5-2020

A Simulation Approach to Evaluate the Impact of Breast Cancer Overdiagnosis on Patient Outcomes

Sierra Wagner

A Simulation Approach to Evaluate the Impact of Breast Cancer Overdiagnosis on Patient Outcomes

A thesis submitted in partial fulfillment of the requirements for the degree of Bachelor of Science in Industrial Engineering with Honors

Author: Sierra Wagner

Date: April 2020

Institution: University of Arkansas, Fayetteville, AR

College of Engineering

Department of Industrial Engineering

Thesis Advisor: Dr. Shengfan Zhang

Committee Member: Dr. Manuel Rossetti

_____

Dr. Shengfan Zhang

Thesis Advisor

_____

Dr. Manuel Rossetti

Committee Member

Table of Contents

Abstract

Breast cancer overdiagnosis risk is difficult to estimate and varies significantly across current research. This research establishes a simulation approach to examine the relationship between breast cancer overdiagnosis and patient outcome and understand the impact that the range of breast cancer overdiagnosis rate estimates in the current literature has on patient outcomes. Overdiagnosis is represented in this study by a set of disease regression probabilities. Using microsimulation, we evaluate patient outcome, measured by number of mammograms and lifetime breast cancer mortality risk, as a function of treatment policy and regression probability. We use numerical experiments to evaluate treatment policies and disease regression probabilities, and we conclude through sensitivity analysis that treatment policy is a statistically significant factor for patient outcome and regression probability, or overdiagnosis rate, is only partially statistically significant for patient outcome.

1. Introduction

Breast cancer is the second most common cancer in American women, and there is a 12% chance that a woman in the U.S. will develop breast cancer in her life (American Cancer Society (ACS), 2019). Most breast cancers begin as ductal carcinoma in situ (DCIS), or pre-clinical cancer, where there is no symptom present (Duffy et al., 1995). DCIS is the condition where the cells lining the milk ducts in the breast have become cancerous and is considered non-invasive (Martin, 2019). Breast cancer is considered invasive when the tumor reaches two to five centimeters or spreads into surrounding breast tissue or lymph nodes, and it is classified as metastatic breast cancer when the cancer cells have spread to distant organs or tissue in the body (Cancer Treatment Centers for America, 2020).

1.1 Screening Overdiagnosis

The current technology for breast cancer detection is mammography, which is used to identify abnormal areas of the breast that may be signs of cancer. Although diagnosing cancer in its early stages helps to develop treatment plans, frequent mammography screenings can result in overdiagnosis. Overdiagnosis is the diagnosis of early stage disease that does not give rise to symptoms during the patient's lifetime or have lethal potential (Welch & Black, 2010). Measuring and observing overdiagnosis is not entirely straightforward. Overdiagnosis occurs when cancer does not progress beyond DCIS during the patient's lifetime or it progresses slowly enough for the patient to die of other causes. Cases which are classified as overdiagnosis can therefore only be observed in retrospect. Figure 1 is a representation of overdiagnosis.

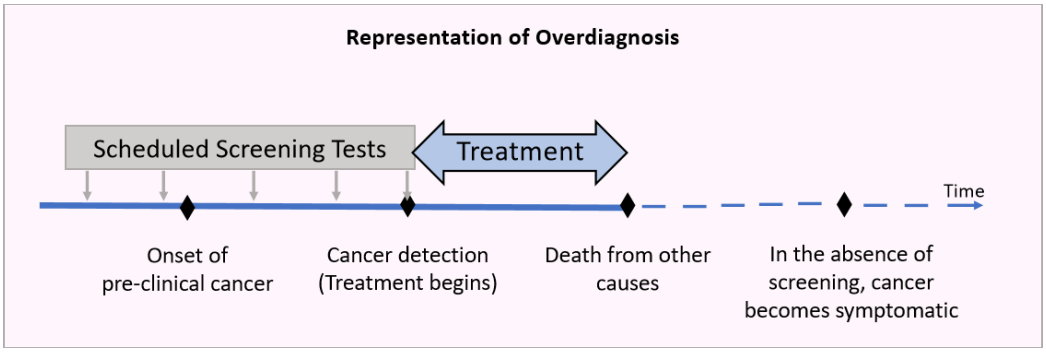

Figure 1: Representation of overdiagnosis, adapted from Madadi et al. (2018)

Overdiagnosis is considered one of the significant harms of breast cancer screening (Welch & Black, 2010) because it leads to overtreatment, which puts patients' well-being at risk and incurs unnecessary costs. Some levels of overdiagnosis and overtreatment are inevitable, since deaths from other causes, like accidents or other health complications, are always possible. However, breast cancer surgeries and treatments are strenuous, costly, and can adversely affect the patient's quality of life. Therefore, cases of treatment where the cancer would never have progressed or become symptomatic during the patient's lifetime have unnecessary negative consequences.

To be most effective, screening policies need to target the at-risk population and balance the tradeoffs between screening too frequently, thus performing unnecessary tests, and not screening often enough, thereby missing cases (Brailsford et al., 2012). Various organizations such as the ACS and USPSTF (U.S. Preventive Services Task Force) have guidelines for screening mammography to help detect breast cancer early. However, the harms of overdiagnosis and overtreatment have cast controversy on breast cancer screening practices, resulting in the evaluation and adjustment of screening guidelines to promote less frequent screening, as was reflected in the updated 2015 ACS guideline.

As of 2015, the ACS recommends annual mammograms beginning at age 45 and notes that women 55 and older can switch to biennial mammograms (ACS, 2019). While this recommendation is in part a result of increased awareness of the harms of overdiagnosis, it is also shaped by research that shows breast cancer grows differently as a patient ages. For instance, studies have shown that although the risk of developing breast cancer increases as a

patient ages, breast cancer is less aggressive in older women (Tabár et al., 2000). Slower cancer growth explains why the ACS recommends that women 55 and older only need to be screened every two years.

1.2 Literature Review

As one of the first modeling efforts on breast cancer screening, Maillart et al. (2008) evaluated a broad range of breast cancer screening policies to identify a set of "efficient" policies as measured by a lifetime breast cancer mortality risk and the expected number of mammograms. The purpose of their study was to determine whether it was more beneficial to prescribe more frequent screening in younger women or older women (Maillart et al., 2008) based on its effect on lifetime breast cancer mortality risk.

Their study limited its evaluation to two-phase screening policies, or policies which consist of only two different screening intervals in the patient's lifetime. They evaluated different screening policies by varying the beginning and ending age for screening, the age at which the initial screening interval switches to the second screening interval, as well as the length of the screening interval itself. The study concluded that to efficiently achieve a lifetime risk that was comparable to the current risk among U.S. women, screening should begin relatively early in life and continue relatively late in life, regardless of the screening intervals(s) adopted. The assessment of dynamic breast cancer screening policies in Maillart et al. provides the basis for the development of the research that is to be described.

There are a number of other studies which explore the impact of screening policies and the relationship of their efficacy with screening adherence, mortality, as well as other factors. Madadi et al. (2015) considered patient adherence behavior and its impact on the efficacy of mammography screening guidelines. While existing screening policies do not take patient behavior into consideration and assume perfect adherence, compliance to mammography guidelines had been revealed as low. As such, Madadi et al. developed a randomized discrete-

time finite-horizon partially observable Markov chain model to evaluate a wide range of screening policies which incorporated heterogeneity in patients' adherence behavior.

To consider the potential harms of mammography (e.g. risk of developing radiation-induced breast cancer) and different screening policies, patient outcomes were compared in terms of lifetime breast cancer mortality risk and total quality adjusted life years. Lifetime mortality risk can be defined as the probability of dying from breast cancer in a woman's life (Maillart et al., 2008). The study by Madadi et al. found that high/perfect adherence always results in lower risk of dying from cancer, and that this benefit outweighs the risk of developing radiation-induced breast cancer from screening.

Brailsford et al. (2012) described a simulation model for screening for breast cancer which includes behavioral factors to model women's decisions to adhere to recommendations and attend mammography screenings. Brailsford et al. constructed a three-phase simulation to model breast cancer and screening policies. Their approach combined methods for simulating breast cancer screening and psychological models of health behavior to model individual women with both physiological and psychological attributes to observe screening attendance rates. The study examined the effect that different tumor growth models have on the model outputs. Overall, Brailsford et al. found that the choice of tumor growth model makes little difference to the relative increase or decrease in patient screening attendance brought about by the different screening scenarios which are assessed.

These studies assessed different screening policies by measuring the impact of various dynamic screening intervals, patient adherence behaviors, and psychological and growth tumor models respectively. These studies and other relevant literature contribute to understanding factors which are affected by screening policies, like overdiagnosis and patient mortality. However, there is a lack of research in the current literature which directly explores the impact that differing overdiagnosis risk estimates have on the performance of screening policies.

