have chosen the STM model because of its ability to reflect time, something that are limited when a simpler model, like decision tree, is used. By the ability to reflect time, we meant if it requires a time dependent parameters, time to an event or repeated events. From the beforehand mentioned frameworks we have
chosen the cohort Markov model to proceed our study. The principal advantage of cohort STM is its transparency, efficiency, it is relatively simple to develop, ease of debugging, communicate and analyze if the number of states is not too large. The main disadvantage is that transition probabilities do not depend on history, neither on past states nor on time spent in the current state. This can be very limiting for clinical studies where these factors tend to be strong determinants of what happen next, like in healthcare.
Chapter 3
Markov chain modeling

3.1 Problem statement

The objective of this study is to investigate how the chemoprevention therapy with two different drugs, tamoxifen and raloxifene, affects the quality-adjusted life in years of the patients with high risk to develop breast cancer. The purpose is to find out, for each age group assumed in the study, if the ingestion of the drug is better than placebo and if the side effects impact the decision whether or not to take the drug. Then, the two drugs are also compared between them.

3.2 Markov Model

The model created in this thesis uses an individual-based Markov microsimulation. In the Markov model, we can effectively track over time patients following a course and fall into certain disease stages. The different therapies of chemoprevention, use of tamoxifen or raloxifene pills, will change the chance of relapse differently. The transition between stages happen according to provided probabilities that we imputed into the model. The structure of the present simulation model is based on a previously published modeling study (M Kondo, 2009). A modeled individual must be in only one state in any cycle. At any given time, a high-risk woman occupies one of the following eight health states: (1) high-risk women healthy, (2) invasive breast cancer, (3) noninvasive breast cancer, (4) endometrial cancer, (5) pulmonary embolism, (6) cataract, (7) hip fracture and (8) dead (Figure 4).
As time progresses, women can transit from one health state to another, which is shown by arrows. We have assumed that the transition happens at the end of each state. The time span of each stage is set at 1 year (cycle length), since trials report annual incidence rates. The termination criteria on the Markov process is repeating it until death or age 100, whichever comes first, since all events are expected to occur within this horizon. Women who survive after the age of 100 years are assumed to die regardless of breast cancer development.

Chapter 4
Results and discussion

4.1 Modeling details and results

The model used in this study was coded in Java. We have coded three different models: one for tamoxifen, one for raloxifene and one for the placebo group (code included in appendix B). All of them use the same assumptions, as follows:
There are 3 groups of age being variable inputted to the code: 35, 50, 60 years old.

For each age group we run the code for a sample of 10,000 individuals.

From the disease state to dead state we assumed the table of natural cause of death for the United States population.

The codes are very similar, differing only in the appropriate transition probability matrix.

The probabilities are the most important part of the code. To get the probabilities used on the code we did research on the available literature and publications to get real incidence rates from published studies. We transformed the average annual breast cancer incidence rates in Breast Cancer Prevention Trials (Figure 4) into transition probabilities (Dawn Hershman, 2002).

![Table of Incidence Rates](image)

Figure 5: Annual Incidence rates per 1,000 for outcomes of the BCPT used in the Markov Model.
Another part of the data, such as utilities weight, were found on the article Cost-effectiveness of breast cancer prevention in Japan (M Kondo, 2009). However, some important data we were not able to find in the literature. Therefore, we assumed an average for each one of the beforehand mentioned groups of age. This ensures a full transition probability matrix.

The results are shown in the table and in the graphs below.

![Graph showing QALY results comparison](image)

**Figure 6:** QALY results comparison between present study, previous studies and placebo for tamoxifen

The metric used in the Markov analysis is the quality-adjusted life year (QALY) which measures both the quality and quantity of life lived. This first graph compares the QALY gotten from taking tamoxifen on the present study, the QALY published from previous studies and placebo. As we can see, there is a difference of almost 2 years from the previous studies and this one right now. The
differences can be justified based on the average that we have used, since we did not have all the probabilities needed. In addition, previous studies were done in Japan, and the transition from disease states and death are based on the table of natural death for the United States population. These demographics differences can have had impact on our results and making them a little bit lower than was previously published.

