ABSTRACT

HASSANI GOODARZI, SHADI. Modeling Ductal Carcinoma in Situ Management. (Under the direction of Julie S. Ivy.)

Ductal Carcinoma In Situ (DCIS) is a type of non-invasive breast cancer starting in milk ducts. A DCIS tumor cannot spread to the vital organs before breaking through the duct, so it is not life threatening. Currently, almost all DCIS cases are treated to prevent them from becoming invasive. In this dissertation, we explored the management of DCIS when patients can opt for watchful waiting, i.e., taking more observations before treating, and only treating the DCIS when there is enough evidence suggesting DCIS cancer cells will become invasive breast cancer, and possibly metastasize.

In this dissertation the effect of taking observations was evaluated, on an individual patient level using a partially observable Markov decision process (POMDP) and on the population level using discrete event simulation. We used accelerated failure time models to perform survival analysis on the publicly available breast cancer data, SEER. We built the recurrence prediction models which were utilized in the simulation to model life after treatment for breast cancer patients and to calculate quality adjusted life years, probability of death, and the effect of treatment on a patient's life.

The results showed average quality adjusted life years for DCIS patients undergoing active surveillance is not significantly different from those who treat their cancer immediately after diagnosis. This suggests that active surveillance can be a viable option particularly for patients with low risk DCIS, such as an older patient with low grade DCIS. However, more data, possibly from clinical trials with active surveillance on DCIS, is needed to identify optimal survival strategies.

Modeling Ductal Carcinoma in Situ Management

by
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DEDICATION

To my parents, my grandma, and my dear friend Diana.

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I would like to thank my dear advisor, Dr. Julie Ivy, for introducing me to health care engineering, her feedback on my work and inspiring me every step of the way. She helped me grow, taught me to be persistent and not to give up; for that I am eternally thankful.

I am very grateful to my research committee, Dr. Wilson, Dr. Mayorga, and Dr King, who with their feedbacks and questions guided the enhancement of this research.

I am truly indebted to my parents, with their love and patience encouraged me all through my life to be a better version of myself. I owe everything to them and their support.

My dear Alex for his kindness, positivity, being there for me and for inspiring me to dream.

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INTRODUCTION

1.1 Background and Motivation

According to Centers for Disease Control and Prevention (CDC), cancer is the second leading cause of death in the United States [1]. Cancer was known to man since ancient times [2], but it was not until about 140 years ago that current definition of cancer, based on findings of German scientist Rudolph Virchow (1821-1902), started to take shape [3]. Virchow defined cancer as: “Cancer is a genetic disease, arising from an accumulation of mutations that promote clonal selection of cells with increasingly aggressive behavior” [4].

The word cancer includes a range of disorders, from those that are lethal if left untreated (or even if treated) to indolent lesions with low potential for distant progression and mortality [5]. It is usually assumed that cancer progresses in a linear and orderly fashion from early stages to local, regional and distant stages and eventually results in death of the patient. Based on this assumption, it is believed that detecting cancer in its early stages would reduce cancer deaths significantly in the population. Consequently, population cancer screening was started for the purpose of finding cancer before it progresses and causes death. However, for some cancers such as breast cancer, screening has not had the expected effect on mortality or the incidence of regional cancers. It seems that by screening we are also finding slow-growing cancers that might not have harmed the patient if not detected and treated. In other words, we are overdiagnosing some breast cancer cases [6]. This finding has resulted in researchers studying the attributes of the disease, types, and possible pathways for different types of breast cancer to determine which cases have a higher chance of being overdiagnosed

1.2 Breast Cancer

Breast cancer, defined as the abnormal growth of cells in breast tissue, is the second most common cancer among women after skin cancer and the second leading cause of cancer deaths in women, second only to lung cancer [7]. More than 99% of breast cancer cases are diagnosed in women [8]. The American Cancer Society (ACS) estimated in 2017 in the United States, there would be approximately 252,710 new cases of invasive breast cancer, and 63,410 new cases of carcinoma in situ (CIS-non-invasive form of breast cancer) diagnosed in women and about 40,610 women would die from the disease [9].

Breast cancers are classified based on the histological type of cancer cells (microscopic anatomy). Most breast cancers are carcinomas. Cancers with carcinoma type start in epithelial cells which line different organs and tissues like milk ducts in the breast. Breast tumors can be a combination of carcinoma and invasive or in-situ cancer (in-situ cancers are confined to one place) or be a mixture of both, i.e., invasive carcinoma and carcinoma in situ can exist at the same time as well [10]. Two of the most common types of breast cancer are invasive ductal carcinoma and ductal carcinoma in situ (DCIS).

Invasive (or Infiltrating) Ductal Carcinoma

About eight in ten of invasive breast cancers are invasive ductal carcinoma. This type of breast cancer starts in the milk duct, cancer cells break through the duct, invade the surrounding breast tissues, and become invasive. Invasive cancer cells can spread to vital organs via blood vessels or the lymph system and metastasize [10]. In this dissertation, we use the general term invasive breast cancer (IBC) to refer to invasive ductal carcinoma.

Ductal Carcinoma in Situ (DCIS)

DCIS is a type of non-invasive, nonobligatory precursor to IBC. DCIS starts in milk ducts when epithelial cells, lining the inner part of the duct, go through abnormal changes and start to proliferate, but remain confined to the duct. The incidence of DCIS increased from 4.8 per 100,000 to 34.6 per 100,000 from 1980 to 2007, which parallels the introduction of mammography screening [11]. One reason for this increase is that mammography, using low-dose x-ray imaging, is able to detect DCIS before it becomes clinically symptomatic (e.g., a palpable mass) [12]. If a mammogram diagnoses a DCIS that would not have become symptomatic during a patient's lifetime, an overdiagnosis has happened. Currently, about one in five cases of breast cancer found by mammography are DCIS. According to the ACS, of the 60,290 new cases of breast carcinoma in situ found in 2015, 83% were DCIS [13].

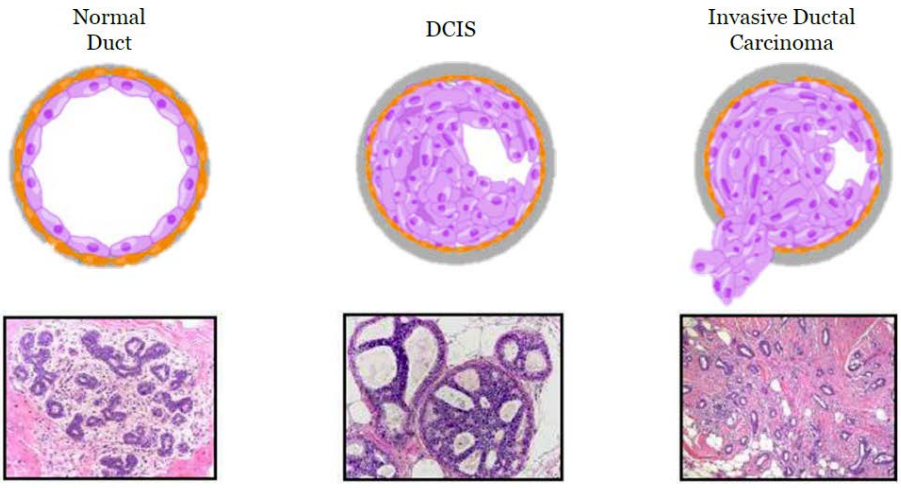

Figure 1.1 Evolution of DCIS from a normal duct to invasive cancer— Schematic cross sections of the duct are shown on the top row and the corresponding microscopic images are shown on the bottom row [14] [15].

The main difference between DCIS and IBC is that in DCIS, cancer cells have not yet spread to the surrounding breast tissue, and therefore cannot metastasize to other vital organs. However, it is still possible for cancer cells to break through the duct, become invasive and therefore become life-threatening. The evolution from a duct with normal cells to IBC is shown in Figure 1.1. Currently, there is not a definitive way to identify which DCIS cases will become invasive, so almost all cases are treated with surgery. Radiation and/or an endocrine therapy such as Tamoxifen are sometimes added to the treatment. Many believe this has led to inability to distinguish DCIS cases and consequent treatment of all DCIS overtreatment since DCIS would not have harmed the patient if left untreated [10].

In the breast cancer literature, parallel and linear pathways have been suggested to describe the relationship between DCIS and IBC. In a linear pathway, DCIS is a direct precursor to IBC, therefore treating DCIS can prevent later IBC [15]. In a parallel pathway, DCIS and IBC have a common progenitor but they progress independently from each other, therefore treating DCIS does not affect on IBC prevention and it would be overtreatment [16]. Currently it is not known which pathway best describes the biological relationship between DCIS and IBC, but there is evidence of overdiagnosis and overtreatment. So it seems if there are two DCIS progression pathways possible, some of DCIS cases may follow a linear pathway and others follow a parallel pathway. Next, we discuss some of the evidence presented in the literature on overdiagnosis and overtreatment.

Overdiagnosis and Overtreatment

Mammography has the potential to reduce breast cancer deaths by diagnosing breast cancer in its early stages. However, there is a higher probability that a mammogram will

identify cases with slow-growing tumors compared to no screening. These tumors might not become clinically symptomatic or life-threatening during a patient's lifetime. While it is estimated that up to 10 breast cancer deaths per 1000 women aged 50-74 can be avoided by annual screening, up to 68 breast cancers per 1000 women are overdiagnosed [1]. The Independent UK Panel on Breast Cancer Screening estimated for every breast cancer death prevented, about three overdiagnosed cases will be identified and hence overtreated because of mammography screening [17].

Overdiagnosis is usually defined as the detection of breast cancer, via screening, that would not have become symptomatic during a patient's lifetime if no screening had occurred [18]. If we treat this overdiagnosed breast cancer it is called overtreatment, which only harms the patient. In addition to the anxiety caused by the cancer diagnosis, different treatment methods have associated risks and costs, and decrease quality of life for patients. Fatigue and psychological burden continue to reduce the quality of life for some DCIS patients long after completing their treatment course [19]. Patients also still have to go through screening (mammogram screening and possibly a biopsy) after treatment completion because of the risk of recurrence. From a cost perspective, it is estimated that over a 10-year period, treatment and required screening for DCIS can cost up to $28,000 compared to $9,000 for screening alone for each patient. So if we overtreat a DCIS patient, we are spending $19,000 more, decreasing quality of life for that patient and not extending her lifetime nor preventing a later IBC [20].

Ozanne et al. [21] showed an almost seven-fold increase in the number of diagnosed DCIS cases since the introduction of screening, of which nearly all were treated, did not decrease the number of invasive breast cancer cases as anticipated. They concluded that either the baseline rate of IBC has been increasing or we have been overtreating some DCIS cases that were never going to become invasive. They simulated 25 years of screening with

different probabilities for the progression of DCIS to IBC. They concluded that although some data sources published prior to the introduction of mammogram screening suggest an increase in the baseline rate of IBC, the increase found is not close to the increase that would have been expected if the majority of DCIS cases were progressing to IBC. Bleyer and Welch [22] estimated that 31% of all breast cancers diagnosed in women 40 years or older in the United States were overdiagnosed during the period 1979-2008. Review of the body of evidence on overdiagnosis and overtreatment has prompted countries like the United Kingdom to start trials to look at the effect of active surveillance versus surgery in DCIS patients [23].

Some of the evidence about the percentage of DCIS cases that turn into IBC comes from the cases that were misdiagnosed as benign and were later followed as they became more severe. Erbas et al. [24] reviewed four of these cases. Sanders et al. [25] published the results of a 40-year follow-up of 45 low-grade DCIS cases in Nashville, TN, diagnosed from 1950 to 1989. They observed 16 progressions to IBC, 11 of which happened during the first 10 years after DCIS diagnosis.

Based on the current state of knowledge, it is not possible to say which DCIS is going to progress into IBC. This has motivated studies to identify genetic biomarkers that might improve the identification of DCIS aggressiveness and the estimation of the probability of DCIS turning into IBC. These studies are mostly conducted with a limited number of patients and information on follow-up is often not available, limiting the impact of their findings. Groen et al. [26] published a list of some of these biomarkers with a summary of the findings on each of them.

This dissertation explores the overdiagnosis of DCIS from an optimal treatment timing standpoint. In this dissertation, overdiagnosis is defined as the diagnosis of indolent cancer, i.e., the cancer that will not become invasive during a patient's lifetime; and if this

overdiagnosed cancer is treated, it is defined as overtreatment.