While it cannot be identified whether a particular patient has been overdiagnosed during their lifetime, it should be possible to estimate the rate and risk of overdiagnosis. Unfortunately, patient overdiagnosis risk is difficult to estimate and varies significantly across

current research. For example, a randomized control trial by Zackrisson et al. (2006) reported an overdiagnosis rate estimate of 10%, whereas a modeling study by Seigneurin et al. (2011) reported an overdiagnosis rate estimate of 28%. The decision-making process for breast cancer screening and treatment is consequently made more difficult by the uncertainty of patient overdiagnosis risk.

1.3 Aim of Research

To continue with more personalized treatment plans and evaluate the efficacy of dynamic screening and treatment policies, there is a need to better understand individuals' overdiagnosis risk. In order to understand the range of overdiagnosis rate estimates in the current literature and the impact that they have on patient outcomes, the research objective in this study is to quantify the impact of different overdiagnosis risk estimates on patient outcomes, as measured by lifetime breast cancer mortality risk and number of mammograms. We consider a current screening policy which is still recommended by many organizations (annual screening from age 40) and two treatment policies (treat all cancers immediately and treat only invasive cancers). The simulation model established in this research provides opportunities to explore more combinations of screening and treatment policies in future research.

The remainder of the thesis is organized as follows. Section 2 explains the methodology of the research and provides a detailed explanation of the base simulation model. It also walks through the validation process for the base model and outlines the model development and testing process. Section 3 communicates the key findings from the model development and testing. Section 4 discusses the results from Section 3 with respect to the objectives of the research, and it provides recommendations for future research.

2. Methods

2.1 Methodology

Simulation allows for exploration of hypothetical scenarios which could be time consuming and expensive to test in real life. Simulation is widely used in healthcare modeling because of its power and flexibility (Davies & Davies, 1994). It can provide additional measures to help healthcare planners and managers with decision making, and breast cancer screening is considered one of the classic areas of application for healthcare simulation modeling with studies dating back to the 1970s (Brailsford et al., 2012).

Arena® simulation software is used in this study to create a microsimulation model that represents the flow of patients through the breast cancer screening process. Microsimulation is a simulation technique that uses microlevel units, or individuals, as the unit of analysis (Lymer & Brown, 2012). It moves individuals through time, updating each attribute for each time interval based on probabilities determined from appropriate data sources (Lymer & Brown, 2012). Microsimulation can be used to model individuals through their history and cancer progression dependent on previous events and individual characteristics (Brailsford et al., 2012). This method of simulation was chosen because it would allow for the recording of individual patient lifetimes, observation of patient outcomes, and the examination of the effect of various treatment patterns and overdiagnosis risk estimates.

We represent overdiagnosis risk in the model by incorporating a series of regression probabilities. Medical studies have suggested that breast cancer may spontaneously regress without treatment (as summarized in Zhang & Ivy, 2012). Regression is a way to represent overdiagnosis because it effectively allows us to consider patients who were previously diagnosed with DCIS to be cancer free, as the cancer does not ultimately affect their health.

2.2 Construction of Base Model

2.2.1 Discussion of microsimulation framework

The microsimulation framework in this study integrates two components which were identified as key for modeling disease progression and the cancer detection process. The first component, representing disease progression, is based upon a Markov chain model (Ross, 2014) that was devised to describe patient health state and changes over time. The second component, representing the cancer detection process, models screening practices or policies. The patient health state, determined by the first component of the model, acts as a signal to the screening component of the model. An outline of the simulation framework with the two components can be seen below in Figure 2.

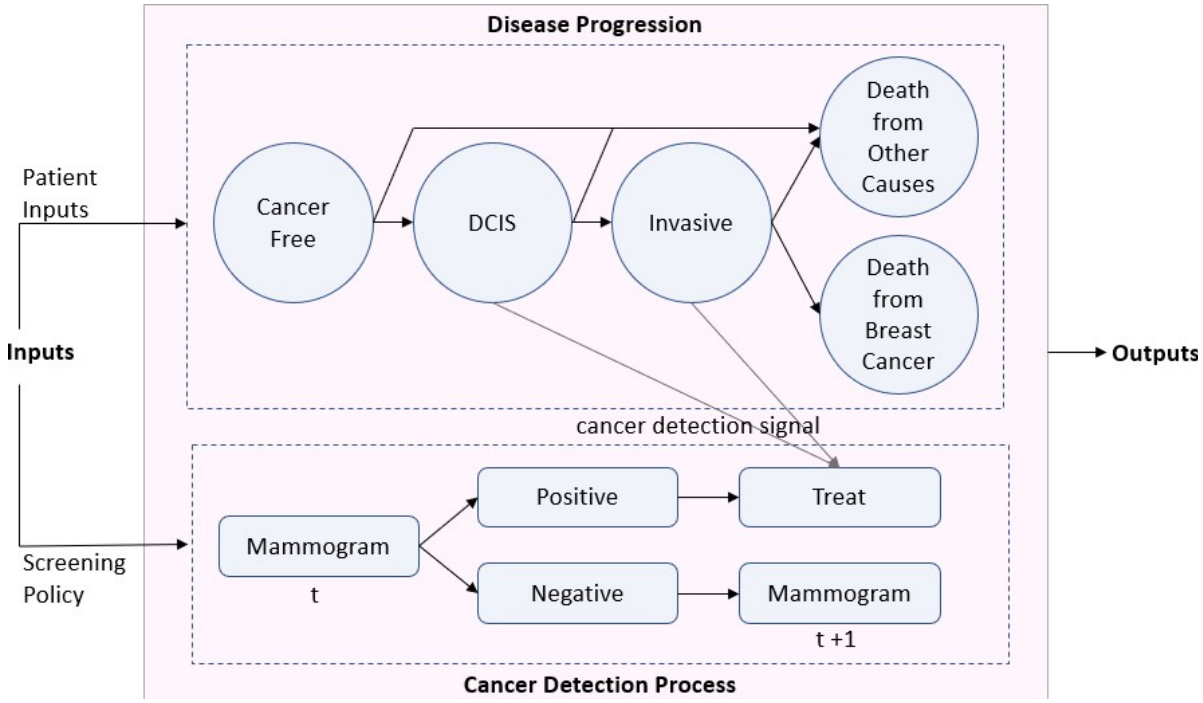

Figure 2: Outline of the simulation framework and model components

As previously stated, the disease progression and patient health state in this model are represented by a Markov chain model. In this simulation study, the Markov chain modeling patient health state has the following five states:

1. Cancer Free
2. DCIS (early stage, noninvasive)
3. Invasive Cancer (advanced stage)
4. Death from Breast Cancer
5. Death from Other Causes

Given a current health state, the probability that a patient will stay in their current state or transition to another state can be determined. There are also probabilities associated with the sensitivity of the mammogram, or likelihood of detection which are dependent on the patient's age and cancer state. This is important for the second component of the simulation model, which represents the cancer detection process. Additionally, lifetime breast cancer mortality risk (r_α) can be assigned based on the patient's age and health state. This is important for assessing patient outcomes.

The behavior and progression of a Markov chain is summarized by putting transition probabilities in matrix form (Cassady & Nachlas, 2008). The breast cancer transition probabilities used in this study for health state, mammogram sensitivity, and lifetime breast cancer mortality risk were extracted from Maillart's 2008 study of dynamic breast cancer screening policies. These transition probabilities can be seen in Table I of the Appendix. Note that these values are updated every five years, i.e., the same transition probabilities, mammogram sensitivity, and lifetime breast cancer mortality risk (r_α) values are used in each five-year interval. The intervals range from [25, 29], [30, 34], …, [80, 84], and [85, 100]. These intervals, or age groups, are represented by α.

2.2.2 Inputs/Outputs/Assumptions

As seen in Figure 2, the inputs of this simulation model include patient inputs, or characteristics, and screening policy. Patient characteristics include age and health state. All patients in the simulation are initialized at age 25 and assigned health state 1 (cancer free). Initializing all patients to age 25 is consistent with Maillart's 2008 study and assigning them with health state 1 is consistent with an ACS report for incidence rates for women under 25. This report found that a mere 1.3 cases per 100,000 were identified for 20-24 year-olds between 1998 and 2002 (ACS, 2005).

The screening policy used in this study prescribes annual mammograms beginning at age 40, continuing throughout the patient's life. To make this simulation computationally efficient and to remain consistent with Maillart's study, patients will be observed from age 25-100. Patients who do not die of other causes or breast cancer (health state 4 or 5) are disposed after they reach age 100. This is because the number of women who survive beyond age 100 is negligible according to the US Life Table.

The outputs of the simulation include statistics for the average age of patients, the expected lifetime number of mammograms, and lifetime breast cancer mortality risk. These statistics characterize patient outcomes and provide the basis for assessment.

2.2.3 Overview of the Base Model

Overview of the simulation model

To build a base model for simulating breast cancer development and mammography screening, we developed a conceptual model (Figure 3) which summarizes the flow of patients through the breast cancer screening process.