![Figure 7: QALY results comparison between present study, previous studies and placebo for raloxifene](image)

The second graph is almost the same as the previous figure, but now it is comparing the QALY gained from taking raloxifene. Again, there is a difference of almost 3 years from the previous studies and this one right now. The differences are justifiable for the same reason as beforehand mentioned case of tamoxifen.
Figure 8: QALY results comparison between tamoxifen × raloxifene × placebo

Figure 8 is comparing both drugs and the use of placebo. As we can see for all age group tamoxifen return better QALY than raloxifene. This was expected and can validate other similar results found on previous studies.

Tamoxifen helps patients to get better results on the chemoprevention treatments, however it is still the one with most side effects.
Chapter 5
Conclusions

To address the unresolved issues related to the poor uptake of breast cancer prevention therapies, the main objective of this study is comparing the outcomes of taken these chemoprevention therapies. The results and code generated here is only the first step among a greater expected result in the future. The expected result would improve the number of patients taking the medicine and would lower the incidence rate of breast cancer in the United States.

The present study was the development of a model and validation to predict risk/benefits by taking into account patient demographics such as age and race. The model simulated the disease course followed by high-risk women.

Unfortunately, according to the study results, we cannot conclude that the ingestion of both drugs would increase the QALY for all age groups. For some age groups the results of QALY are lower than in the placebo group, this result was not desired, since the drug should improve the quality of life of a patient. However, this was expected, since other studies have shown the same results when compared to the placebo for certain age groups starting the prophylaxis.

Another result was about the comparison between tamoxifen and raloxifene, and as we were expecting, tamoxifen is best to the purpose of chemoprevention. It results in higher rates of QALY then raloxifene. Other studies had already identified this result, but ours is a validation of the previous ones.

The reasons why we possibly did not get better results when compared to placebo group are the lack of information and data. There was a lot of information that we could not access, so in order to continue the study we have
used averages for some probabilities. The averages that we have used are real and demonstrated results reasonable approximating previous studies. However, to continue this study and improve the use in future work it is necessary to have access to more complete data about the incidence rate of breast cancer and side effects when patients are taking these medicines.
REFERENCES


http://www.breastcancer.org/symptoms/understand_bc/statistics


**APPENDIX**

**Appendix A: Abbreviations**

List of abbreviations:

AHP: Analytic Hierarchy Process
ANP: Analytic Network Process
ASCO: American Society of Clinical Oncology
DCIS: Ductal carcinoma in situ
ER: Estrogen receptor
FDA: Food and Drug Administration
LCIS: Lobular carcinoma in situ
QUALYs: Quality adjusted life years
SEER: Surveillance, Epidemiology, and End Results
SERMs: Selective Estrogen Receptor Modulator
Appendix B: Java codes of Markov model

Tamoxifen

package patientModel;
import java.io.File;
import java.io.FileNotFoundException;
import java.io.FileOutputStream;
import java.io.PrintStream;
import dummyModel.Patient;

public class patientTamoxifen extends iPatient {
    private static double [] utility = {1.00, 0.98, 0.89, 0.88, 0.7, 0.96, 0.61, 0};
    double[] qualityOfLife = new double[utility.length];

    @Override
    public String getState() {
        return null;
    }

    public void run() {
        int state = 0;
        int futureState = 0;
        int finalState = 7;
        int age = 90;
        int[] countStates = new int[8];
        while (state != finalState) {
            double r = Math.random();
            double sum = 0;
            ...
double x = super.getx(age);

double [][] transition = {
    {0.96595, 0.00404, 0.00183, 0.00000, 0.00136, 0.01458, 0.00000, x},
    {0.00000, 0.00000, 0.00000, 0.00000, 0.00000, 0.00000, 0.00000, x},
    {0.00000, 0.00000, 0.00000, 0.00000, 0.00000, 0.00000, 0.00000, x},
    {0.00000, 0.00000, 0.00000, 0.00000, 0.00000, 0.00000, 0.00000, x},
    {0.00000, 0.00000, 0.00000, 0.00000, 0.00000, 0.00000, 0.00000, x},
    {0.01118, 0.00000, 0.00000, 0.00000, 0.00000, 0.98882, 0.00000, x},
    {0.00000, 0.00000, 0.00000, 0.00000, 0.00000, 0.00000, 0.00000, x},
    {0.00000, 0.00000, 0.00000, 0.00000, 0.00000, 0.00000, 0.00000, 1.00000}
};

for (int j = state; j < transition[0].length - 1; j++) {
    sum += transition[state][j];
    age++;
    if (r < sum) break;
    else futureState = j + 1;
}

state = futureState;
countStates[state]++;
age++;
if (age >= 100)
    state = 7;
}