DCIS Overdiagnosis and Overtreatment Models

Most of the papers in the current literature focus on estimating rates of overdiagnosis in DCIS. These papers usually use the rare cases of untreated DCIS with simulation to estimate the expected rate of overdiagnosis in a population. In these papers, overdiagnosis is defined as cancer which will not become symptomatic if left unscreened. Yen et al. [27] used Markov processes with the Swedish Two-County Trial data and data from service screening programs in the UK, Netherlands, Australia and the USA to estimate the rate of non-invasive DCIS, i.e., DCIS that does not turn into invasive breast cancer in the patient's lifetime. They estimated 37% of DCIS cases to be non-progressive. Duffy et al. [28] used Markov chain Monte Carlo simulation on the Swedish Two-county Trial and the Gothenburg Trial to estimate overdiagnosis for breast cancer cases in the trials. They estimated that roughly 15% of DCIS cases found by screening might have been overdiagnosed. Seigneurin et al. [29] designed a stochastic simulation model to estimate the proportion of non-progressive breast cancers among all cases of IBC and DCIS detected during the period 1991-2006 in Isere, France. They estimated 31.9% of all cases of carcinoma in situ, detected with screening mammography, were overdiagnosed. De Gelder et al. [18] used the MISCAN (MIcro-simulation SCreening ANalysis) model to simulate the screening population in the Netherlands to show the effect of the denominator used to estimate what percentage of breast cancers are overdiagnosed. They showed that the percentage of overdiagnosis would be different if we are estimating the percentage of breast cancers at the screening age or older that are overdiagnosed compared to if we were estimating the percentage of breast cancers happening only at the screening age that are overdiagnosed. Depending on the

estimator used, the rate of overdiagnosis ranged from 2.8% to 9.7%. Gunsoy et al. [30] used simulation with Markovian states to estimate breast cancer overdiagnosis in the United Kingdom for women going through screening who were aged 40-49. They estimated a range of 0.5% to 2.9% overdiagnosis for all breast cancers detected via mammogram for this age group.

Ryser et al. [31] quantified the effect of no treatment for DCIS for sample patients. They computed 10-year disease-specific cumulative mortality for different ages with active surveillance (40, 50, 60, 70, and 80 years) using the natural history parameters from the literature. In their active surveillance, a diagnosed DCIS is not treated until it changes to invasive cancer. They showed the 10-year mortality gap between active surveillance and usual care (treating all DCIS cases) decreases substantially for older patients and when a lower IBC under-staging probability for mammograms was assumed. The IBC under-staging probability is defined as the probability of staging IBC as stage 0 (DCIS).

1.3 Problem Definition

In this dissertation, we seek to optimize DCIS treatment time to minimize the harms of overdiagnosis and the risk of later IBC. There are different approaches for managing a diagnosed DCIS. The most conservative approach is to treat all DCIS cases with surgery and possibly radiation or chemotherapy; this is the standard treatment which is followed by physicians unless the patient refuses to receive a treatment [32]. A less conservative approach is active surveillance, which is also called watchful waiting, i.e., not to treat DCIS after diagnosis, continue screening the patient, and only treat breast cancer when DCIS evolves to IBC [31]. Our approach is to find a strategy to treat DCIS when there is enough evidence to suggest the expected treatment benefits outweigh the risks and possible harms

thereof.

Considering the issue of overdiagnosis and because DCIS is not life-threatening, there is a question regarding the value of delaying treatment to allow for more observations to be taken with the goal of identifying the optimal treatment based on the patient's DCIS behavior.

We model the progression of DCIS diagnosis in the absence of treatment as a discrete Markov chain. The length of each time period in this Markov chain is assumed to be six months, which is the time physicians suggest for a follow-up mammogram to check for tumor changes, after seeing an abnormality that is not suggestive of cancer [33]. After six months, when a new observation is taken there might be a change in the tumor suggestive of its growth or there might be no change. These observations can shape the physician's belief about the pathway that DCIS is taking, i.e., whether it is the type that would evolve to IBC within the patient's lifetime (progressive DCIS: DCIS-P) or not (indolent DCIS: DCIS-I). We propose to identify the treatment threshold for this belief such that if the physician's belief about the progressiveness of DCIS is greater than the treatment threshold, then DCIS is treated. Otherwise another observation is taken in six months to update the physician's belief. We propose two approaches to study DCIS treatment policy: discrete event simulation and a partially observable Markov decision process (POMDP). The idea of using threshold for treatment decision comes from solving the POMDP model in Chapter 3 which was then implemented in a population simulation model.

In the population simulation model, patients are diagnosed with IBC and DCIS based on the US incidence rates. For each DCIS patient, we randomly assign the DCIS type to be progressive (DCIS-P) or non-progressive (DCIS-I). At each decision epoch, i.e., at the end of each 6-month period, an observation is taken from DCIS patients, we update our belief, and based on the defined threshold decide the treatment the patient should receive. The

expected quality-adjusted life years (QALYs) for each patient over their lifetime is used to evaluate different treatment strategies. The simulation model is used to calculate QALYs for patient groups, e.g., non-Hispanic African American 60-year-olds diagnosed with DCIS, as a function of their treatment.

1.4 Dissertation Organization

The content of the dissertation is as follows. In Chapter 2, we discuss breast cancer in more detail and introduce breast cancer terminology used in later chapters. In Chapter 3, we formulate the DCIS POMDP and present an illustrative example of optimal policies. In Chapter 4 we present the results from the Surveillance, Epidemiology, and End Results (SEER) data analysis and introduce a process of for developing recurrence prediction models (which are inputs for the simulation model) using survival analysis methods. Chapter 5 introduces the discrete event simulation model developed to evaluate DCIS treatment strategies in the U.S. female population using the solution structure for optimal treatment timing found in Chapter 3 and recurrence prediction models in Chapter 4.

CHAPTER

2

BREAST CANCER CONCEPTS

In this chapter, we introduce the concepts related to breast cancer including ductal carcinoma in situ (DCIS) and its progression. These breast cancer attributes are used in creating survival models for breast cancer to simulate disease progression over a patient's lifetime.

2.1 Anatomy

Breast

The breast is the tissue overlaying chest muscle. It consists of two major tissues: fat tissues, and glandular tissues, which carry milk in lactating women. Glandular tissues are organized into sections called lobes. Lobes contain smaller structures called lobules. Lobules are glands that can produce milk, the milk is carried out by a network of tubes called ducts. These milk ducts carry milk from lobules to the nipple in lactating women. Connective tissue, lymph nodes, lymph vessels, and blood vessels are also present in breast tissues [34].

Lymph System

The lymph system is part of the body's immune system. It is a network of lymph vessels and lymph nodes which collect fluid, waste material, and other things (such as viruses and bacteria) that are in the body tissues, outside the bloodstream. The clear fluid carried in lymph vessels is called lymph. Lymph vessels carry lymph fluid to lymph nodes which act as filters. The immune cells in lymph nodes can (i) fight infection by attacking germs in lymph fluid and destroying them; and (ii) try to filter cancer cells, both of which result in swollen lymph nodes. Swollen lymph nodes are often the earliest sign of the distant spread of cancer cells. Cancer may start in lymph nodes, but often cancer cells that are separated

from the tumor spread to other organs using lymph systems and blood vessels[35].

2.2 Cancer

Cancer is a general name given to more than 100 diseases. The common feature of all cancers is that they all start when abnormal cells, created by genetic mutation, grow out of control. If left untreated cancer might cause illness and death.

Cells can become cancerous because of changes to their deoxyribonucleic acid (DNA). Normal cells with damaged DNA either die or repair their DNA but cancer cells do not repair their DNA. Instead, they continue multiplying, producing more cancer cells containing the same damaged DNA. Individuals can have cells with damaged DNA inherited from their parents or the DNA of cells can be damaged because of something like smoking or tanning.

Cancer cells may accumulate and form a lump or collection of cells called tumors and invade nearby tissues. Most cancers form tumors, but not all tumors are cancerous. Benign, or noncancerous, tumors – such as freckles and moles – stop growing, do not spread to other parts of the body, and do not create new tumors. Malignant or cancerous, tumors crowd out healthy cells, interfere with body functions, and draw nutrients from body tissues. Cancer cells can spread through the body via blood vessels or the lymphatic system. The process is called metastasis.

Cancers are classified in two ways: by the type of tissue in which cancer originates (histological classification) or by the location or organ in the body where cancer first developed (primary site) [36].

Histological Types of Cancer

The major types of cancer are carcinoma, sarcoma, melanoma, lymphoma, and leukemia. Carcinomas – the most commonly diagnosed cancers (õ90% of all diagnosed cancers) – start in epithelial cells that line different organs and tissues. They can originate in the skin, lungs, breasts, pancreas, and other organs and glands. Lymphomas are cancers of white blood cells such as Hodgkin's disease. Leukemia is cancer that starts in blood-forming tissues such as bone marrow and does not usually form solid tumors. Sarcomas arise in bone, muscle, fat, or cartilage and are relatively uncommon. Melanomas are cancers that arise in the cells that make the pigment in skin [37].

2.3 Breast Cancer

Breast cancer usually starts in milk ducts or lobules. It can be invasive or non-invasive. In non-invasive breast cancer, cancer cells do not invade normal tissue within or outside the breast and are confined to the ductal-lobular system where they have first started growing. Non-invasive cancers are sometimes called in-situ ("in the same place") or pre-invasive. On the other hand, if cancer cells spread to normal cells within (other than the original tissue) or outside of the breast, cancer is considered to be invasive. In some cases, both invasive and non-invasive cancer can be seen at the same time. The treatment of breast cancer, in this case, will be based on the characteristics of the invasive cancer.

From the histological perspective, most breast cancers are carcinomas, that start in epithelial cells. Breast tumors can be a combination of carcinoma and invasive or in-situ cancer, in some rare cases, cancer cells might not form a tumor. Each type of breast cancer is classified further into subtypes based on its morphology, shape, and structure that can

be seen under a microscope [38].

Ductal Carcinoma in Situ (DCIS)

DCIS is the most common non-invasive or pre-invasive type of breast cancer which starts in the milk ducts when epithelial cells, lining the inside of the milk duct mutate to cancer cells. About one in five cases of breast cancers found on a mammogram, an X-ray image of the breast, are DCIS. Before the introduction of mammogram screening, DCIS constituted less than 5% of breast cancer cases[39].

DCIS was first described by Dr. Joseph Bloodgood about a century ago, but its natural history is still poorly understood [40]. In DCIS, cancer cells have not yet spread to the surrounding breast cells; therefore while they are confined to duct they cannot metastasize to other vital organs via blood vessels or lymph system. However, it is still likely that cancer cells break through the duct and become invasive. Once cancer cells are out of the duct, cancer is no longer considered DCIS and it is called invasive ductal carcinoma. Currently, there is not a definitive way to identify which DCIS cases are going to become invasive so almost all cases are treated in order to avoid later invasive breast cancer. Even after DCIS treatment, there is a chance for breast cancer recurrence. Approximately half of the breast cancer recurrence cases are invasive [39].

DCIS is classified into four major subcategories based on the cancer cells architecture (Figure 2.1):

1. Papillary: Cancer cells form finger-like patterns inside the duct. If smaller cells follow a papillary format, the DCIS is described as micropapillary.

2. Cribriform: There are gaps between cancer cells filling the duct with a Swiss cheese pattern.

3. Solid: Cancer cells completely fill the duct.

4. Comedo: When cancer cells fill the duct, some cancer cells that do not have access to nutrition die and form a plug of necrotic tissue.