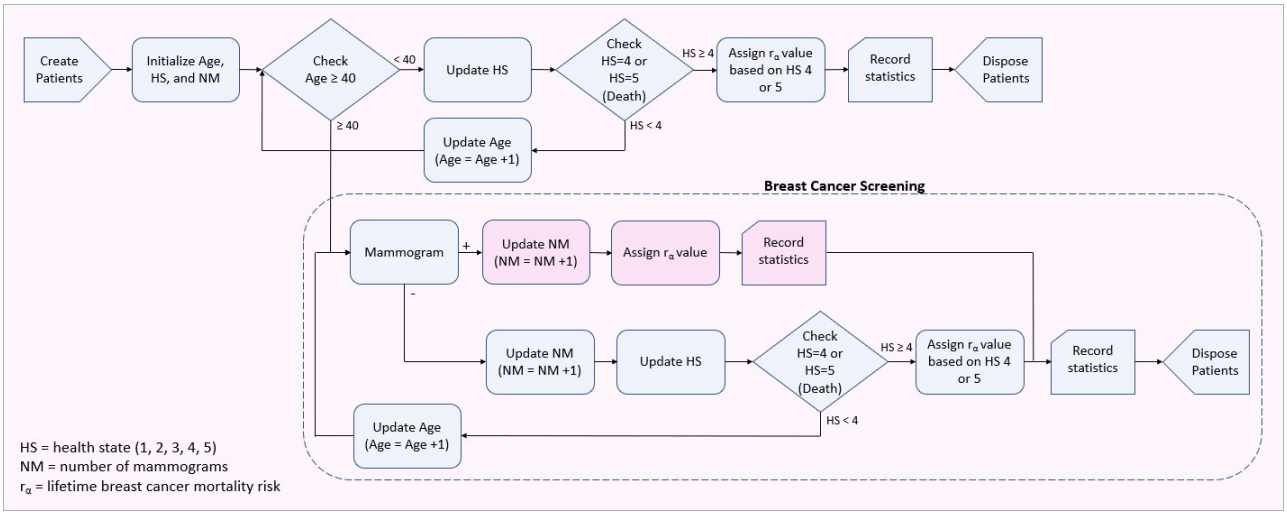

Figure 3: Conceptual model for the simulation, summarizing the flow of patients

Patients are introduced into the simulation and their attributes for age, health state, and number of mammograms are initialized. Patients start at age 25, health state 1 (cancer free), and 0 number of mammograms.

Since the screening policy dictates that mammography screening should not begin until the patient reaches age 40, patients age 25-39 move through a separate loop in the model than those age 40+. The loop for ages 25-39 updates the patient's health state and age. The patient health state is updated based on transition probabilities which are a function of the patient's age (α) and current health state. After their health state has been updated, the patient's age is incremented by 1 year. Patients who reach health state 4 (death from breast cancer) or 5 (death from other causes) before age 40 are disposed from the model. Patients with health state 4 are assigned an r_α value of 1, and patients with health state 5 are assigned an r_α value of 0 before being disposed.

Patients who are 40 years old enter the breast cancer screening section of the model. The patient goes for a mammogram and receives a positive or negative result which is determined by a probability. The probability that the mammogram returns a positive result, or the sensitivity of the mammogram, is a factor of age (α) and the current health state of the patient.

When a patient receives a positive mammogram result, they proceed on the cancer detected path indicated in pink in Figure 3. Their number of mammogram attribute is incremented by 1, and their health state is checked. Patients with health state 2 or 3 (DCIS or invasive cancer) are assumed to begin treatment. Patients who begin treatment are assigned an r_α value, which is determined by their age (α) and health state, and are disposed from the model.

Patients who receive a negative mammogram result are passed through a loop which increments their number of mammograms by 1, updates their health state, and increments their age by 1. Patients whose health state is updated to 4 or 5 in this loop are disposed from the model. Patients continue to loop through the breast cancer screening process until they advance to health state 2, 3, 4, 5, or eventually reach age 101 and are disposed from the model.

The Health State Updating Process

As previously stated, the patient health state is updated based on transition probabilities (Table I, Appendix) which are a function of the patient's age (α) and current health state. In the simulation, the health state updating process is modeled within submodels. Figure 4 shows the conceptual model for these submodels, which has been simplified to show the path of patients which fall into one of the thirteen total α groups.

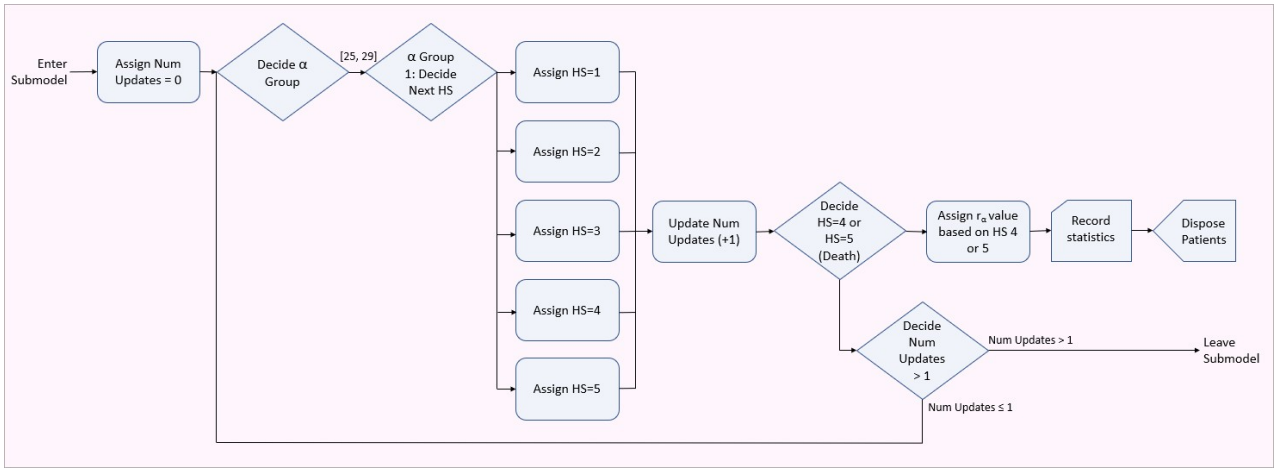

Figure 4: Conceptual model for the Health State Updating Process, simplified to show the flow of patients through one α group which includes patients age 25-29

It is important to note that the transition probabilities for health state in Table I (Appendix) assume six-month transition periods. Since breast cancer screening occurs at annual intervals, patient health state must be updated twice before the patient leaves the submodel to go for their next age update or mammography screening. To accomplish this loop, the patient is assigned an attribute, myNumUpdates, which is incremented by 1 each time the health state is updated. This attribute is used to keep track of the number of times the patient has looped through the submodel.

The submodel checks the patient's age and directs them to the appropriate α group. Once they arrive to their α group, the path to their next health state is determined by their health state transition probability. The transition probabilities for each age group are represented by a variable in the model. The variable uses the patient's current health state to determine the probability that the patient will stay in their current health state or advance to another. This probability is used to determine the patient's path and update the patient's health state.

After updating the patient's health state and incrementing the patient's number of updates, patients who have advanced to health state 4 or 5 are assigned an r_α value and disposed from the model. Otherwise, patients in health state 1-3 loop through the submodel a second time and then leave the submodel.

The Mammogram Process

As previously stated, the probability that the mammogram returns a positive result, or the sensitivity of the mammogram, is a factor of the α group and the current health state of the patient. The process for determining if a patient receives a positive or negative mammogram result is modeled in a submodel. Figure 5 shows the conceptual model for the mammogram submodel.