//String row = "";
for (int i = 0; i < countStates.length - 1; i++) {
// row += i+"-"+countStates[i]+"",;
} 

for (int i = 0; i < countStates.length-1; i++) {
    qualityOfLife[i] = countStates[i] * utility[i];
    // row += qualityOfLife[i]+"",;
}

for (int i = 0; i < qualityOfLife.length; i++) {
    qaly += qualityOfLife[i];
}

QALY.add(qaly);
}

public static void main(String[] args) throws FileNotFoundException {
    for(int n=0; n<10000;n++) {
        patientTamoxifen patient = new patientTamoxifen();
        patient.run();
    }

    File diskFile = new File("dataTamoxifen.xls");
    FileOutputStream diskFileStream = new FileOutputStream(diskFile);
    PrintStream target = new PrintStream(diskFileStream);
    for(int i=0; i<QALY.size();i++) target.println(QALY.get(i));
}
}
**Raloxifene**

```java
package patientModel;

import java.io.File;
import java.io.FileNotFoundException;
import java.io.FileOutputStream;
import java.io.PrintStream;
import dummyModel.Patient;

public class patientRaloxifene extends iPatient {
    private static double[] utility = {1.00, 0.98, 0.89, 0.88, 0.7, 0.96, 0.61, 0};
    double[] qualityOfLife = new double[utility.length];

    @Override
    public String getState() {
        return null;
    }

    public void run() {
        int state = 0;
        int futureState = 0;
        int finalState = 7;
        int age = 90;
        int[] countStates = new int[8];
        while (state != finalState) {
            double r = Math.random();
            double sum = 0;
            double x = super.getx(age);

            double double[][] transition = {
                {1-x-
```
0.02003,0.00502,0.00223,0.00000,0.00109,0.01169,0.00000,x},
{0.00000,0.00000,0.00000,0.00000,0.00000,0.00000,0.00000,x},
{0.00000,0.00000,0.00000,0.00000,0.00000,0.00000,0.00000,x},
{0.00000,0.00000,0.00000,0.00000,0.00000,0.00000,0.00000,x},
{0.00000,0.00000,0.00070,0.00000,0.00000,0.00000,0.00000,x},
{0.00885,0.00000,0.00000,0.00000,0.00000,1-x-0.00885,0.00000,x},
{0.00000,0.00000,0.00000,0.00000,0.00000,0.00000,0.00000,x},
{0.00000,0.00000,0.00000,0.00000,0.00000,0.00000,0.00000,1.0000}

);  
for(int j=state; j<transition[0].length-1;j++){
    sum += transition[state][j];
    age++;
    if ( r < sum ) break;
    else futureState = j+1;
}
state=futureState;
countStates[state]++;
age++;
if (age>= 100)
    state=7;
}
//String row = "";
for (int i = 0; i < countStates.length-1; i++) {
    // row += i""-""+countStates[i]+"",";  
}
for (int i = 0; i < countStates.length-1; i++) {
    qualityOfLife[i] = countStates[i] * utility[i];
    // row += qualityOfLife[i]+",";
}
for (int i = 0; i < qualityOfLife.length; i++) {
    qaly += qualityOfLife[i];
}
QALY.add(qaly);
}

public static void main(String[] args) throws FileNotFoundException {
    for(int n=0; n<10000;n++) {
        patientR aloxifene patient = new patientR aloxifene();
        patient.run();
    }
    File diskFile = new File("dataR aloxifene.xls");
    FileOutputStream diskFileStream = new FileOutputStream(diskFile);
    PrintStream target = new PrintStream(diskFileStream);
    for(int i=0; i<QALY.size();i++) target.println(QALY.get(i));
}
}
package patientModel;
import java.io.File;
import java.io.FileNotFoundException;
import java.io.FileOutputStream;
import java.io.PrintStream;

public class patientPlacebo extends iPatient {
    private static double [] utility = {1.00, 0.98, 0.89, 0.88, 0.7, 0.96, 0.61, 0};
    double[] qualityOfLife = new double[utility.length];