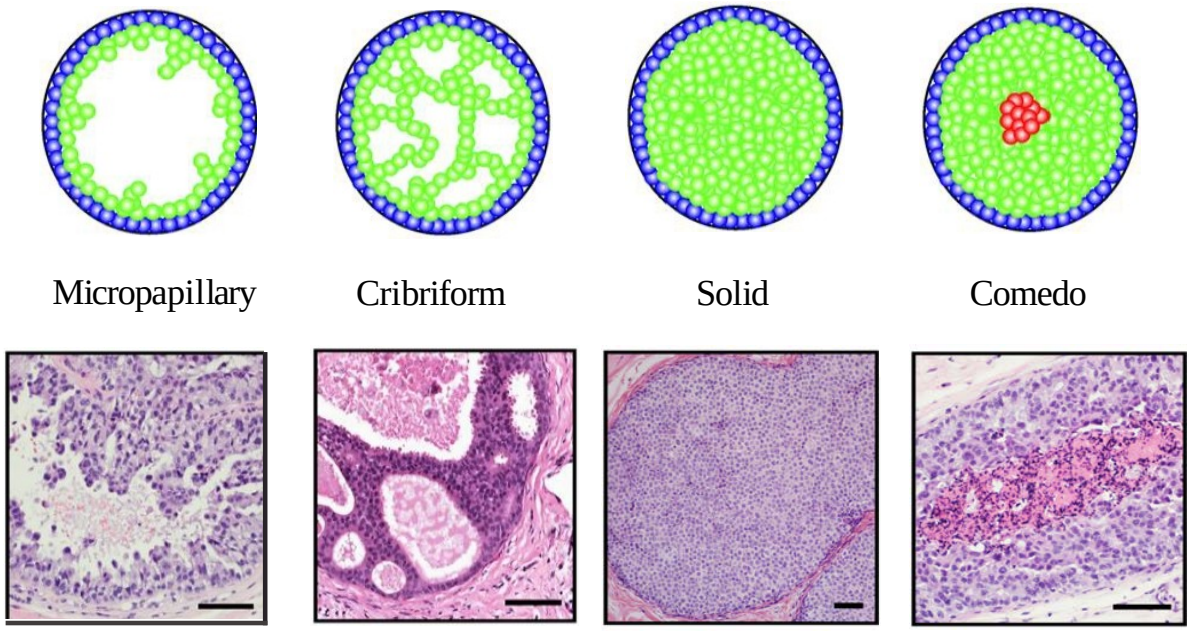

Figure 2.1 DCIS Morphologies: Schematic cross sections of the duct in each morphology are shown on the top row and the corresponding microscopic images are shown on the bottom row. [41]

The first three types of DCIS are commonly put together into a non-comedo group to be compared to comedo lesions. Comedo lesions tend to have more aggressive behavior compared to non-comedo lesions. Sometimes DCIS is accompanied by Lobular Carcinoma in Situ (LCIS), when cancer cells start growing in lobules, milk-producing glands, or invasive breast cancer [42] [43].

Invasive (or infiltrating) Ductal Carcinoma

About eight in ten invasive breast cancers are invasive ductal carcinoma (IDC), also called infiltrating ductal carcinoma. This type of breast cancer starts in the duct and occurs when cancer cells break through the duct and invade the surrounding breast tissues becoming invasive [10]. Over time these cancer cells can affect lymph nodes and spread to other organs.

2.4 Breast Cancer Screening

Breast cancer screening has been recommended by clinical guidelines published by the U.S. Preventive Services Task Force (USPSTF) [1] and American Cancer Society (ACS) [44] for patients and their health care providers to find breast cancers early before clinical symptoms (e.g., a palpable lump) appear. A mammogram is the most commonly used technique for breast cancer screening. Breast cancers found by a mammogram tend to be smaller and confined to the breast. Mammography is not perfect, although the cancers found using it are less likely to require aggressive treatments (e.g., mastectomy that requires removing the entire breast), there is a small chance (estimated to be between 0 to 10%) that some cancers are found that would not have caused any problems if not detected [45]. DCIS usually does not have clinical symptoms. Its diagnosis can be a combination of physical exam, mammogram and biopsy [46].

Physical Exam: If DCIS presents itself clinically, a lump can be felt during the physical exam, although DCIS physical presentation rarely happens. DCIS cases not found in the physical exam can often be found in a mammogram. DCIS also can have symptoms like breast pain or nipple discharge.

Mammogram: A mammogram is an X-ray image of the breast. Old DCIS cells die and create flecks of calcium called calcification or micro-calcification. Calcification appears as white specks or shadowy areas on a mammogram.

Biopsy: After DCIS is detected by a mammogram, a tissue sample is taken via biopsy from the affected area. A pathologist then analyzes the biopsy sample by a microscope to determine if breast cancer is present and the breast cancer characteristics such as grade and stage. The chance that a biopsy or surgery causes cancer to spread to other parts of the body is extremely low [38].

2.4.1 Breast Cancer Stage

Staging provides a means to measure how much cancer has advanced. Breast cancer is staged based on three major variables: the size of the tumor, lymph node involvement, and if the cancer has spread to other organs such as bones. The stage of cancer is usually expressed on a scale of 0,..., IV with Stage 0 describing non-invasive breast cancer and Stage IV describing breast cancer that has metastasized to other organs. The breast cancer stages are defined as follows:

- In situ: Breast cancer is present only in the layer of cells in which it began like ducts or lobules. (Stage 0)
- Local: The cancer is confined to the breast, with no evidence of spread to other lymph nodes or organs. (Stage I and Stage IIa)
- Regional: The nearby lymph nodes, primarily those in the armpit (axillary lymph nodes), are involved. (Stage IIb and Stage III)
- Distant: The cancer is found in distant lymph nodes and organs of the body. (Stage

IV) [47][48]

2.4.2 Breast Cancer Grade

Pathologists assign grade numbers to cancer tissue based on the portion of cells that have normal cell structure, the size and shape of the nucleus, and the number of dividing cells (which is a measure of how fast cancer cells are growing and dividing). Generally, the higher the grade, the faster cancer grows and the more likely it spreads. The cancer tissue characteristics associated with each grade are: Grade 1 corresponds to well-differentiated or low-grade, Grade 2 to moderately differentiated or intermediate grade, and Grade 3 to poorly differentiated or high-grade [49]. DCIS is graded based on how abnormal cells look under the microscope and if they have any necrosis (area of dead or dying cells). Necrosis happens because cancer cells in the middle of the duct, which do not have direct access to nutrition, die and form a plug of dead cells. When cancer cells fill the duct and form necrotic tissue, it is called Comedo DCIS. Comedo DCIS is associated with higher grade. [50]

2.4.3 DCIS Progression Pathways

As mentioned before if DCIS cancer cells break through the duct, DCIS becomes invasive ductal carcinoma (IBC). Several biological pathways have been suggested to describe the progression of atypical hyperplasia (an increased number of cells with abnormal morphology) to different grades of DCIS (an increased number of cells with very abnormal morphology inside the duct) to IBC (an increased number of abnormal cells outside the duct) grades. These pathways, shown in Figure 2.2, where grades 1,2, or 3 represent low, intermediate, or high grade for DCIS and IBC, respectively, are described below.

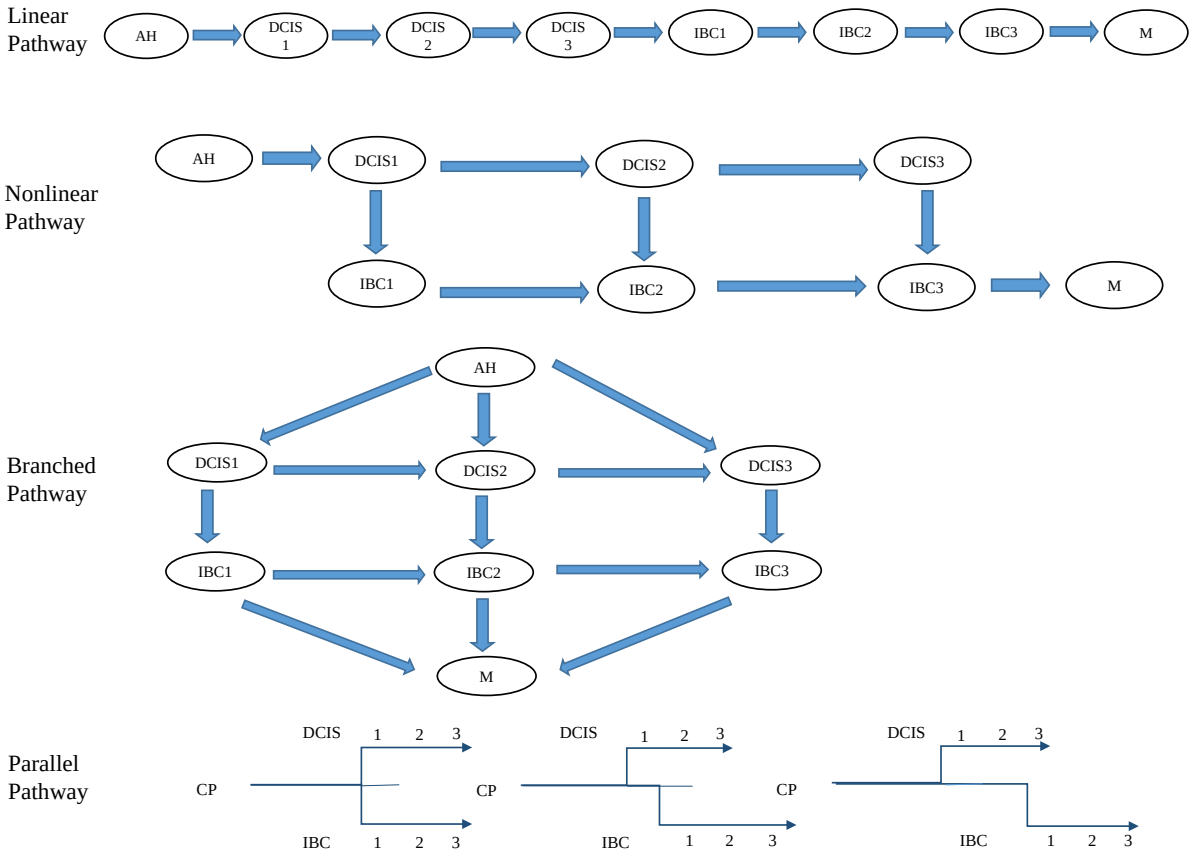

Figure 2.2 DCIS progression pathways.
Atypical hyperplasia (AH), common progenitor (CP), ductal carcinoma in situ (DCIS), invasive ductal carcinoma (IDC), and metastasis (M). Grades of DCIS and IDC are indicated by 1, 2, and 3.

Linear Pathway: The linear pathway starts with atypical hyperplasia which sequentially progresses to low-grade DCIS (DCIS 1), intermediate grade DCIS (DCIS 2), high-grade DCIS (DCIS 3), low-grade IBC (IBC 1), intermediate grade IBC (IBC 2), high-grade IBC (IBC 3) to metastasis (M). In one of the few papers on the evaluation of DCIS pathways, Subramanian and Axelrod 2001[51] were unsuccessful in simulating the linear pathway for DCIS and IBC co-occurrence data using a genetic algorithm.

Nonlinear Pathway: One of the alternatives to the linear pathway is a nonlinear pathway

which adds transitions from DCIS 1 to IBC 1, from DCIS 2 to IBC 2 and from DCIS 3 to IBC 3 to the linear model.

Branched Pathway: This pathway is built by additional four more possible transitions to the nonlinear model: a transition from atypical hyperplasia to DCIS 2, atypical hyperplasia to DCIS 3, IBC 1 to metastasis, and IBC 2 to metastasis.

Parallel Pathway: In this pathway, it is assumed DCIS and IBC start from a common progenitor but then diverge on two independent pathways parallel to each other. These two parallel pathways can start at different times. Sontag and Axelrod [16] showed that a parallel pathway performed best in explaining the DCIS and IBC co-occurrence matrix, obtained from data based on the root mean squared deviation (RMSD). The next best-performing pathway among the four was the branched pathway.

2.4.4 Biomarkers

Biomarkers are defined by the World Health Organization (WHO) as any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of an outcome or disease[52]. Many biomarkers have been identified for breast cancer but data on many of these biomarkers are not collected due to insufficient evidence of their role in breast cancer progression. Estrogen receptor and recently HER2 receptors are among well-established biomarkers that are currently assessed in all breast cancer cases. They have been used as prognostic factors as well as for determining biomarker specific targeting therapies.

Estrogen Receptors (ER) and Progesterone Receptor (PR): Receptors are proteins in or on specific cells that can attach to certain substances that flow in blood around the body like hormones. Estrogen and progesterone receptors can be present on both normal and

cancer cells in the breast. These hormones often fuel the growth of cancer cells. Breast cancer cells taken via biopsy are evaluated for both estrogen and progesterone receptors. If too much estrogen is present on cancer cells then the breast cancer is called ER-positive and if too much progesterone is present it is called PR-positive. Cancer cells can have PR, ER, both, or neither. About two out of three breast cancers have at least one of these two receptors. Hormonal therapy can be used to treat these breast cancers. They work by lowering the amount of hormone in the body or preventing hormone from attaching to the breast cancer cells. Tamoxifen is a hormonal therapy that has been used for 30 years by women with ER+ breast cancer tumors.

HER2: Human epidermal growth factor receptor 2, which is often shortened to HER2, is a growth-promoting protein that when present in a cell drives the production of HER2 protein. Cells that have too many of HER2 genes are called HER2 positive (HER2+). About one in five breast cancers are HER2+. HER2+ breast cancer cells tend to be more aggressive, however, they are responsive to anti-HER2 therapy [53].

Breast cancers are classified based on hormone receptors and HER2 status.

Hormone positive: If progesterone or estrogen receptors or both are present on cancer cells, tumors are called hormone receptor positive or hormone positive (HR+). HR+ breast cancers are more common in women after menopause. They tend to grow slower compared to HR- tumors but the cancer may recur after treatment.