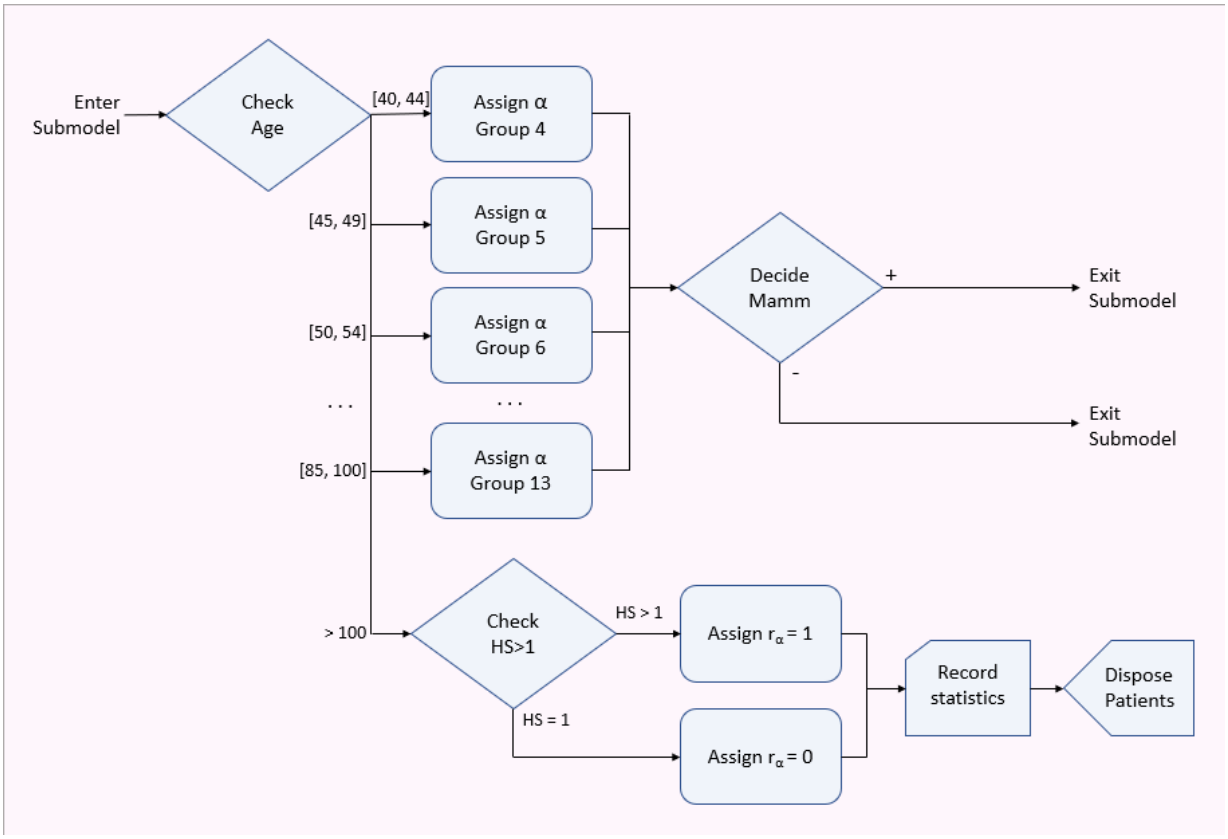

Figure 5: Conceptual model for the Mammogram Process which determines if cancer is detected by the mammogram

The submodel checks the patient's age and directs them to the appropriate α group. Once they arrive at their α group, they are assigned an attribute which specifies their α group. This α group, as well as their current health state is used to determine the probability that the mammogram detects cancer and returns a positive result. If the mammogram is positive, the patient leaves the submodel on the cancer detected path which was indicated in pink in

Figure 3. Otherwise the patient leaves the submodel and continues to loop through the model, having their age and health state updated.

This submodel also checks for patients that age out of the model. After patients reach age 100, they are disposed from the model. Patients who have cancer after they reach age 100 are assumed to die of cancer and are assigned an r_α value of 1 before being disposed. Patients who do not have cancer when they reach 100 are assumed to die of other causes are assigned an r_α value of 0 before being disposed.

2.3 Base Model Validation

In order to ensure that the base model accurately represents the flow of patients through the breast cancer screening process, the model outputs were validated with the findings from Maillart's 2008 study. The base model was tested under the same parameter inputs as Maillart's study and was run with 1000 entities and 10 replications. To verify and validate the simulation model, statistics were collected using the attribute called myNumMamm which keeps track of the number of mammograms that each patient has in their lifetime.

To verify that the model accurately guides patients through the screening process and adheres to the chosen guideline which prescribes annual mammograms beginning at age 40, statistics were recorded for the number of mammograms for patients who are disposed from the model from age 25-39 or at age 101. The number of mammograms for patients who are disposed from age 25-39 was reported as 0. This indicates that the model correctly prevents patients from beginning mammography screening before age 40. The number of mammograms for patients who are disposed from the model at age 101 was 61. This verifies that patients who never progress beyond health state 1 (cancer free) go for 1 mammogram a year from age 40-100.

Statistics for patient age and number of mammograms were also recorded for all patients when they are disposed from the model. The average number of mammograms per patient was recorded as 12.57 of $\pm$ 0.32. Comparing this value with the average age further

verifies the screening section of the model. The average age of patients when they are disposed from the model was reported as 51.33 ± 0.30, indicating that on average patients should receive approximately 12 mammogram screenings from age 40-51.

After verifying the screening behavior of the simulation model, statistics were collected to validate the model with Maillart's 2008 study. To do so, we compared the observed average number of mammograms for patients who never develop breast cancer to Maillart's expected value. The average number of mammograms for patients who never develop breast cancer was recorded as 30.29 ± 1.51. Under the same screening policy and parameter inputs, Maillart reported an expected value of 41.54 mammograms for patients who never develop breast cancer. This difference can be attributed to differences in methodology and further investigation is needed.

2.4 Model Development and Testing

We modified the base model to perform numerical experiments and sensitivity analysis which would allow us to quantify the impact that different overdiagnosis risks and treatment policies have on patient outcomes. The numerical experiment tests two treatment policies and six variations of health state transition probabilities, which account for disease regression (or overdiagnosis risk).

A slight adjustment was made to the simulation model to test two different treatment policies. The two treatment policies tested in this experiment are listed below:

1. **Treatment Policy 1:** All patients whose mammography test detects cancer (HS=2 or HS=3) are assumed to begin treatment immediately and leave the model (this is the rule used in the base model).
2. **Treatment Policy 2:** Only patients whose mammography test detects invasive cancer (HS=3) begin treatment. Patients with non-invasive cancer (HS=2) do not begin treatment and remain in the model.

Treatment Policy 1 is the policy that was used to create the base model. Therefore, to implement Treatment Policy 2, a simple decide module was added to the simulation to identify patients with invasive cancer who begin treatment and to identify patients with non-invasive cancer who continue to update and monitor their health state in the screening process. This addition is indicated by the red circle in Figure 6 which shows the updated conceptual model for the flow of patients through the simulation.

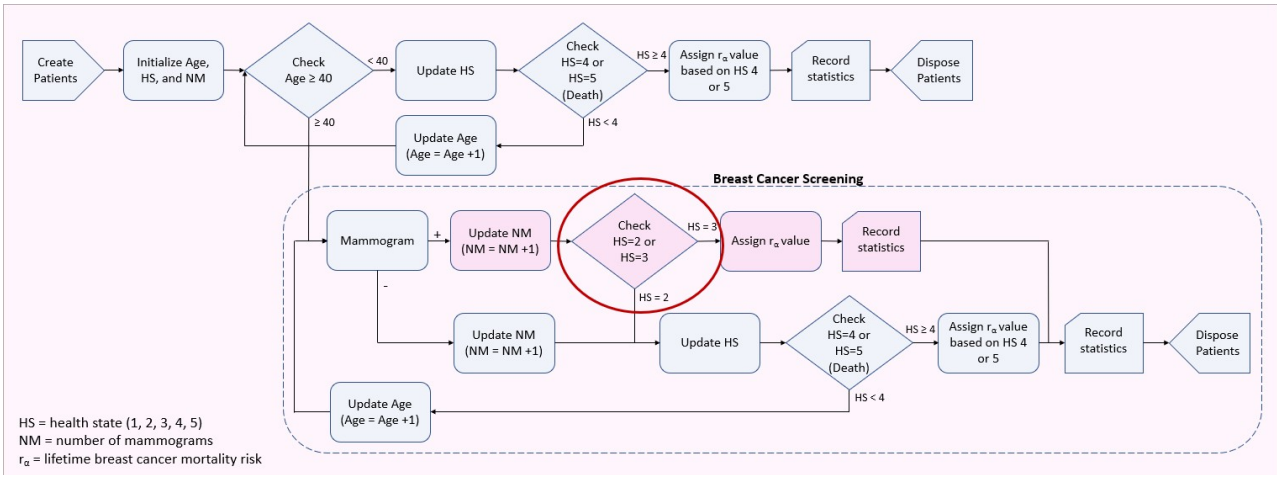

Figure 6: Conceptual model for the simulation development, summarizing the flow of patients through Treatment Policy 2

In this experiment, we only consider disease regression from the DCIS stage to the cancer free state (health state 2 to health state 1). This disease regression is represented by the red arrow in Figure 7. The six variations of health state transition probabilities that were used in the numerical experiment were generated by incorporating a series of regression probabilities into the transition probabilities used in the base model. The regression probabilities include 0% (base case, no regression), 5%, 10%, 15%, 20%, and 25%. This range of regression probabilities does not exceed 25% because an observational study by Zahl et al. (2004) found a regression probability of approximately 22%. These percentage of cancers are considered harmless to the patients (overdiagnosed) and therefore patients will stay in the cancer free state.