    @Override
    public String getState() {
        return null;
    }

    public void run() {
        int state = 0;
        int futureState = 0;
        int finalState = 7;
        int age = 90;
        int[] countStates = new int[8];
        while (state != finalState) {
            double r = Math.random();
            double sum = 0;
            double x = super.getx(age);

            double [[[]] transition = {
                {0.96715, 0.00018, 0.00629, 0.00068, 0.00032, 0.02172, 0.00086, x},
            }
for(int j=state; j<transition[0].length-1; j++) {
    sum += transition[state][j];
    age++;
    if (r < sum) break;
    else futureState = j + 1;
}
state = futureState;
countStates[state] ++;
age ++;
if (age >= 100)
state=7;

    //String row = "";
    for (int i = 0; i < countStates.length-1; i++) {
        //    row += i""+""+countStates[i]+",";
    }

    for (int i = 0; i < countStates.length-1; i++) {
        qualityOfLife[i] = countStates[i] * utility[i];
        //    row += qualityOfLife[i]+"";
    }

    for (int i = 0; i < qualityOfLife.length; i++) {
        qaly += qualityOfLife[i];
    }

    QALY.add(qaly);
}

public static void main(String[] args) throws FileNotFoundException {
    for(int n=0; n<10000;n++) {
        patientPlacebo patient = new patientPlacebo();
        patient.run();
    }

    File diskFile = new File("dataPlacebo.xls");
    FileOutputStream diskFileStream = new FileOutputStream(diskFile);
    PrintStream target = new PrintStream(diskFileStream);
    for(int i=0; i<QALY.size();i++) target.println(QALY.get(i));
Ipatient (includes Natural death table from the United States population)

package patientModel;

import java.io.File;

import java.io.FileNotFoundException;

import java.io.FileOutputStream;

import java.io.PrintStream;

import java.util.ArrayList;

public abstract class iPatient {

    protected double cost = 0, qaly = 0;

    protected int age = 0, relative = 0;

    protected String race = null;

    protected boolean hysterectomy, LCIS, atypicalHyperpalsia;

    String stateName[] = {"healthy",
               "noninvasiveBC","invasiveBC","endometrialCancer",
               "pulmonaryEmbolism","cataract","hipFracture","dead");

    protected static ArrayList<Double> QALY= new ArrayList<Double>();

    public abstract String getState();

    public double getx(int age){
        this.age=age;
        double rate[]={
            0.0060506,
            0.0004273,
            0.0002764,
            0.0001852,
            0.0001619,
            0.0001457,
            0.0001305,
            0.0001162,
            0.0001029,
            0.0000905,
            0.0000781,
            0.0000667,
            0.0000553,
            0.0000439,
            0.0000325,
            0.0000211,
            0.0000114,
            0.0000000,};
0.0001487,
0.0001342,
0.0001226,
0.0001107,
0.0000988,
0.0000907,
0.000093,
0.0001131,
0.0001548,
0.0002112,
0.0002747,
0.0003337,
0.0003818,
0.0004139,
0.000434,
0.0004531,
0.0004751,
0.0004935,
0.0005077,
0.0005194,
0.0005316,
0.0005459,
0.0005618,
0.0005804,
0.0006036,
0.0006335,
0.0006713,
0.0007177,
0.0007694,
0.0008287,
0.0008928,
0.0009665,
0.0010565,
0.0011662,
0.0012926,
0.0014253,
0.0015628,
0.001713,
0.001713,
0.001877,
0.0020517,
0.0022361,
0.0024251,
0.0026165,
0.0028124,
0.0030203,
0.0032467,
0.0034972,
0.0037728,
0.0040695,
0.0043831,
0.0488331,
0.0542505,
0.0602308,
0.0668238,
0.0740815,
0.0820582,
0.0908095,
0.1003921,
0.1003921,
0.1108626,
0.1222767,
0.1346879,
0.1481462,
0.1626965,
0.1783766,
0.1952155,
0.2132316,
0.2324301,
0.2528017,
0.2743207,
0.2969435,
0.320837976,
0.345470723,
0.370961693,
0.397192157,
0.424027102,
0.451317672,
0.478904253,
0.5066201,
0.534295317,
0.561761,
0.588853331,
0.615417411,
0.641310644,
0.666405534,
0.690591779,
0.713777628,
0.735890491,
0.756876869,
0.776701665,
0.795347007,
1
};

double x= rate[age];
return x;
}

public void save(String filename) throws FileNotFoundException{
}
}