Hormone Negative: If neither progesterone nor estrogen receptors are present on breast cancer cells, they are called hormone-receptor-negative, hormone negative (HR-,) or steroid receptor-negative (SR-). HR- cancers are more common in women who are pre-menopausal and if the cancer recurs, it comes back in first few years after treatment.

Triple Negative: If none of the progesterone, estrogen receptors or excess HER2 are present on cancer cells, they are called triple negative or basal-like tumors. These tumors

tend to be more aggressive, grow and spread quickly. They are not responsive to hormone therapy or anti-HER2 therapy, but there are medications that target this type of breast cancer. Triple-negative tumors are more common in younger women, African-American and Hispanic/Latina women.

Triple Positive: If progesterone, estrogen, and HER2 are present on cancer cells, the tumor is called triple positive. Triple positive tumors are usually treated with both hormone therapy and HER2 blocking agents. [10]

2.5 Breast Cancer Treatment

Breast cancer treatment differs from person to person based on breast cancer stage, tumor characteristics and the patient's overall health and preferences. Breast cancer treatments can be divided into two groups of local and systemic treatments.

Local Treatments

Local treatments remove cancer cells from the tumor's local area such as breast and underarm lymph nodes without affecting other parts of the body. Local treatments include surgery and radiation. The goal of surgery is to remove the entire tumor; however, sometimes normal tissue such as lymph nodes or a rim around the tumor are removed to test them for possible cancer spread. Two types of breast cancer surgery are lumpectomy and mastectomy.

Lumpectomy

Lumpectomy is a breast surgery commonly used as the first option for treating early stage breast cancer. During the surgery the aim is to remove minimal tissue from breast: tumor

and a small rim of normal tissue called normal or clean margins of breast tissue. Lumpectomy is also called breast conserving surgery, excisional biopsy or wide local excision because unlike mastectomy only a portion of the breast is removed. Partial mastectomy is a more extensive version of lumpectomy in that the lining over the chest muscles below the tumor is also removed but it is sometimes grouped with lumpectomy surgeries. Lumpectomy is sometimes followed by radiation to prevent breast cancer recurrence [54].

Mastectomy

Mastectomy is a surgery that removes the entire breast to treat or prevent breast cancer. There are two major types of mastectomy: simple mastectomy and modified radical mastectomy. In the radical mastectomy, more underarm (axillary) lymph nodes are removed compared to simple mastectomy. Breast reconstruction might be done at the same time or after mastectomy to restore the shape of the breast. In patients that are at high risk of breast cancer, mastectomy might be done on both breasts in order to prevent breast cancer from occurring. Some women have the option of choosing between lumpectomy and mastectomy; however, mastectomy may be the only choice for some breast cancer cases [55] [56].

Systemic Treatment

Systemic therapies aim to eliminate cancer cells that might have spread to organs other than the primary site of cancer. This group includes chemotherapy (e.g., for killing cancer cells that might have been left behind), hormone therapy (such as treatments aiming at HR+ tumors), and targeted therapy (such as treatments targeting HER2+ tumors), They are used in addition to surgery, therefore, they are also called adjuvant therapy. Breast

cancer treatment usually includes surgery with other types of treatment like radiation or chemotherapy before and/or after surgery. Surgery is less likely to be an option for more advanced breast cancer. [57][58]

Breast Cancer Recurrence

One of the main concerns after breast cancer treatment is the chance of breast cancer recurrence. With the increasing number of breast cancer survivors, it is estimated that women with a prior breast malignancy have a two to six fold increase in the risk of another breast cancer compared to those without a prior breast cancer event [59]. Recurrence can happen locally (at the original site or near it: local recurrence) or in other parts of the body (distant recurrence). Most breast cancer local recurrences happen in the first five years but long term studies have shown even decades after breast cancer treatment, recurrence may occur. [60]

Fisher [61] showed that there is a 48% to 68% chance of recurrence in female patients treated for invasive breast cancer 25 years after their first breast cancer diagnosis based on the National Surgical Adjuvant Breast and Bowel Project (NSABP) data. The rate of recurrence depended on the treatment they received and whether the lymph nodes were affected by the first breast cancer. Wapnir et al. [62] showed recurrence rates as large as 51.5% after DCIS treatment in long-term follow-up (more than 20 years) in two NSABP randomized clinical trials. The rate of recurrence depended on whether the patient received surgery, radiation or adjuvant therapy. In Chapter 4, we use the Surveillance, Epidemiology, and End Results (SEER) data on breast cancer to build survival models to predict the breast cancer recurrence time in patients. These models in our simulation model to simulate patients' lifetimes.

CHAPTER

3

DCIS DECISION MODEL

Given the uncertainty regarding DCIS pathways, we model the decision problem regarding the first course of treatment for a newly diagnosed DCIS patient. The DCIS treatment decision problem consists of decisions at multiple epochs. When a patient is diagnosed with DCIS, she can choose to receive treatment immediately or she can choose to wait and take another observation. If the patient chooses watchful waiting when she is diagnosed with DCIS, she will come back for a diagnostic mammogram next period and at that point, she will face the same dilemma. There may be new information available but the choices will remain the same, treat this epoch or wait and take another observation. We used a partially observable Markov Decision Process (POMDP) to model this problem because of the sequential decision making and the uncertainty associated with the nature of DCIS diagnosed, i.e., the progressive or non-progressive nature is unknown.

3.1 POMDP in Health Care

Markov decision processes (MDPs) use Markov chains to model the underlying process for improving sequential decision making under uncertainty. Markov chains are used to model systems that have the Markov property. The Markov property for first-order Markov chains holds when the state of the system in the future depends only on the state of the system in the present so we do not need to know the entire history of the chain. In MDPs, the uncertainty is associated with state transitions. Partially observable Markov decision processes (POMDPs) are a generalization of MDPs where in addition to uncertainty in the state transitions, the state is only partially observable at each decision epoch. However, there is a probability distribution associated with the states at each stage based on the observations taken [63].

One of the earliest uses of POMDPs in health care is seen in the work of Smallwood et al.

[64] in which they differentiate between the patient's state of health and the physician's state of knowledge of the patient's health. In this study, a physician's state of knowledge can be updated by a Bayesian rule.

In breast cancer decision making, Ivy [65] used POMDPs to determine an effective breast cancer screening policy considering the conflicting interests of the two decision makers: patient and payer. Maillart et al. [66] used POMDPs to model the natural history of breast cancer and evaluate dynamic age-based screening policies. Ayer et al. [67] built a POMDP model to evaluate screening policies in women with different risks of breast cancer considering the rate of false positives in screening and age dependency. Madadi et al. [68] used a POMDP to evaluate dynamic age-based policies with non-stationary adherence behavior.

In this dissertation, we use a POMDP to model the uncertainty associated with the nature of diagnosed DCIS. In other words given the uncertainty regarding the type of DCIS diagnosed, progressive (DCIS-P) or non progressive (DCIS-I), we assume observations that indicate changes in the grade or size of the DCIS tumor can be used to influence our belief probability of DCIS type: DCIS-P or DCIS-I. DCIS-P is the DCIS that turns to IBC if the patient lives long enough. DCIS-I is the DCIS that would not turn to IBC. The optimal time for treatment is determined based on our belief probability and the expected reward.

3.2 Proposed Model

We formulated a decision model with watchful waiting for DCIS as a finite-horizon POMDP where the patient's health state has both fully and partially observable elements. It is assumed that the DCIS nature is partially observable but IBC is fully observable through screening which occur each epoch (every six months). In other words, we assumed a

mammogram is perfect at diagnosing IBC and distinguishing it from DCIS. However, in the case of DCIS, a mammogram is unable to determine if the DCIS is progressive or not (DCIS-P or DCIS-I). It is assumed that each DCIS case is either progressive (DCIS-P) or non-progressive (DCIS-I) type and there is no transition from one DCIS type to the other, e.g., if a patient is diagnosed with a DCIS-P and does not receive any treatment, the DCIS-P cannot change to DCIS-I. These two types of DCIS are influenced by the previous literature such as Tan et al. [69] who assume there are two types of DCIS (progressive and non-progressive to IBC) and the pathways suggested for DCIS explained in Section 2.4.3. DCIS-P represents the branch pathway and DCIS-I represents the parallel pathway. For simplicity, in this chapter, the independent progression of IBC from DCIS in the parallel pathway is not modeled.

The model considers a patient who has just been diagnosed with DCIS. However, neither the patient nor her doctor knows if the DCIS is progressive, i.e., whether it is DCIS-P or DCIS-I. In current medical practice usually the patient is treated when diagnosed with DCIS [31]. In this dissertation, we assume due to the uncertainty in the nature of DCIS and the penalty associated with overtreatment, i.e., treating DCIS-I which is indolent, the patient and the doctor may decide to consider watchful waiting as a viable option. If the DCIS progresses to IBC, the patient will be treated as soon as possible. Watchful waiting is defined as performing a mammogram (and if necessary a biopsy) for as long as the decision horizon or before making a treatment decision for DCIS.

The patient is assumed to exit the model if she decides to receive treatment for DCIS, is diagnosed with IBC, or dies. Under watchful waiting, at each decision epoch, the observation or mammogram (or biopsy) is used to evaluate if the DCIS has changed. A change (Δ) represents a change in grade for a portion or all of DCIS tumor or growth in size. We denote no change in DCIS tumor by $\overline{\Delta}$. Both change and no change observations are possible in DCIS-I and DCIS-P as shown in Figure 3.1 which shows change in DCIS grade.

Details regarding transition rates for different tumor sizes and grades of DCIS by types are not available. Hence we define the aggregate DCIS states, DCIS-I and DCIS-P and we capture the granularity of the real states and the tumor attributes in the change and no change observations. The possible observations are: DCIS no change, DCIS change, local IBC, regional IBC, or death. It is assumed that if DCIS has progressed to IBC, it becomes completely observable. However, if the patient's health state continues to be DCIS, the observations provide only partial (or imperfect) information the physician regarding the DCIS type. This knowledge is incorporated into the belief probability vector of the patient's health state. Based on the observation, the doctor and patient update the belief probability vector of the DCIS and then a decision is made to treat or wait for another period (epoch) and take an observation. If the observation was IBC, however, there is no choice but to treat the patient. If the patient passed away at any time during the six-month period between the two decision epochs, we assume that the death happened at the end of the period, the reward is assigned at the end of the period, and the patient exits the model. A one period sample path of the DCIS decision process is shown in Figure 3.2.

The underlying state transitions are shown in Figure 3.3. The underlying states are DCIS-P, DCIS-I, local IBC, regional IBC, and death. It is assumed that detected local IBC, regional IBC, and death are absorbing states and the patient leaves the model when she reaches these states. The POMDP sample sequence for one epoch is shown in Figure 3.4. After transitions, we take observations. If the state remains in DCIS (DCIS-I or DCIS-P) the possible observations are change and no change and the actions are to treat or wait. Depending on the action chosen and the state of the patient, the reward is assigned to the patient. This model is used to evaluate the expected reward for actions at each period and to identify the optimal decision based on the belief probability vector [probability of DCIS-P, Probability of DCIS-I, Probability of local IBC, Probability of regional IBC, Probability of

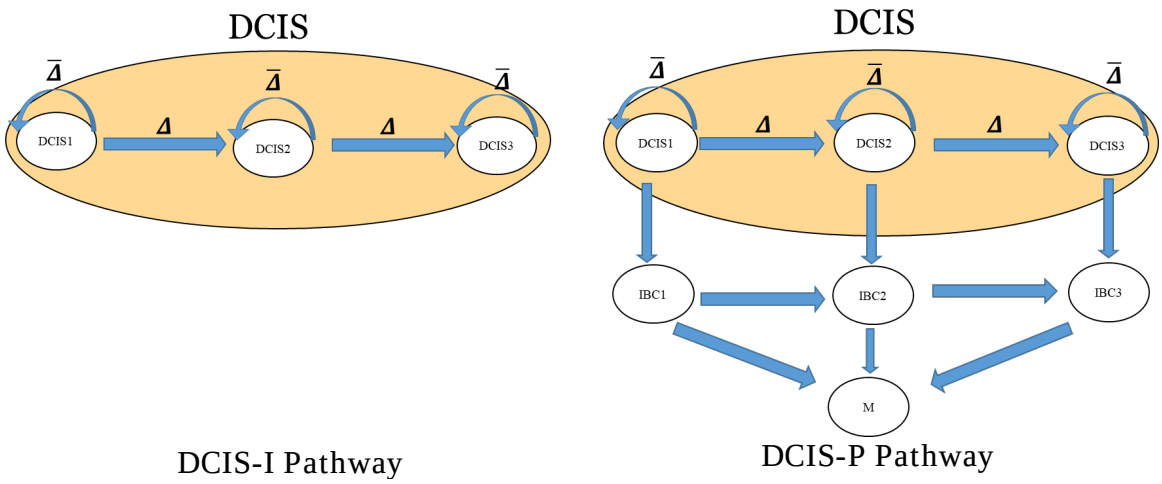

Figure 3.1 DCIS-I and DCIS-P pathways and their corresponding observations-Δ: change observation, $\overline{\Delta}$: no change observation, DCIS1: low-grade DCIS, DCIS2: intermediate grade DCIS, DCIS3: high-grade DCIS, IBC1: low-grade IBC, IBC2: intermediate grade IBC, IBC3: high-grade IBC, M: metastasis.

death] at each decision epoch. Next, we introduce the assumptions used to build the model and its formulation.