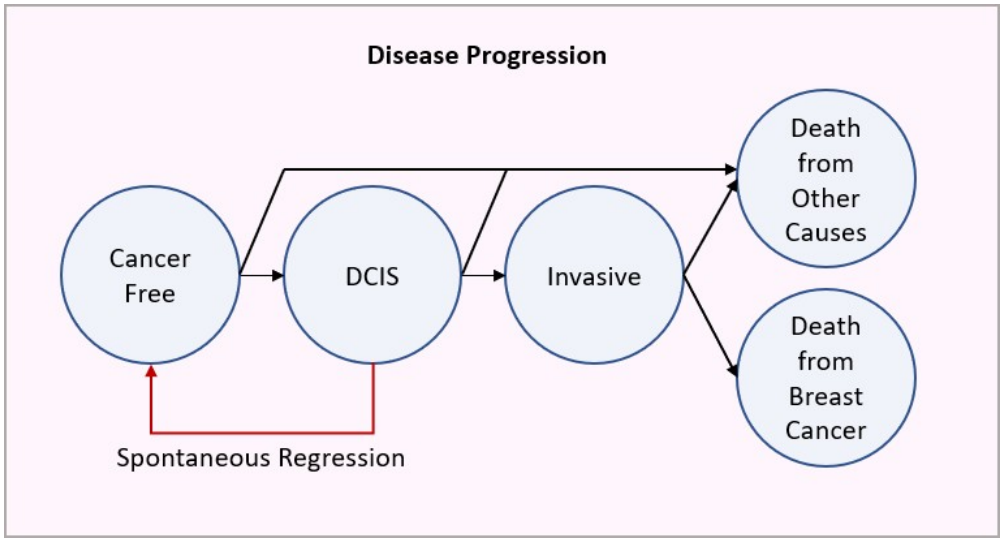

Figure 7: Representation of breast cancer disease progression which incorporates spontaneous regression from DCIS stage cancer to the cancer free state

The simulation was run for all twelve combinations of the two treatment policies and the six health state transition probabilities (Treatment Policy 1 with 0% regression, Treatment Policy 1 with 5% regression, … Treatment Policy 2 with 20% regression, and Treatment Policy 2 with 25% regression). As previously stated in the explanation of the health state updating process, the health state transition probabilities for each age group of patients are represented by variables in the model. For each test, the health state transition probabilities were adjusted to include different regression probabilities (0%, 5%, 10%, 15%, 20%, 25%) by updating the variables in the model.

Each simulation test was run with 1000 entities and 10 replications, and outputs for the expected number of mammograms for patients who never develop breast cancer and lifetime breast cancer mortality risk values (r_α) were recorded for comparison. Two-way ANOVA tests were performed in Minitab® statistical software to observe the impact that different treatment policies and regression probabilities have on patient outcome, as characterized by number of mammograms and lifetime mortality risk.

3. Results

The average outputs for all twelve tests, as summarized by the number of mammograms for patients who never develop breast cancer and lifetime mortality risk values, along with their corresponding confidence intervals (represented by half-width), were recorded and shown in Table 1. Table 1 shows that the transition from Treatment Policy 1 to Treatment Policy 2 resulted in an increase in the number of mammograms and lifetime mortality risk, suggesting that treatment policy is a statistically significant factor for both response variables. As the regression probabilities (or overdiagnosis risk) increase in Table 1, the values for lifetime breast cancer mortality risk decrease, but there does not appear to be a discernable pattern for number of mammograms. This suggests that regression probability may only be a statistically significant factor with respect to lifetime mortality risk.

Table 1: Summary of average outputs from the numerical experiment

	Number of Mammograms		Lifetime Breast Cancer Mortality Risk	
Regression Probability \ Treatment Policy	**1**	**2**	**1**	**2**
0%	30.29 ± 1.51	41.15 ± 0.27	1.03% ± 0.0%	6.42% ± 0.0%
5%	30.39 ± 1.60	41.31 ± 0.36	0.94% ± 0.0%	4.93% ± 0.0%
10%	30.38 ± 1.62	41.32 ± 0.37	0.90% ± 0.0%	4.04% ± 0.0%
15%	30.41 ± 1.56	41.41 ± 0.38	0.82% ± 0.0%	3.47% ± 2.60%
20%	30.46 + 1.73	41.41 ± 0.43	0.77% ± 0.0%	3.04% ± 2.37%
25%	30.51 ± 1.65	41.40 ± 0.40	0.73% ± 0.0%	2.66% ± 2.10%

Since there were two treatment policies and six regression probabilities to be tested, and ten replications per test, there were 120 data points used for the sensitivity analysis (2*6*10=120). The model performance for all 120 data points as summarized by number of mammograms for patients who never develop breast cancer and lifetime breast cancer mortality risk values, along with their corresponding confidence intervals (represented by half-width), can be seen in Table II of the Appendix. The complete results from the sensitivity analysis can be seen in Figure I of the Appendix. The results from the two-way ANOVA tests indicate that:

1. Treatment policy is a statistically significant factor with respect to both number of mammograms and lifetime breast cancer mortality risk, as the p-values are close to zero.
2. Regression probability is a statistically significant factor with respect to lifetime breast cancer mortality risk, as the p-value is close to zero.
3. Regression probability is not a statistically significant factor with respect to number of mammograms, as the p-value is large.

To better visualize the results, the average number of mammograms for patients who never develop breast cancer and the average lifetime breast cancer mortality risk for all 120 replications were plotted in the boxplots shown in Figure 8 and Figure 9 respectively. The blue boxplots represent data associated with Treatment Policy 1 and the pink boxplots represent data associated with Treatment Policy 2.

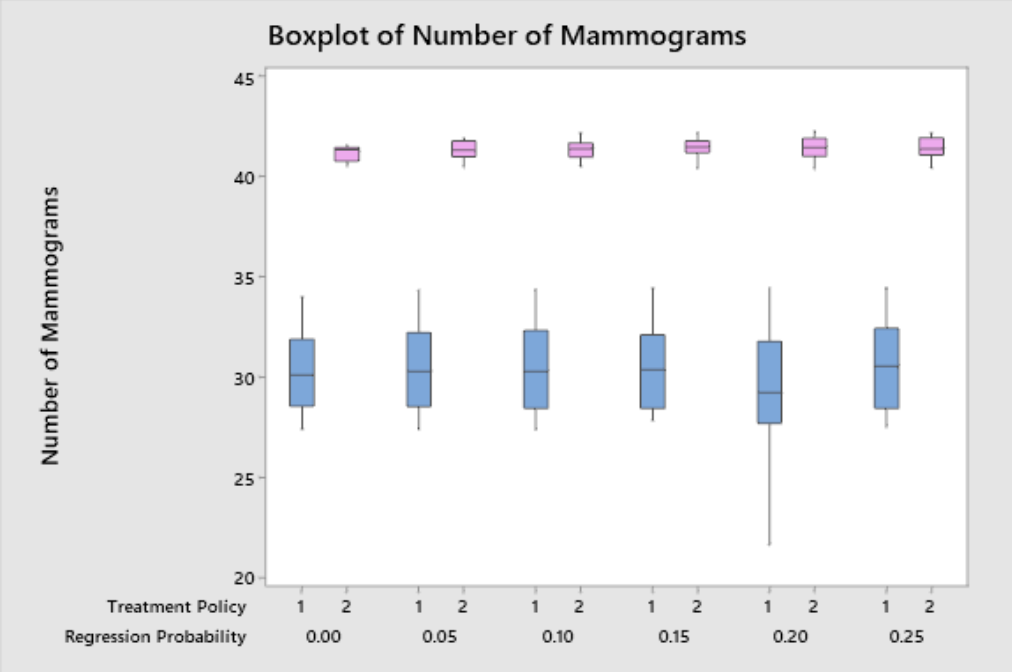

Figure 8: Boxplot of the average number of mammograms for each treatment policy and regression probability

In Figure 8, the mean number of mammograms across all Treatment Policy 1 boxplots do not show a discernable trend and appear to remain relatively consistent across all regression probabilities. The same holds for the mean number of mammograms across all Treatment

Policy 2 boxplots. The overall average number of mammograms for Treatment Policy 1 is 30.22, and, except for the 20% regression probability boxplot, the percent differences between the individual boxplot means and the overall mean are well under 1%. The overall average number of mammograms for Treatment Policy 2 is 41.33, and the percent difference between the individual boxplot means and the overall mean are also well under 1%. This supports the statement that regression probability does not have a statistically significant impact the number of mammograms.

There is, however, a large and consistent difference in the mean number of mammograms for patients who never develop breast cancer between Treatment Policy 1 and Treatment Policy 2 for each level of regression in Figure 8. On average, the mean number of mammograms for Treatment Policy 2 is 11.11 mammograms greater than the mean number of mammograms for Treatment Policy 1. This confirms that treatment policy does statistically impact the number of mammograms.

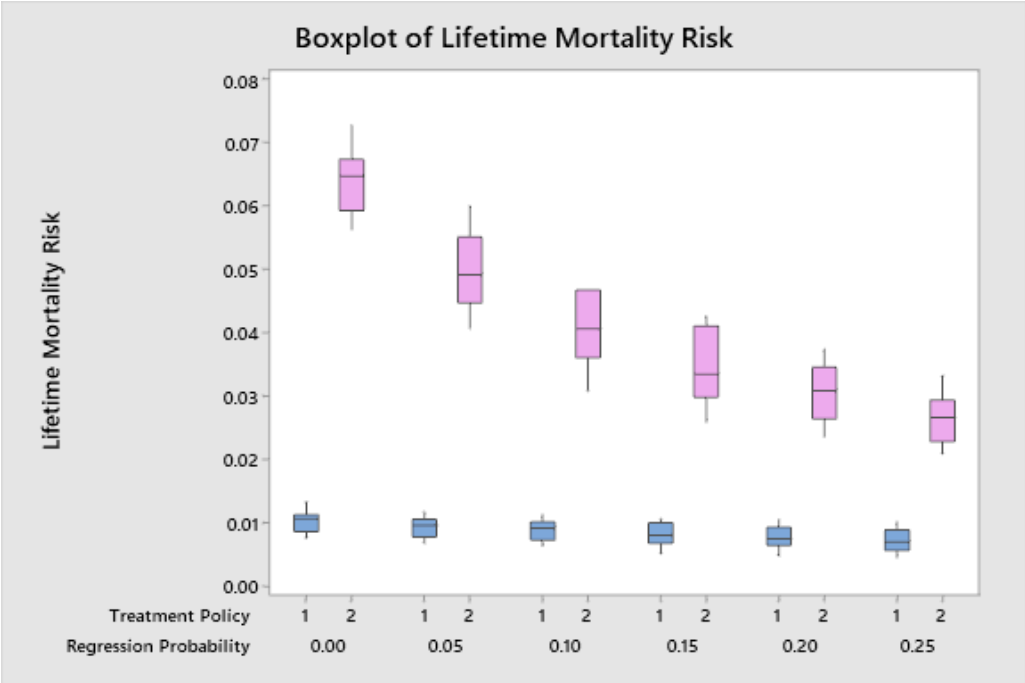

Figure 9: Boxplot of the average lifetime mortality risk for each treatment policy and regression probability

In Figure 9, the mean lifetime breast cancer mortality risk across all Treatment Policy 1 boxplots appears to decrease slightly as the regression probabilities increase along the x-axis. In fact, the average decrease in mean lifetime mortality risk is 0.06%. The mean lifetime mortality risk for the Treatment Policy 2 boxplots shows a definite negative trend as the regression probabilities increase. The trend appears to be exponential, and the average decrease in mean lifetime breast cancer mortality risk across all regression probabilities is 0.75%. The negative trends shown in Figure 9 support the statement that regression probability is a statistically significant factor for lifetime breast cancer mortality risk.

There is also a large and consistent difference in the mean lifetime breast cancer mortality risk between the Treatment Policy 1 and Treatment Policy 2 boxplots across all levels of regression. The difference between treatment policies also appears to be exponential since Treatment Policy 2 experiences more of a dramatic decrease, but on average, the mean lifetime mortality risk of Treatment Policy 2 is 3.23% greater than Treatment Policy 1. This supports that treatment policy has a statistically significant impact on patient lifetime breast cancer mortality risk.

4. Discussion and Conclusion

From a model verification standpoint, it makes sense that both the number of mammograms for patients who never develop breast cancer and the lifetime breast cancer mortality risk would increase with the transition from Treatment Policy 1 to Treatment Policy 2. On average, patients adhering to Treatment Policy 2 would stay in the model longer to monitor their health state and wait to begin treatment until invasive cancer has been detected. While they are waiting for invasive cancer to be detected, the patients would continue to go for mammogram screenings and have an increased lifetime breast cancer mortality risk, as they continue to live with non-invasive cancer. The statistical significance of the treatment policy results indicates that the decision to wait to treat breast cancer is critical to patient outcome.

It was interesting to learn that regression probability was not a statistically significant factor with respect to the average number of mammograms. It was expected to be statistically significant under the assumption that as disease regression increased, patient time in the system would experience an increase and that the number of mammograms would increase accordingly. However, perhaps because the regression probabilities were relatively low, 0-25%, occurrence rates were not high enough to significantly increase the amount of time that patients spent in the system.

It was expected that regression probability would be a statistically significant factor for lifetime breast cancer mortality risk, and the results of this research confirmed this hypothesis. It makes sense that as regression probability increases, the number of patients who progress from non-invasive cancer to invasive cancer and who ultimately die from cancer would decrease, therefore lowering overall lifetime breast cancer mortality risk. The partial statistical significance of the regression probability results indicates that the assumed value for the probability of disease regression (or overdiagnosis risk) is only critical to the lifetime breast cancer mortality risk component of patient outcome.

This research established a simulation approach to examine the relationship between breast cancer overdiagnosis and patient outcome. Overdiagnosis was represented in the model using a set of disease regression probabilities, and patient outcome was measured in terms of

the average number of mammograms and the lifetime breast cancer mortality risk per patient. This model limits its evaluation to consider one breast cancer screening policy, which prescribes annual mammograms beginning at age 40, and two treatment policies, the first of which prescribes treatment of all cancer (non-invasive and invasive) and the second of which restricts treatment to cases of invasive cancer.

The results of this research contribute to understanding the impact that the range of breast cancer overdiagnosis rate estimates in the current literature have on patient outcomes. Understanding overdiagnosis risk will help inform screening recommendations, help develop more personalized treatment plans, reduce overtreatment, and reduce unnecessary healthcare costs. To gain further understanding of the relationship between overdiagnosis and patient outcome, we recommend that future studies investigate more treatment and screening policies. The simulation model developed in this research can be easily modified to incorporate more dynamic screening and treatment policies. The methodology in this research can also be supplemented to explore the relationship between overdiagnosis and other factors, and it can even be applied to examine overdiagnosis with other diseases.

References

American Cancer Society (2019) About and key statistics [PDF file]. Retrieved September 8, 2019 from https://www.cancer.org/content/dam/CRC/PDF/Public/8577.00.pdf

American Cancer Society (2019). American Cancer Society Recommendations for the Early Detection of Breast Cancer. Retrieved October 8, 2019 from https://www.cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/american-cancer-society-recommendations-for-the-early-detection-of-breast-cancer.html

American Cancer Society (2005). Breast Cancer Facts and Figures 2005-2006 [PDF file]. Retrieved March 27, 2020 from https://www.cancer.org/research/cancer-facts-statistics/breast-cancer-facts-figures.html

Brailsford, S., Harper, P., Sykes, J. (2012). Incorporating human behaviour in simulation models of screening for breast cancer. *European Journal for Operational Research,* 219(2), 491-507.

Cancer Treatment Centers of America (2020). Breast Cancer Stages. Retrieved March 23, 2020 from https://www.cancercenter.com/cancer-types/breast-cancer/stages

Cassady, C., Nachlas, J. (2008). *Probability Models in Operations Research*, 1, 137-156.

Davies, R., Davies, H., (1994). Modelling patient flows and resource provision in health systems. *Omega*, 22, 123-131.

Duffy, S. W., Chen, H. H., Tabar, L., & Day, N. E. (1995). Estimation of mean sojourn time in breast cancer screening using a Markov chain model of both entry to and exit from the preclinical detectable phase. *Statistics in medicine*, *14*(14), 1531-1543.

Lymer, S., Brown, Laurie (2012). Developing a Dynamic Microsimulation Model of the Australian Health System: A Means to Explore Impacts of Obesity over the Next 50 Years. *Epidemiology Research International*, 2012(132392), 1-13. https://www.hindawi.com/journals/eri/2012/132392/

Madadi, M., Heydari, M., Zhang, S., Pohl, E., Rainwater, C., & Williams, D. L. (2018). Analyzing overdiagnosis risk in cancer screening: A case of screening mammography for breast cancer. *IISE Transactions on Healthcare Systems Engineering*, *8*(1), 2-20.

Madadi, M., Zhang, S., Henderson, L. M. (2015). Evaluation of breast cancer mammography screening policies considering adherence behavior. *European Journal of Operational Research*, 247(2), 630-640.

Maillart, L., Ivy, J., Ransom, S., Diehl, K. (2008). Assessing Dynamic Breast Cancer Screening Policies. *Operations Research,* 56(6):1411-1427.

Martin, L., J. (2019, February 27). *Invasive Ductal Carcinoma (IDC) & Ductal Carcinoma In Situ (DCIS).* Retrieved from https://www.webmd.com/breast-cancer/ductal-carcinoma-invasive-in-situ#1

Ross, S. M. (2014). *Introduction to probability models*. Academic press.

Seigneurin, A., François, O., Labarère, J., Oudeville, P., Monlong, J., & Colonna, M. (2011). Overdiagnosis from non-progressive cancer detected by screening mammography: stochastic simulation study with calibration to population based registry data. *Bmj*, *343*, d7017.

Tabár, L., Vitak, B., Chen, H. H., Duffy, S. W., Yen, M. F., Chiang, C. F., ... & Smith, R. A. (2000). The Swedish Two-County Trial twenty years later: updated mortality results and new insights from long-term follow-up. *Radiologic Clinics of North America*, *38*(4), 625-651.

Welch, H. G., & Black, W. C. (2010). Overdiagnosis in cancer. Journal of the National Cancer Institute, 102(9), 605-613.

Zackrisson, S., Andersson, I., Janzon, L., Manjer, J., & Garne, J. P. (2006). Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study. Bmj, 332(7543), 689-692.