3.2.1 Assumptions

Assumption 1- Markov property: The patient's health state has the first order Markovian property, i.e., at each decision epoch the health state only depends on the health state in the last decision epoch and the action taken.

Assumption 2- Finite horizon: The decision horizon is assumed to be finite. Although a mammogram uses a low dose of X-ray, repeated exposure to X-rays may cause cancer [45].

Assumption 3- Finite state space and observations: We assumed a limited number of states, i.e., DCIS-P, DCIS-I, local IBC, regional IBC, and death, and a limited number of observations, i.e., change, no change, local IBC, regional IBC, and death.

Assumption 4- Observation likelihood dependent on present state only: We assumed

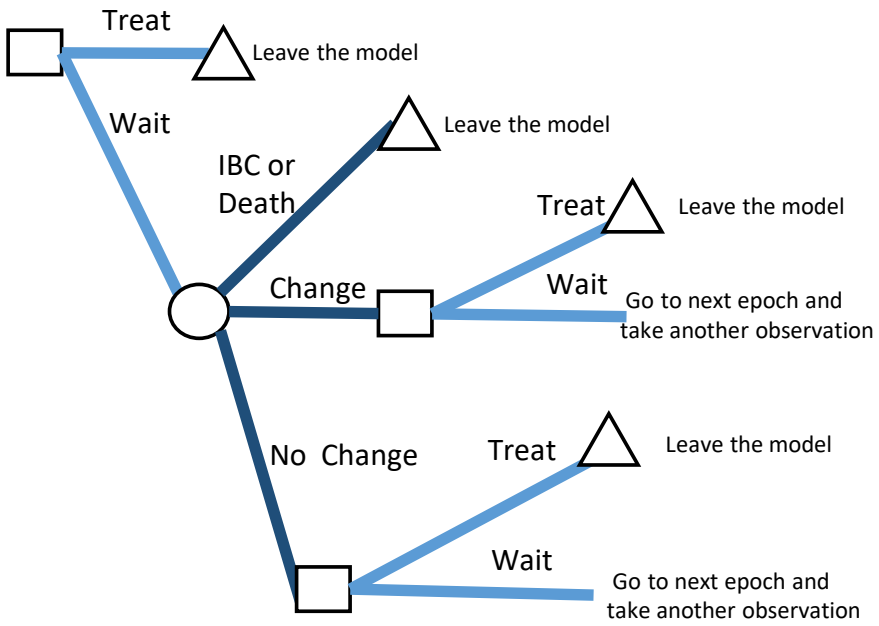

Figure 3.2 A One-period sample path of the DCIS decision process.

the probability of seeing an observation only depends on the current state, in other words, $\text{prob}(y_n = k|s_{n+1} = i, s_n = j) = \text{prob}(y_n = k|s_n = j) = Q(k, j)$ for all $n \in \{1, \ldots, N-1\}$, $i, j \in S$, and $k \in Y$.

3.2.2 Formulation

In this section, we introduce the notation and formulation for our model. The decision process sequence is shown in Figure 3.4. The patient enters the model when first diagnosed with DCIS but it is not known if the patient has DCIS-P or DCIS-I. If the DCIS is DCIS-P, it can progress to IBC local or IBC regional. The patient may die in both states associated with DCIS in the decision horizon. If the patient chooses watchful waiting, her health state changes according to the transition probability matrix P. We take an observation y_n at each

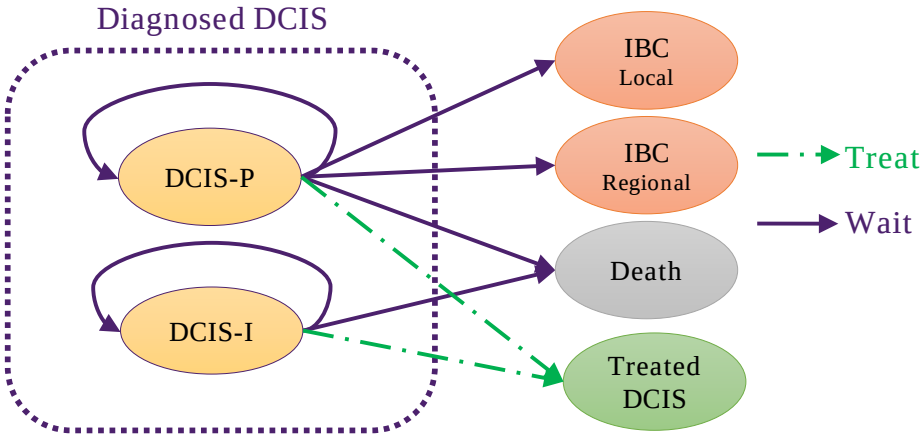

Figure 3.3 State Transition in POMDP model under waiting and treatment actions

epoch to update our belief probability for DCIS-P and DCIS-I. The observation depends on the patient's health state with likelihood matrix Q. After updating the belief probability vector W_{n+1} based on the observation y_n, a decision is made. Based on the action a_n and the state s_n, we calculate the estimated reward $\sum_{s_n \in S} W_n(s_n, y_n) * f(s_n, a_n)$ where $f(s_n, a_n)$ is the reward for taking action a_n in state s_n when n periods remain and $W_n(s_n, y_n)$ is the belief probability for state s_n when there was observation y_n. Our objective is to choose the action at each epoch to maximize our total expected reward, v_N, for a specified decision horizon length of N.

In all the equations, "prob" is short for probability so prob(x) means probability of x, prob$(X|Y)$ means probability of event X happening given that event Y happened, and if A is a matrix then A^T is the transpose of matrix A. The following notation is used for the problem formulation:

$E = \{1, 2, \ldots, N\}$: Set of epochs in which observations are taken and decisions are made. It is assumed that the length of each decision epoch is six months, the number of decision epochs remaining is represented by n, and N is the length of the decision horizon. . If

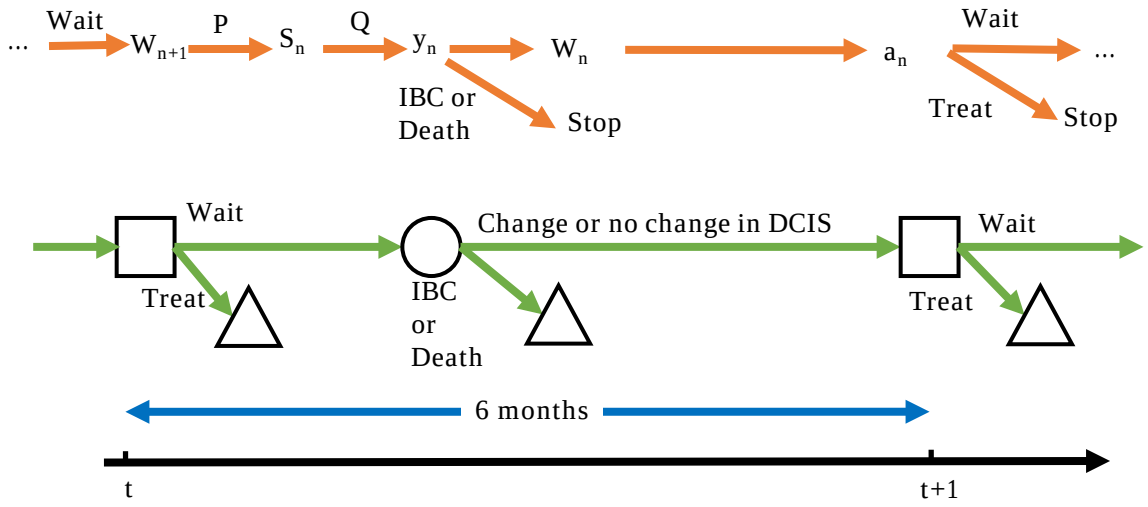

Figure 3.4 Decision making process at each period: At each period t when $n+1$ periods remain, we start with a belief probability W_{n+1} (given that in the last period we chose to wait). Then we use both the transition matrix P and the observation matrix Q to update our belief probability to W_n at the end of period. If the state ended up in death or IBC, the patient exits the model; otherwise we take action a_n.

the patient has not died, developed IBC, or received a treatment for DCIS by time N, it is assumed she exits the model.

s_n : Patient's true health state when n periods remain ($n \in \{0,1,\ldots,N-1,N\}$).

$S = 1,2,\ldots,H$: Set of states possible for s_n, where $H = 5$ and numbers 1, 2, 3, 4, and 5 correspond to DCIS-I, DCIS-P, local IBC (LBC), regional IBC (RBC), and death (DO), respectively.

y_n: Observation when n periods remain, made after state transition s_{n+1} to s_n.

$Y = \{1,2,\ldots,O\}$: Set of possible observations for y_n, where $O = 5$ and numbers 1, 2, 3, 4, and 5 correspond to change (Δ), no change ($\overline{\Delta}$), IBC local (LBC), IBC regional (RBC), and death (DO).

a_n: Action taken when n periods remain. For the wait action it is assumed the next action is selected after observing y_n.

$A(s_n, y_n) = \{1, \ldots, D\}$: Set of actions ($a_n$) possible when in state s_n and observation y_n is taken. For states 1 and 2, i.e., DCIS-I and DCIS-P, with possible observations of change or no change, $D = 2$ and numbers 1 and 2 correspond to the wait and take another mammogram (M) and treat (T) actions, respectively. For states 3 and 4, which are IBC, there is only one action possible, which is to treat so $D = 1$; and for state 5, i.e., death, there is no action but to exit the model so $D = 1$.

P_a: Transition probability matrix (an $H \times H$ matrix) for states under action a. $P_a(i, j)$ is the probability of the state changing from state i to j under action a in one epoch or prob$(s_{n-1} = j | s_n = i, a_n = a)$. In our model, the transition between states happens only when the action is wait; otherwise the patient exits the model. We use P for short as the transition matrix for waiting and getting a mammogram action ($P = P_M$).

Q: Observation probability matrix (an $O \times H$ matrix), where $Q(k, i)$ is the probability of observing $y_n = k$ when patient is in state $s_n = i$ or prob$(y_n = k | s_n = i)$. Because of the perfect observability of local IBC, regional IBC and death states $Q(3,3) = Q(4,4) = Q(5,5) = 1$.

L_n: A $1 \times O$ marginal probability vector with O elements, where $L_n(k)$ represents the probability of observation k when n epochs are left, prob$(y_n = k)$.

$$
\begin{aligned}
L_n(k) &= \text{prob}(y_n = k) \\
&= \sum_{i \in S} \sum_{j \in S} \text{prob}(s_{n+1} = i, s_n = j) * \text{prob}(y_n = k | s_{n+1} = i, s_n = j) \\
&= \sum_{i \in S} \sum_{j \in S} Z_{n+1}(i) * P(i, j) * Q(k, j) \qquad (3.1) \\
&\text{for all } n \in \{1, \ldots, N-1\} \text{ and } k \in Y. \\
L_n &= Z_{n+1} * P * Q^T
\end{aligned}
$$

Line 3 of the above formulation above follows from the previous line according to assump-

tion 4, $\text{prob}(y_n = k | s_{n+1} = i, s_n = j) = Q(k, j)$, i.e., the probability of an observation in each epoch only depends on the probability of the state in the current epoch and not the previous epoch.