Zahl P, Andersen JM, Mæhlen J. Spontaneous Regression of Cancerous Tumors Detected by Mammography Screening. *JAMA.* 2004;292(21):2579–2580. doi:10.1001/jama.292.21.2579

Zhang, S., & Ivy, J. S. (2012). Analytic modeling of breast cancer spontaneous regression. *IIE Annual Conference.Proceedings,* , 1-6. Retrieved from https://search.proquest.com/docview/1151086484?accountid=8361

Appendix

α : age group of the patient

P_α : one-step transition matrix representing the transition of patient age α from current health state i to health state j (i, j ϵ [1,5])

a_α : sensitivity of mammogram

r_α : patient lifetime mortality risk for health state j = 1, 2

Table I: Markov process parameter estimates by age, from Maillart et al. (2008)

$\alpha \in [25, 29]$

$$p_\alpha = \begin{pmatrix} 0.99970 & 0.000038010 & 0 & 0 & 0.00026405 \\ 0 & 0.79140 & 0.20833 & 0 & 0.00026405 \\ 0 & 0 & 0.85369 & 0.14604 & 0.00026405 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.078156 \quad 0.75033 \quad 0.81860] \quad r_\alpha = [0.21734 \quad 0.53185]$

$\alpha \in [30, 34]$

$$P_\alpha = \begin{pmatrix} 0.99952 & 0.00013403 & 0 & 0 & 0.00034808 \\ 0 & 0.79132 & 0.20833 & 0 & 0.00034808 \\ 0 & 0 & 0.85369 & 0.14596 & 0.00034808 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.078156 \quad 0.75033 \quad 0.81860] \quad r_\alpha = [0.21734 \quad 0.53185]$

$\alpha \in [35, 39]$

$$P_\alpha = \begin{pmatrix} 0.99915 & 0.00030863 & 0 & 0 & 0.00053717 \\ 0 & 0.79113 & 0.20833 & 0 & 0.00053717 \\ 0 & 0 & 0.85370 & 0.14577 & 0.00053717 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.078156 \quad 0.75033 \quad 0.81860] \quad r_\alpha = [0.21734 \quad 0.53185]$

$\alpha \in [40, 44]$

$$P_\alpha = \begin{pmatrix} 0.99858 & 0.00060193 & 0 & 0 & 0.00081799 \\ 0 & 0.79085 & 0.20833 & 0 & 0.00081799 \\ 0 & 0 & 0.87870 & 0.12048 & 0.00081799 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.078156 \quad 0.75033 \quad 0.81860] \quad r_\alpha = [0.21734 \quad 0.53185]$

$\alpha \in [45, 49]$

$$P_\alpha = \begin{pmatrix} 0.99784 & 0.00097505 & 0 & 0 & 0.0011804 \\ 0 & 0.79049 & 0.20833 & 0 & 0.0011804 \\ 0 & 0 & 0.87870 & 0.12011 & 0.0011804 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.078156 \quad 0.75033 \quad 0.81860] \quad r_\alpha = [0.21734 \quad 0.53185]$

$\alpha \in [50, 54]$

$$P_\alpha = \begin{pmatrix} 0.99703 & 0.0012814 & 0 & 0 & 0.0016911 \\ 0 & 0.86317 & 0.13514 & 0 & 0.0016911 \\ 0 & 0 & 0.85732 & 0.14099 & 0.0016911 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.073921 \quad 0.85449 \quad 0.93224] \quad r_\alpha = [0.21228 \quad 0.54090]$

$\alpha \in [55, 59]$

$$P_\alpha = \begin{pmatrix} 0.99563 & 0.0016822 & 0 & 0 & 0.0026897 \\ 0 & 0.86218 & 0.13514 & 0 & 0.0026897 \\ 0 & 0 & 0.85732 & 0.13999 & 0.0026897 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.073921 \quad 0.85449 \quad 0.93224] \quad r_\alpha = [0.21228 \quad 0.54090]$

$\alpha \in [60, 64]$

$$P_\alpha = \begin{pmatrix} 0.99371 & 0.0019797 & 0 & 0 & 0.0043137 \\ 0 & 0.87664 & 0.11905 & 0 & 0.0043137 \\ 0 & 0 & 0.89090 & 0.10479 & 0.0043137 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.052669 \quad 0.85449 \quad 0.93224] \quad r_\alpha = [0.18063 \quad 0.50227]$

Table I: Continued

$\alpha \in [65, 69]$

$$P_\alpha = \begin{pmatrix} 0.99086 & 0.0022136 & 0 & 0 & 0.0069270 \\ 0 & 0.87402 & 0.11905 & 0 & 0.0069270 \\ 0 & 0 & 0.89090 & 0.10217 & 0.0069270 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.052669 \quad 0.85449 \quad 0.93224] \quad r_\alpha = [0.18063 \quad 0.50227]$

$\alpha \in [70, 74]$

$$P_\alpha = \begin{pmatrix} 0.98656 & 0.0023770 & 0 & 0 & 0.011064 \\ 0 & 0.86394 & 0.12500 & 0 & 0.011064 \\ 0 & 0 & 0.86253 & 0.12641 & 0.011064 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.044040 \quad 0.85449 \quad 0.93224] \quad r_\alpha = [0.14048 \quad 0.41010$

$\alpha \in [75, 79]$

$$P_\alpha = \begin{pmatrix} 0.97945 & 0.0025088 & 0 & 0 & 0.018045 \\ 0 & 0.85695 & 0.12500 & 0 & 0.018045 \\ 0 & 0 & 0.86253 & 0.11942 & 0.018045 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.044040 \quad 0.85449 \quad 0.93224] \quad r_\alpha = [0.14048 \quad 0.41010]$

$\alpha \in [80, 84]$

$$P_\alpha = \begin{pmatrix} 0.96702 & 0.0023996 & 0 & 0 & 0.030581 \\ 0 & 0.84442 & 0.12500 & 0 & 0.030581 \\ 0 & 0 & 0.86253 & 0.10689 & 0.030581 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.044040 \quad 0.85449 \quad 0.93224] \quad r_\alpha = [0.14048 \quad 0.41010]$

$\alpha \in [85, 100]$

$$P_\alpha = \begin{pmatrix} 0.92519 & 0.0020751 & 0 & 0 & 0.072740 \\ 0 & 0.80226 & 0.12500 & 0 & 0.072740 \\ 0 & 0 & 0.86253 & 0.064729 & 0.072740 \\ 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$a_\alpha = [0.044040 \quad 0.85449 \quad 0.93224] \quad r_\alpha = [0.14048 \quad 0.41010]$

Table II: Summary of all replications of the numerical experiment used for sensitivity analysis

	Treatment Policy 1				Treatment Policy 2			
	0% regression probability				0% regression probability			
	Num Mamm	± h.w.	r_α	± h.w.	**Num Mamm**	± h.w.	r_α	± h.w.
Rep. 1	31.68	insufficient	0.85%	0.45%	41.33	0.8863	5.95%	1.34%
Rep. 2	32.51	insufficient	1.06%	0.44%	41.52	0.6608	6.49%	1.11%
Rep. 3	34.00	insufficient	1.17%	0.48%	41.54	0.8681	7.26%	1.35%
Rep. 4	29.35	insufficient	1.33%	0.45%	40.63	0.8308	6.67%	1.51%
Rep. 5	27.40	insufficient	0.92%	0.40%	40.81	0.8310	5.64%	1.07%
Rep. 6	30.86	insufficient	0.87%	0.42%	41.41	0.9820	6.32%	1.06%
Rep. 7	31.28	insufficient	1.12%	0.49%	41.32	0.7077	5.87%	1.08%
Rep. 8	29.01	insufficient	1.09%	0.48%	41.39	1.0076	6.81%	1.06%
Rep. 9	28.16	insufficient	0.77%	0.48%	41.05	0.8623	6.45%	1.24%
Rep. 10	28.69	insufficient	1.07%	0.53%	40.53	0.9756	6.71%	1.03%
	5% regression probability				5% regression probability			
	Num Mamm	± h.w.	r_α	± h.w.	**Num Mamm**	± h.w.	r_α	± h.w.
Rep. 1	32.11	insufficient	0.76%	0.37%	41.28	0.8197	4.90%	1.07%
Rep. 2	32.56	insufficient	0.95%	0.41%	41.67	0.7503	4.95%	correlated
Rep. 3	34.32	insufficient	1.16%	0.48%	41.89	0.8181	5.66%	1.17%
Rep. 4	29.46	insufficient	1.17%	0.41%	40.63	0.9255	4.58%	1.33%
Rep. 5	27.40	insufficient	0.87%	0.39%	41.08	0.6971	4.07%	1.06%
Rep. 6	31.11	insufficient	0.78%	0.39%	41.32	0.8597	4.61%	0.88%
Rep. 7	31.28	insufficient	1.00%	0.46%	41.74	0.6723	4.15%	0.84%
Rep. 8	28.65	insufficient	1.03%	0.46%	41.87	0.8127	5.99%	1.11%
Rep. 9	28.16	insufficient	0.69%	0.37%	41.13	0.8589	4.93%	1.09%
Rep. 10	28.68	insufficient	0.98%	0.53%	40.46	0.9956	5.46%	1.09%
	10% regression probability				10% regression probability			
	Num Mamm	± h.w.	r_α	± h.w.	**Num Mamm**	± h.w.	r_α	± h.w.
Rep. 1	32.26	insufficient	0.65%	0.33%	41.29	1.0219	4.02%	1.00%
Rep. 2	32.56	insufficient	0.94%	correlated	41.46	0.6404	3.84%	1.05%
Rep. 3	34.37	insufficient	1.11%	0.47%	41.76	0.8681	4.68%	1.19%
Rep. 4	29.56	insufficient	1.11%	0.39%	40.51	0.9333	4.11%	1.13%
Rep. 5	27.40	insufficient	0.87%	0.39%	41.24	0.8197	3.09%	0.91%
Rep. 6	31.00	insufficient	0.75%	0.40%	41.47	1.0450	3.62%	0.79%
Rep. 7	31.28	insufficient	0.91%	0.44%	41.62	0.8114	3.57%	0.77%
Rep. 8	28.54	insufficient	0.99%	0.45%	42.15	0.7325	4.67%	1.03%
Rep. 9	28.16	insufficient	0.67%	0.36%	41.08	0.8406	4.11%	1.01%
Rep. 10	28.68	insufficient	0.98%	0.53%	40.54	1.0150	4.69%	0.87%

Table II: Continued

	Treatment Policy 1				Treatment Policy 2			
	15% regression probability				**15% regression probability**			
	Num Mamm	± h.w.	r_α	± h.w.	**Num Mamm**	± h.w.	r_α	± h.w.
Rep. 1	32.00	insufficient	0.53%	0.26%	41.38	1.0000	3.43%	0.92%
Rep. 2	32.45	insufficient	0.87%	0.42%	41.53	0.7915	3.19%	0.86%
Rep. 3	34.44	insufficient	1.03%	0.46%	41.75	0.9246	4.25%	1.20%
Rep. 4	29.76	insufficient	1.06%	0.36%	40.68	0.9612	3.71%	1.02%
Rep. 5	27.83	insufficient	0.74%	0.26%	41.36	0.9449	2.61%	0.77%
Rep. 6	31.00	insufficient	0.70%	0.40%	41.63	0.9273	2.99%	0.74%
Rep. 7	31.28	insufficient	0.71%	0.30%	41.86	0.8159	2.96%	0.76%
Rep. 8	28.53	insufficient	0.99%	0.46%	42.17	0.6660	4.17%	1.21%
Rep. 9	28.16	insufficient	0.62%	0.32%	41.33	0.8973	3.26%	0.90%
Rep. 10	28.68	insufficient	0.96%	0.53%	40.41	0.9792	4.08%	0.84%
	20% regression probability				**20% regression probability**			
	Num Mamm	± h.w.	r_α	± h.w.	**Num Mamm**	± h.w.	r_α	± h.w.
Rep. 1	32.90	insufficient	0.49%	0.22%	41.39	1.0220	3.25%	0.78%
Rep. 2	21.66	insufficient	0.90%	0.43%	41.46	0.6935	2.92%	0.76%
Rep. 3	34.44	insufficient	1.03%	0.46%	42.01	1.0470	3.45%	0.92%
Rep. 4	29.76	insufficient	1.04%	0.36%	40.54	1.0990	3.29%	1.19%
Rep. 5	27.83	insufficient	0.71%	0.26%	41.16	0.8990	2.37%	0.74%
Rep. 6	31.10	insufficient	0.69%	0.40%	41.63	0.8605	2.62%	0.62%
Rep. 7	31.41	insufficient	0.69%	0.30%	41.87	0.7936	2.65%	0.74%
Rep. 8	28.54	insufficient	0.79%	0.36%	42.26	0.6309	3.73%	1.02%
Rep. 9	27.26	insufficient	0.52%	0.30%	41.40	0.8371	2.68%	0.85%
Rep. 10	28.68	insufficient	0.83%	0.52%	40.38	0.8629	3.47%	0.93%
	25% regression probability				**25% regression probability**			
	Num Mamm	± h.w.	r_α	± h.w.	**Num Mamm**	± h.w.	r_α	± h.w.
Rep. 1	32.97	insufficient	0.47%	0.20%	41.22	1.0400	2.86%	0.83%
Rep. 2	32.25	insufficient	0.86%	0.43%	41.52	0.7545	2.63%	0.73%
Rep. 3	34.44	insufficient	1.01%	0.46%	41.99	0.9171	2.81%	0.75%
Rep. 4	29.98	insufficient	1.00%	0.35%	40.67	1.1390	2.70%	0.98%
Rep. 5	28.09	insufficient	0.65%	0.24%	41.21	0.7920	2.10%	0.74%
Rep. 6	31.10	insufficient	0.59%	0.34%	41.68	0.8163	2.22%	0.65%
Rep. 7	31.52	insufficient	0.67%	0.29%	41.90	0.7769	2.44%	0.71%
Rep. 8	28.54	insufficient	0.79%	0.36%	42.15	0.7007	3.32%	0.75%
Rep. 9	27.53	insufficient	0.50%	0.30%	41.24	0.8699	2.30%	0.73%
Rep. 10	28.68	insufficient	0.74%	0.48%	40.43	0.7302	3.18%	0.86%

Figure I: Minitab® output for the sensitivity analysis

General Linear Model: Number of Mammograms versus Treatment Policy, Regression Rate

Method

Factor coding (-1, 0, +1)

Factor Information

Factor	Type	Levels	Values
Treatment Policy	Fixed	2	1, 2
Regression Rate	Fixed	6	0.00, 0.05, 0.10, 0.15, 0.20, 0.25

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Treatment Policy	1	3703.35	3703.35	1179.79	0.000
Regression Rate	5	4.32	0.86	0.28	0.926
Error	113	354.71	3.14		
Lack-of-Fit	5	5.37	1.07	0.33	0.893
Pure Error	108	349.34	3.23		
Total	119	4062.38			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
1.77172	91.27%	90.80%	90.15%

Coefficients

Term	Coef	SE Coef	T-Value	P-Value	VIF
Constant	35.777	0.162	221.21	0.000	
Treatment Policy					
1	-5.555	0.162	-34.35	0.000	1.00
Regression Rate					
0.00	-0.053	0.362	-0.15	0.883	1.67
0.05	0.063	0.362	0.17	0.862	1.67
0.10	0.069	0.362	0.19	0.848	1.67
0.15	0.135	0.362	0.37	0.710	1.67
0.20	-0.393	0.362	-1.09	0.280	1.67

Regression Equation

Number of Mammograms = 35.777 - 5.555 Treatment Policy_1 + 5.555 Treatment Policy_2
- 0.053 Regression Rate_0.00 + 0.063 Regression Rate_0.05
+ 0.069 Regression Rate_0.10 + 0.135 Regression Rate_0.15
- 0.393 Regression Rate_0.20 + 0.179 Regression Rate_0.25

Fits and Diagnostics for Unusual Observations

Obs	Number of Mammograms	Fit	Resid	Std Resid
3	34.000	30.168	3.832	2.23 R
23	34.320	30.285	4.035	2.35 R
43	34.370	30.291	4.079	2.37 R
63	34.440	30.356	4.084	2.38 R
82	21.660	29.829	-8.169	-4.75 R
83	34.440	29.829	4.611	2.68 R
103	34.440	30.400	4.040	2.35 R

R Large residual

Figure I: Continued

General Linear Model: Lifetime Mortality Risk versus Treatment Policy, Regression Rate

Method

Factor coding (-1, 0, +1)

Factor Information

Factor	Type	Levels	Values
Treatment Policy	Fixed	2	1, 2
Regression Rate	Fixed	6	0.00, 0.05, 0.10, 0.15, 0.20, 0.25

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Treatment Policy	1	0.031284	0.031284	618.09	0.000
Regression Rate	5	0.005629	0.001126	22.24	0.000
Error	113	0.005719	0.000051		
Lack-of-Fit	5	0.004106	0.000821	54.95	0.000
Pure Error	108	0.001614	0.000015		
Total	119	0.042632			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
0.0071143	86.58%	85.87%	84.87%

Coefficients

Term	Coef	SE Coef	T-Value	P-Value	VIF
Constant	0.024769	0.000649	38.14	0.000	
Treatment Policy					
1	-0.016146	0.000649	-24.86	0.000	1.00
Regression Rate					
0.00	0.01244	0.00145	8.57	0.000	1.67
0.05	0.00457	0.00145	3.15	0.002	1.67
0.10	-0.00009	0.00145	-0.06	0.952	1.67
0.15	-0.00335	0.00145	-2.30	0.023	1.67
0.20	-0.00572	0.00145	-3.94	0.000	1.67

Regression Equation

Lifetime Mortality Risk = 0.024769 - 0.016146 Treatment Policy_1
+ 0.016146 Treatment Policy_2 + 0.01244 Regression Rate_0.00
+ 0.00457 Regression Rate_0.05 - 0.00009 Regression Rate_0.10
- 0.00335 Regression Rate_0.15 - 0.00572 Regression Rate_0.20
- 0.00786 Regression Rate_0.25

Fits and Diagnostics for Unusual Observations

Obs	Lifetime Mortality Risk	Fit	Resid	Std Resid	
13	0.07260	0.05336	0.01924	2.79	R
18	0.06810	0.05336	0.01474	2.14	R
38	0.05990	0.04549	0.01441	2.09	R

R Large residual