Z_n: A $1 \times H$ probability vector where $Z_n(i)$ represents the probability of being in state $s_n = i$ when n epochs are left.

$$\begin{aligned} Z_n(j) &= \text{prob}(s_n = j) \\ &= \sum_{k \in Y} \text{prob}(y_n = k) * \text{prob}(s_n = j | y_n = k) \\ &= \sum_{k \in Y} L_n(k) * \text{prob}(s_n = j | y_n = k) \\ &\text{for all } n \in \{1, \ldots, N-1\} \text{ and } j \in S. \end{aligned} \tag{3.2}$$

$\text{prob}(s_n | y_n)$: Conditional probability of being in health state s_n if observing y_n when n epochs are left.

$$\begin{aligned} \text{prob}(s_n = i | y_n = k) &= \frac{\text{prob}(s_n = i) * \text{prob}(y_n = k | s_n = i)}{\text{prob}(y_n = k)} = \\ \sum_{j \in S} \frac{\text{prob}(s_{n+1} = j) * \text{prob}(s_n = i | s_{n+1} = j) * \text{prob}(y_n = k | s_n = i)}{\text{prob}(y_n = k)} &= \\ \sum_{j \in S} \frac{Z_{n+1}(j) * P(j, i) * Q(k, i)}{L_n(k)} &\text{ for all } n \in \{1, \ldots, N-1\},\ i \in S \text{ and } k \in Y. \end{aligned} \tag{3.3}$$

$W_n(s_n, y_n)$: Belief probability of being in state s_n when n periods remain after taking an observation y_n. W_n in each epoch is a prior for the next epoch and after taking an observation it is updated to the posterior W_{n-1}. As shown in Figure 3.4, the state transition and observation happen between W_{n+1} and W_n. $W_n(\cdot, y_n)$ is a vector with H elements where the ${s_n}^{th}$ element represents the belief probability of being in state s_n after observing y_n.

$\hat{L}_n$: A current estimate of marginal probability vector with O elements, where $\hat{L}_n(k)$

represents the current estimate of the probability of observation k when n epochs are left.

$\hat{Z}_n$: A current estimate of probability vector where $\hat{Z}_n(i)$ represents the current estimate of probability of being in state $s_n = i$ when n epochs are left.

We assume the following initial values:

$$\begin{cases} \hat{Z}_N = \omega(\cdot) = (\alpha,\ 1-\alpha,\ 0,\ 0,\ 0) \\ W_N = \hat{Z}_N \end{cases} \tag{3.4}$$

Then for $n = N-1, N-2, \ldots, 1$, compute Equations 3.5-3.8:

$$\hat{L}_n(k) = \sum_{i \in S} \sum_{j \in S} \hat{Z}_{n+1}(i) * P(i,j) * Q(k,j) \text{ for all } k \in Y. \tag{3.5}$$

Sample y_n from probability vector $\hat{L}_n$, (3.6)

$$W_n(i,k) = \sum_{j \in S} \frac{\hat{Z}_{n+1}(j) * P(j,i) * Q(k,i)}{\hat{L}_n(k)} \text{ for all } i \in S \text{ and } k \in Y \tag{3.7}$$

$$\hat{Z}_n = W_n(\,\cdot\,, y_n). \tag{3.8}$$

$f_n(s_n, a_n)$: Reward associated with taking action a_n when the true health state of the patient is s_n and n periods remain. It is equal to:

- $r_1(n)$: Reward for waiting six months when $s_n = 1$ or $s_n = 2$ and $a_n = 1$. It can be estimated by multiplying the quality-adjusted life year (QALY) of having DCIS in later years explained in Section 5.2.5 by 0.5. QALYs are assumed to be age dependent therefore $r_1(n)$ depends on number of epochs remaining and the patient's age when n periods remain.

  We might estimate the rewards with the simulation model described in Chapter 5. The simulation model simulates a patient after DCIS treatment and calculates her expected cumulative QALY through the end of the decision horizon, during which events such as cancer recurrence and death may occur.

- $r_2(n)$: Reward for treating DCIS-I, i.e., $s_n = 1$ and $a_n = 2$.

- $r_3(n)$: Reward for treating DCIS-P, i.e., $s_n = 2$ and $a_n = 2$.

- $r_4(n)$: Reward for being diagnosed with local IBC (LBC), i.e., $s_n = 3$.

- $r_5(n)$: Reward for being diagnosed with regional IBC (RBC), i.e., $s_n = 4$.

- $r_6(n)$: Reward for death, i.e., $s_n = 5$.

I_{a_n}: The indicator variable which shows if the patient continues in the model in the next epoch after action a_n where $I_{a_n} = 1$ if $a_n = \mathrm{M}$ and $I_{a_n} = 0$ otherwise.

$v_n(W_n, a_n)$: Estimator of the expected reward of taking action a_n when the belief probability vector is W_n and n periods remain. Then $v_n(W_n(\cdot, y_n), a_n)$ is given by

$$v_n(W_n(\cdot, y_n), a_n) = \sum_{s_n \in S} W_n(s_n, y_n) * f(s_n, a_n) + I_{a_n} * \sum_{y_{n-1} \in Y} \hat{L}_{n-1}(y_{n-1}) * v^{\star}_{n-1}(W_{n-1}(\cdot, y_{n-1})) \quad (3.9)$$

for $n = N, N-1, \ldots, 1$, where $v^{\star}_0(W_n(\cdot, y_n))$ is given by Equation (3.11) and $v^{\star}_n(W_n(\cdot, y_n))$ is

the optimum reward when belief probability vector is $W_n(\cdot, y_n)$ and n periods remain:

$$v_n^\star(W_n(\cdot, y_n)) = \max_{a_n \in A} \Big(\sum_{s_n \in S} W_n(s_n, y_n) * f(s_n, a_n) + I_{a_n} * \sum_{y_{n-1} \in Y} \hat{L}_{n-1}(y_{n-1}) * v_{n-1}^\star(W_{n-1}(\cdot, y_{n-1})),$$

where

$$\mathrm{v}_n^\star(W_n(\cdot, y_n)) = \max \begin{cases} r_1(n) * \{W_n(1, y_n) + W_n(2, y_n))\} + & \\ \hat{L_{n-1}}(1) v_{n-1}^\star(W_{n-1}(\cdot, 1)) + & \text{if } a_n = M \\ L_{n-1}(2) * v_{n-1}^\star(W_{n-1}(\cdot, 2)) + & \\ L_{n-1}(3) * r_4(n) + L_{n-1}(4) * r_5(n) + L_{n-1}(5) * r_6(n) & \\ & \\ W_n(1, y_n) * r_2(n) + W_n(2, y_n) * r_3(n) & \text{if } a_n = T \end{cases} \tag{3.10}$$

And for $n = 0$ we have

$$v_0^\star(W_0(\cdot, y_0)) = v_0(W_0(\cdot, y_0), a_0) = g. \tag{3.11}$$

It is assumed that at the end of the decision horizon the only action (a_0) is do nothing and the observation (y_0) is no change. The salvage value,g, can be estimated by calculating average cumulative QALYs for a group of women with the same age, race and ethnicity by starting the patients in the simulation with a DCIS with prob(DCIS-I) = $W_N(1)$ and prob(DCIS-P) = $W_N(2)$. The starting belief probabilities ($W_N(1)$, $W_N(2)$) might be estimated from the proportion of DCIS-I and DCIS-P in the population with a certain DCIS grade or we can assume they are both equal 0.5, i.e., since we have no information yet we assume they have the same likelihood. We find the optimal treatment strategy by finding the action set for N epochs that maximizes $v_n(W_n, a_n)$ for $n = N$.

We used the following pseudo code to solve the POMDP using dynamic programming and coded the algorithm in Python [70]:

Algorithm 1 POMDP Dynamic Programming

$n \leftarrow N$ ▷ decision horizon

$W \leftarrow \omega$ ▷ initial belief probability W_N

procedure $v^\star(W,n)$ ▷ estimated optimal reward function when n periods remain for belief probability W

while $n \neq 0$ **do**

$Z \leftarrow W$ ▷ estimated state probability $\hat{Z}_n$

$L(y) \leftarrow \sum_{s' \in S} \sum_{s \in S} Z(s) * P(s,s') * Q(y,s') \quad y \in Y$ ▷ estimated marginal probability for next epoch (Equation 3.5)

$W'(s',y) \leftarrow \sum_{s \in S} \frac{Z(s) * P(s,s') * Q(y,s')}{L(y)} \quad y \in Y, \quad s' \in S$ ▷ belief probability for next epoch (Equation 3.7) Sample y' from probability vector L ▷ observation for next epoch

$Z(s) \leftarrow W'(s,y') \quad s \in S$ ▷ estimated state probability for next epoch (Equation 3.8)

$I(1) \leftarrow 1$ ▷ indicator function for $a = 1$ or wait

$I(2) \leftarrow 0$ ▷ indicator function for $a = 2$ or treat

$v^\star(W,n) \leftarrow \max_{a \in A} \left(\sum_{s \in S} W(s) * f(s,a) + I(a) * \sum_{y \in Y} L(y) * v^\star(W'(\cdot, y), n-1) \right.$ ▷ optimal reward (Equation 3.10)

end while

if $n = 0$ **then**

$v^\star(W,n) \leftarrow g$ ▷ end of the horizon reward (Equation 3.11)

end if

return $v^\star(W,n)$

end procedure

3.2.3 Illustrative Problem

An illustrative problem was created to explore the structure of optimal policies and the computational complexity associated with solving the proposed POMDP. For simplicity, it is assumed $f_n(s_n, a_n)$ is time and age independent for all states and $g = 0$. The following values for the parameters are used.

$[r_1(n), r_2(n), r_3(n), r_4(n), r_5(n), r_6(n)] = [0.01, 8, -1, -6, -34, 0]$

As defined in Section 3.2.2, the numbers 1, 2, 3, 4, and 5 represent states DCIS-I, DCIS-P, LBC, RBC,and DO respectively and the numbers 1, 2, 3, 4, and 5 represent observations Δ, $\overline{\Delta}$, LBC, RBC, and DO, respectively. The transition matrix P and observation matrix Q used in the example are shown below.

$$P = \begin{bmatrix} 0.995 & 0 & 0 & 0 & 0.005 \\ 0 & 0.951 & 0.043 & 0.001 & 0.005 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}, Q = \begin{bmatrix} 0.1 & 0.8 & 0 & 0 & 0 \\ 0.9 & 0.2 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

The transition probabilities for breast cancer states are estimated from Tan et al. [71], and the probability of death is estimated from the life tables [72]. We assume the decision horizon is $N = 10$. Starting from a first diagnosis of DCIS at age 54 with no other information, we assume $W_N = (0.5, 0.5, 0, 0, 0)$ where elements of W_n are ordered from states 1 through 5 as defined above. We coded the model in Python [70] and solved it by recursively maximizing the expected reward function at each epoch using dynamic programming. The optimal solution is to wait when diagnosed with DCIS at age 54 if we start with $W_N = (0.5, 0.5, 0, 0, 0)$.

In Figure 3.5, each point corresponds to the optimal action given the decision maker's belief probability as a function of the patient's age. The points shown in Figure 3.5 the optimal decision when the expected reward for that point is calculated considering age 59 to be the end of decision horizon. Figure 3.5 plots the the belief probability sample path for each action.

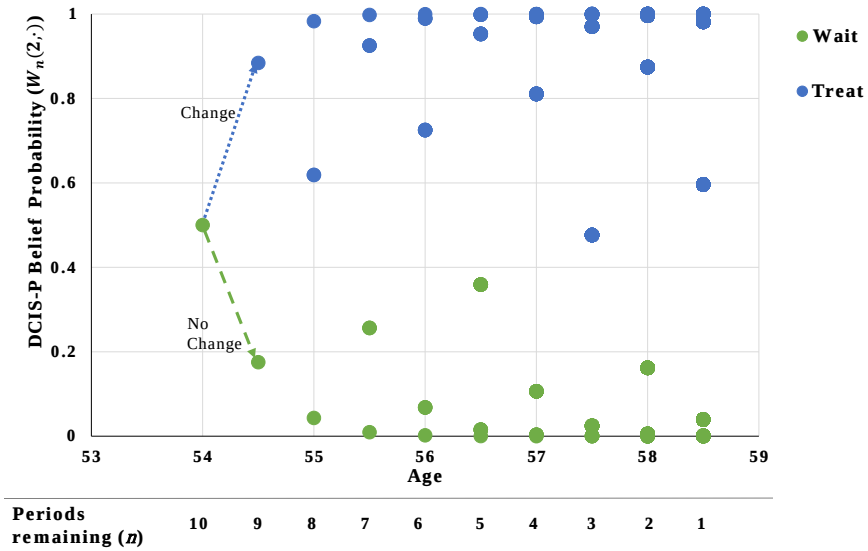

Figure 3.5 Optimal solution at each age and period with the corresponding action for the optimal decision when end of decision horizon is at age 59 and $W_N = (0.5, 0.5, 0, 0, 0)$ and $N = 10$. Each point is a posterior belief probability for a prior belief probability point in previous epoch by observing change or no change.

Next, we examine the effect of DCIS subtypes on the optimal decision. According to Kurbel et al. [73], the rates of DCIS progression to IBC are different for the four molecular subtypes of DCIS including Luminal A, Luminal B, Triple negative, and steroid receptor-negative HER2+ (SR-HER2+). Luminal A tumors are typically ER+ or PR+ and HER2- with grade 1 and 2. Luminal B tumors tend to be ER+ or PR+, may be HER2- or HER2+ and tend to have factors that lead to a poorer prognosis such as higher tumor grade, larger tumor size,

and lymph node-positive [74]. SR-HER2+ are tumors that are PR-negative and ER-negative but HER2+. Kurbel et al. showed that if the progression rate for a triple-negative DCIS was γ then progression rate is going to be $\frac{1}{2}\gamma$, $\frac{2}{3}\gamma$,and $\frac{1}{3}\gamma$ for Luminal A, Luminal B, and SR-HER2+, respectively. We assumed these rate proportions applied to the progression of DCIS-P to IBC. We also assumed the probability of this progression for each type follows an exponential distributionÅs a result, the probability of progression for the general population is the same as the probability of minimum of the four exponential distributions for the four sub-types of DCIS. The rate for the minimum of multiple exponential distributions is the sum of the rates of those distribution so we have: $\lambda = \gamma + \frac{1}{2}\gamma + \frac{2}{3}\gamma + \frac{1}{3}\gamma$. We have from Tan et al. [71] the probability of DCIS-P turning to IBC, i.e., probability of one of the four DCIS subtypes turning to IBC, in one epoch is 0.043, by assuming exponential distribution for it, we calculate λ to be 0.043 ($1 - \exp(-\lambda * 1) = 0.043 \rightarrow \exp(-\lambda) = 0.95 \rightarrow \lambda \approx 0.043$). We solved the problem for different values of prior, W_N, in the set $\{(0.01, 0.99, 0, 0, 0), (0.02, 0.98, 0, 0, 0), \ldots, (0.99, 0.01, 0, 0, 0), \}$, for triple-negative DCIS ($P(2,3) = 0.0172$) and SR-HER2+ DCIS ($P(2,3) = 0.0057$) to explore the effect of DCIS molecular subtypes on the optimal policy. We assumed the Q matrix is not affected by DCIS subtype. P_T and P_S are the transition probability matrix for triple negative and SR-HER2+, respectively.

$$P_T = \begin{bmatrix} 0.995 & 0 & 0 & 0 & 0.005 \\ 0 & 0.977 & 0.017 & 0.001 & 0.005 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}, P_S = \begin{bmatrix} 0.995 & 0 & 0 & 0 & 0.005 \\ 0 & 0.9883 & 0.0057 & 0.001 & 0.005 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

The results from solving the model for the two subtypes of DCIS are presented in Figure

3.6. The result suggests the optimal solution has a threshold structure, i.e., if the belief probability of DCIS-P ($W_n(2)$) is less than a specific value (threshold), the optimal solution is to "wait"; otherwise the optimal solution is to "treat". As maybe expected this threshold is higher for SR-HER2+ type because it progresses slower than the triple negative subtype.

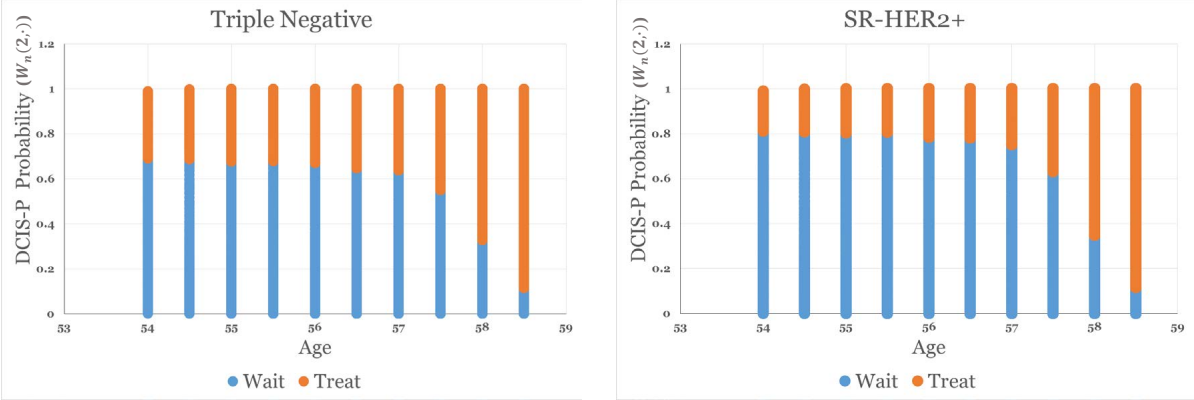

Figure 3.6 Optimal solution for different values of W_n at each period with the corresponding action that creates optimal decision for triple negative and SR-HER2+ DCIS types.

Next, we evaluate the effect of age on the optimal policy. According to Duffy et al. [28] the mean sojourn time (the duration of the pre-clinical detectable phase) for breast cancer tends to be shorter in women aged 40-49 compared to women aged 50-59 and 60-69. If we interpret this as an indicator of how aggressive a cancer is depending on age, we can say DCIS-P tends to progress faster to IBC in younger women compared to older women. Based on this assumption and using the probability for triple negative and SR-HER2+, we solved the problem for a 49-year-old patient diagnosed with DCIS when the transition probability matrices before age 50 and age 50 and over are equal to the transition probability matrix for triple negative and transition probability matrix for SR-HER2+, respectively. Figure 3.7 has the same threshold structure. Also, the threshold goes up at age 50 when the probability

transition matrix changes to a less aggressive DCIS. In all the examples, the threshold value decreases closer to the end of the decision horizon, this may be because we assume that the patient leaves the model after the end of decision horizon and there is less information to be gained as we are closer to the end of the horizon.

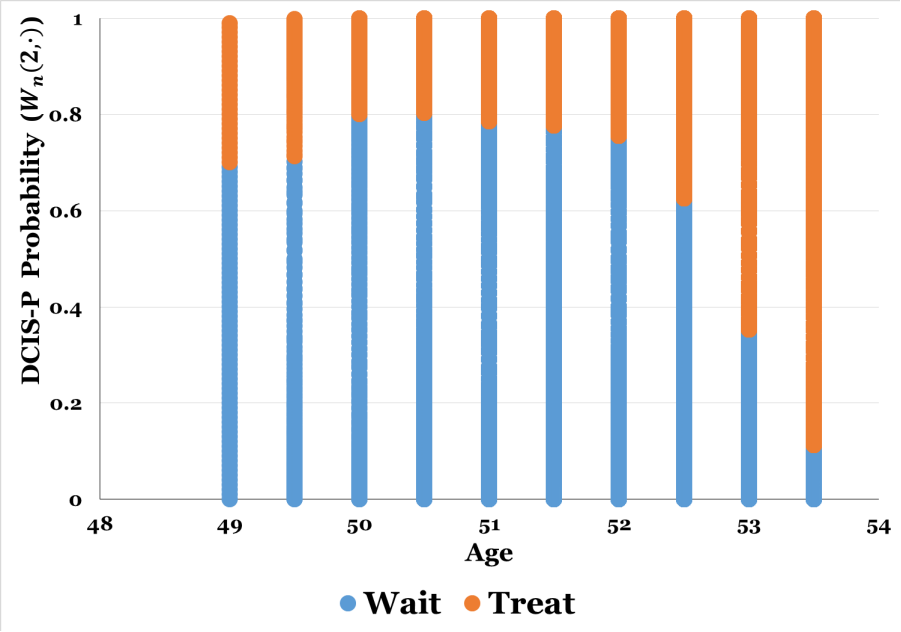

Figure 3.7 Optimal solution for different values of W_n at each period with the corresponding action that creates optimal decision when DCIS-P progression is age dependent.

In this chapter we used the POMDP to model decision making in DCIS patients and solved POMDP using dynamic programming. Solving the illustrative examples suggest there is a threshold structure which is used in Chapter 5. the next chapter, we use the SEER database for breast cancer patients to obtain inputs for the simulation model and in Chapter 5 we use the same structure described in this chapter to test different values for DCIS-P belief probability treatment threshold in the simulation model to evaluate the effect of watchful waiting at the population level.

CHAPTER

4

SEER DATA ANALYSIS AND SURVIVAL MODELS

We used the Surveillance, Epidemiology, and End Results (SEER) data [75] to assign tumor attributes and to predict breast cancer recurrence and mortality in breast cancer patients within the simulation model. In this chapter, we first introduce the breast cancer data from SEER Program, then present recurrence prediction models used in the simulation model. Recurrence is considered because after treating the patients, cancer might relapse that can affect their lifespan and cumulative quality of life.

4.1 Data Analysis

4.1.1 SEER Data

"The Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute provides information on cancer statistics in an effort to reduce the cancer burden among the U.S. population" [76]. SEER has been collecting data on cancer cases since 1973 from a number of registries across the U.S. The number of registries has grown since 1973 and now includes 18 registries representing approximately 26% of the U.S. population (based on the 2010 census) [77]. In this dissertation, we used the SEER November 2014 data submission [75] which includes cancer cases recorded from Jan 1, 1973 to Dec 31, 2012.

For our study, we chose female patients aged 35 and over, with African American or white race including Hispanic and non-Hispanic ethnicity. We excluded invasive breast cancers with Stage 0 including Paget disease of the breast, which was beyond the scope of our research. The demographic information for IBC and DCIS cases of this population is shown in Tables 4.1 and 4.3 and their tumor characteristics are summarized in Tables 4.2 and 4.4, respectively. We can see from these Tables that more than 50% of the SEER data was collected after 2000 and almost 90% of the records belong to white patients. In all

races, women 50 years and older are at a higher incidence of both IBC and DCIS, and more than 90% of them are treated with surgery. SEER does not include information on systemic treatments and only contains information on radiation and surgery types as treatments. For this summary, we aggregated the codes used in SEER database, the summary of SEER coding used is presented in Appendix B. For the grade category, we aggregated breast cancer cases with grade III and grade IV into the high grade group in the summary tables. In the SEER data, ER status and PR status were not documented prior to 1990, most of the tumors documented after 1990 are hormone positive (HR+). Collection of HER2 status started in 2010, most of the tumors recorded after 2010 are HER2-. African American patients are more likely to be diagnosed with higher stage breast cancers compared to white patients, this might be one of the reasons for lower breast cancer survival rates in the African American population, and may be affected by less access to screening [78]. Less than 1% of SEER records belong to Hispanic African American patients which correspond to the percentage of Hispanic African American in U.S. female population older than 35 (about 0.6%) as shown in Appendix C.

We used SEER data for two purposes in the simulation model: (i) To assign tumor characteristics to a breast cancer tumor based on the patient's age at diagnosis, race, ethnicity and type of breast cancer (invasive vs. DCIS) in the simulation model; and (ii) To predict recurrence for each breast cancer case after diagnosis. Throughout this chapter, SAS Enterprise Guide 6.1 [79] was used for data preparation, analysis, and model development.

Table 4.1 SEER IBC population demographics-(%): Shows the percentage from the subpopulation, W: white, AA: African American

	Non-Hispanic W	Non-Hispanic AA	Hispanic W	Hispanic AA	Total
Age Groups					
<50	155,236 (18.19%)	27,295 (27.03%)	25,202 (31.69%)	463 (36.54%)	208,196 (20.11%)
50-59	190,483 (22.32%)	26,403 (26.14%)	20,983 (26.38%)	316 (24.94%)	238,185 (23.01%)
60-69	208,000 (24.37%)	22,597 (22.38%)	16,891 (21.24%)	265 (20.92%)	247,753 (23.93%)
70-79	180,789 (21.18%)	15,902 (15.75%)	11,269 (14.17%)	155 (12.23%)	208,115 (20.1%)
>80	118,942 (13.94%)	8,793 (8.71%)	5,191 (6.53%)	68 (5.37%)	132,994 (12.85%)
Year of diagnosis					
1973-1979	55,344 (6.48%)	3,707 (3.67%)	1,489 (1.87%)	14 (1.1%)	60,554 (5.85%)
1980-1989	105,553 (12.37%)	8,407 (8.32%)	3,410 (4.29%)	41 (3.24%)	117,411 (11.34%)
1990-1999	169,282 (19.84%)	17,755 (17.58%)	13,389 (16.83%)	167 (13.18%)	200,593 (19.38%)
2000-2009	399,241 (46.78%)	52,261 (51.75%)	43,895 (55.19%)	730 (57.62%)	496,127 (47.92%)
2010-2012	124,030 (14.53%)	18,860 (18.68%)	17,353 (21.82%)	315 (24.86%)	160,558 (15.51%)
Vital Status by 2012					
Alive	495,244 (58.03%)	57,459 (56.9%)	57,076 (71.76%)	885 (69.85%)	610,664 (58.99%)
Dead	358,206 (41.97%)	43,531 (43.1%)	22,460 (28.24%)	382 (30.15%)	424,579 (41.01%)
Treatment					
Surgery	809,217 (94.82%)	91,046 (90.15%)	73,996 (93.03%)	1,160 (91.55%)	975,419 (94.22%)
No surgery	39,722 (4.65%)	9,333 (9.24%)	5,264 (6.62%)	104 (8.21%)	54,423 (5.26%)
Unknown	4,511 (0.53%)	611 (0.61%)	276 (0.35%)	3 (0.24%)	5,401 (0.52%)
Radiation					
No radiation given	473,340 (55.46%)	56,263 (55.71%)	43,136 (54.23%)	664 (52.41%)	573,403 (55.39%)
Radiation given	353,827 (41.46%)	40,369 (39.97%)	33,568 (42.2%)	560 (44.2%)	428,324 (41.37%)
Unknown	26,283 (3.08%)	4,358 (4.32%)	2,832 (3.56%)	43 (3.39%)	33,516 (3.24%)
Total	853,450 (82.44%)	100,990 (9.76%)	79,536 (7.68%)	1,267 (0.12%)	1,035,243 (100%)

Table 4.2 SEER IBC population tumor attributes-(%): Shows the percentage from the subpopulation, W: white, AA: African American

	Non-Hispanic W	Non-Hispanic AA	Hispanic W	Hispanic AA	Total
Stage					
I	336200 (39.39%)	30344 (30.05%)	28387 (35.69%)	428 (33.78%)	395359 (38.19%)
II	209,912 (24.6%)	31,088 (30.78%)	25,987 (32.67%)	422 (33.31%)	267,409 (25.83%)
III	79,046 (9.26%)	14,543 (14.4%)	11,622 (14.61%)	197 (15.55%)	105,408 (10.18%)
IV	31,031 (3.64%)	6,629 (6.56%)	3,594 (4.52%)	87 (6.87%)	41,341 (3.99%)
Unknown	197,261 (23.11%)	18,386 (18.21%)	9,946 (12.51%)	133 (10.5%)	225,726 (21.8%)
Grade					
Low	139,860 (16.39%)	10,257 (10.16%)	11,776 (14.81%)	146 (11.52%)	162,039 (15.65%)
Intermediate	276,505 (32.4%)	28,118 (27.84%)	27,377 (34.42%)	389 (30.7%)	332,389 (32.11%)
High	224,185 (26.27%)	40,532 (40.13%)	28,322 (35.61%)	542 (42.78%)	293,581 (28.36%)
Unknown	212,900 (24.95%)	22,083 (21.87%)	12,061 (15.16%)	190 (15%)	247,234 (23.88%)
ER Status					
Positive	488,050 (57.19%)	49,021 (48.54%)	48,499 (60.98%)	743 (58.64%)	586,313 (56.64%)
Negative	110,165 (12.91%)	25,535 (25.28%)	15,465 (19.44%)	324 (25.57%)	151,489 (14.63%)
Borderline	2,001 (0.23%)	281 (0.28%)	204 (0.26%)	1 (0.08%)	2,487 (0.24%)
Unknown	92,337 (10.82%)	14,039 (13.9%)	10,469 (13.16%)	144 (11.37%)	116,989 (11.3%)
Not 1990+	160,897 (18.85%)	12,114 (12%)	4,899 (6.16%)	55 (4.34%)	177,965 (17.19%)
PR Status					
Positive	410,740 (48.13%)	39,716 (39.33%)	40,490 (50.91%)	599 (47.28%)	491,545 (47.48%)
Negative	176,255 (20.65%)	33,477 (33.15%)	21,912 (27.55%)	450 (35.52%)	232,094 (22.42%)
Borderline	4,208 (0.49%)	504 (0.5%)	388 (0.49%)	3 (0.24%)	5,103 (0.49%)
Unknown	101,350 (11.88%)	15,179 (15.03%)	11,847 (14.9%)	160 (12.63%)	128,536 (12.42%)
Not 1990+	160,897 (18.85%)	12,114 (12%)	4,899 (6.16%)	55 (4.34%)	177,965 (17.19%)
HER2 Status					
Positive	14,854 (1.74%)	2,771 (2.74%)	2,614 (3.29%)	51 (4.03%)	20,290 (1.96%)
Negative	97,299 (11.4%)	14,018 (13.88%)	12,959 (16.29%)	234 (18.47%)	124,510 (12.03%)
Borderline	2,801 (0.33%)	523 (0.52%)	417 (0.52%)	8 (0.63%)	3,749 (0.36%)
Unknown	9,076 (1.06%)	1,548 (1.53%)	1,363 (1.71%)	22 (1.74%)	12,009 (1.16%)
Not 2010+	729,420 (85.47%)	82,130 (81.32%)	62,183 (78.18%)	952 (75.14%)	874,685 (84.49%)
Total	853,450 (82.44%)	100,990 (9.76%)	79,536 (7.68%)	1,267 (0.12%)	1,035,243 (100%)

Table 4.3 SEER DCIS population demographics-(%): Shows the percentage from the subpopulation, W: white, AA: African American

	Non-Hispanic W	**Non-Hispanic AA**	**Hispanic W**	**Hispanic AA**	**Total**
Age Groups					
<50	25,505 (22.09%)	3,574 (24.34%)	3,345 (31.23%)	51 (27.57%)	32,475 (23.02%)
50-59	30,721 (26.6%)	4,141 (28.2%)	3,172 (29.61%)	57 (30.81%)	38,091 (27%)
60-69	28,728 (24.88%)	3,704 (25.22%)	2,363 (22.06%)	43 (23.24%)	34,838 (24.7%)
70-79	21,765 (18.85%)	2,448 (16.67%)	1,436 (13.41%)	25 (13.51%)	25,674 (18.2%)
>80	8,762 (7.59%)	818 (5.57%)	395 (3.69%)	9 (4.86%)	9,984 (7.08%)
Year of diagnosis					
1973-1979	1,554 (1.35%)	111 (0.76%)	40 (0.37%)	0 (0%)	1,705 (1.21%)
1980-1989	6,835 (5.92%)	590 (4.02%)	252 (2.35%)	2 (1.08%)	7,679 (5.44%)
1990-1999	25,331 (21.94%)	2,744 (18.69%)	1,749 (16.33%)	28 (15.14%)	2,9852 (21.16%)
2000-2009	63,617 (55.09%)	8,281 (56.39%)	6,330 (59.1%)	117 (63.24%)	78,345 (55.54%)
2010-2012	18,144 (15.71%)	2,959 (20.15%)	2,340 (21.85%)	38 (20.54%)	23,481 (16.65%)
Vital Status by 2012					
Alive	93,506 (80.97%)	11,813 (80.44%)	9,527 (88.95%)	160 (86.49%)	115,006 (81.53%)
Dead	21,975 (19.03%)	2,872 (19.56%)	1,184 (11.05%)	25 (13.51%)	26,056 (18.47%)
Treatment					
Surgery	112,811 (97.69%)	14,141 (96.3%)	10,379 (96.9%)	176 (95.14%)	137,507 (97.48%)
No surgery	2,543 (2.2%)	520 (3.54%)	325 (3.03%)	9 (4.86%)	3,397 (2.41%)
Unknown	127 (0.11%)	24 (0.16%)	7 (0.07%)	0 (0%)	158 (0.11%)
Radiation					
No radiation given	69,232 (59.95%)	8,742 (59.53%)	6,312 (58.93%)	95 (51.35%)	84,381 (59.82%)
Radiation given	44,262 (38.33%)	5,643 (38.43%)	4,212 (39.32%)	87 (47.03%)	54,204 (38.43%)
Unknown	1,987 (1.72%)	300 (2.04%)	187 (1.75%)	3 (1.62%)	2,477 (1.76%)
Total	11,5481 (81.87%)	14,685 (10.41%)	10,711 (7.59%)	185 (0.13%)	141,062 (100%)

Table 4.4 SEER DCIS population tumor attributes-(%): Shows the percentage from the subpopulation, W: white, AA: African American

	Non-Hispanic W	Non-Hispanic AA	Hispanic W	Hispanic AA	Total
Morphology					
Comedo	17,839 (15.45%)	2,027 (13.8%)	1,608 (15.01%)	25 (13.51%)	21,499 (15.24%)
Solid	7,323 (6.34%)	779 (5.3%)	692 (6.46%)	13 (7.03%)	8,807 (6.24%)
Cribriform	10,600 (9.18%)	1,408 (9.59%)	1,169 (10.91%)	25 (13.51%)	13,202 (9.36%)
Papillary	4,586 (3.97%)	866 (5.9%)	449 (4.19%)	7 (3.78%)	5,908 (4.19%)
Micropapillary	2,932 (2.54%)	462 (3.15%)	322 (3.01%)	13 (7.03%)	3,729 (2.64%)
Unknown	72,201 (62.52%)	9,143 (62.26%)	6,471 (60.41%)	102 (55.14%)	87,917 (62.33%)
Grade					
Low	11,739 (10.17%)	1,902 (12.95%)	1,155 (10.78%)	19 (10.27%)	14,815 (10.5%)
Intermediate	30,299 (26.24%)	4,159 (28.32%)	3,364 (31.41%)	56 (30.27%)	37,878 (26.85%)
High	35,131 (30.42%)	3,934 (26.79%)	3,483 (32.52%)	56 (30.27%)	42,604 (30.2%)
Unknown	38,312 (33.18%)	4,690 (31.94%)	2,709 (25.29%)	54 (29.19%)	45,765 (32.44%)
ER Status					
Positive	41,284 (35.75%)	6,373 (43.4%)	4,476 (41.79%)	83 (44.86%)	52,216 (37.02%)
Negative	9,203 (7.97%)	1,114 (7.59%)	957 (8.93%)	13 (7.03%)	11,287 (8%)
Borderline	147 (0.13%)	23 (0.16%)	10 (0.09%)	1 (0.54%)	181 (0.13%)
Unknown	56,458 (48.89%)	6,474 (44.09%)	4,976 (46.46%)	86 (46.49%)	67,994 (48.2%)
Not 1990+	8,389 (7.26%)	701 (4.77%)	292 (2.73%)	2 (1.08%)	9,384 (6.65%)
PR Status					
Positive	33,583 (29.08%)	5,343 (36.38%)	3,681 (34.37%)	72 (38.92%)	42,679 (30.26%)
Negative	13,934 (12.07%)	1,743 (11.87%)	1,418 (13.24%)	21 (11.35%)	17,116 (12.13%)
Borderline	283 (0.25%)	38 (0.26%)	30 (0.28%)	2 (1.08%)	353 (0.25%)
Unknown	59,292 (51.34%)	6,860 (46.71%)	5,290 (49.39%)	88 (47.57%)	71,530 (50.71%)
Not 1990+	8,389 (7.26%)	701 (4.77%)	292 (2.73%)	2 (1.08%)	9,384 (6.65%)
HER2 Status					
Positive	747 (0.65%)	119 (0.81%)	85 (0.79%)	1 (0.54%)	952 (0.67%)
Negative	1,525 (1.32%)	334 (2.27%)	188 (1.76%)	2 (1.08%)	2,049 (1.45%)
Borderline	177 (0.15%)	40 (0.27%)	21 (0.2%)	2 (1.08%)	240 (0.17%)
Unknown	15,695 (13.59%)	2,466 (16.79%)	2,046 (19.1%)	33 (17.84%)	20,240 (14.35%)
Not 2010+	97,337 (84.29%)	11,726 (79.85%)	8,371 (78.15%)	147 (79.46%)	117,581 (83.35%)
Total	115,481 (81.87%)	14,685 (10.41%)	10,711 (7.59%)	185 (0.13%)	141,062 (100%)

4.1.2 Data Preparation

For predicting breast cancer recurrence, we calculated the time to the next breast cancer for each patient. In the SEER data, each record represents a tumor diagnosed in a certain month and year in a patient. There are multiple records for some of the patients, i.e., multiple tumors were diagnosed in those patients some of which might be recurrences of the earlier tumors. We created a field for each patient to keep track of the diagnosed tumors for her. This field contains the sequence number of breast cancer tumors in each patient called BC rank, and it ranged from one to five for our population. If a patient has BC rank of five, this means she had five tumor records which were sorted by date of diagnosis, so the record for the first tumor diagnosed has the BC rank of one, the record for the second tumor has the BC rank of two and so on. We divided the records by BC rank into five groups and calculated time to the subsequent recurrence or time to event (TE) for each patient, e.g., TE to third breast cancer (BC rank=2) is time of diagnosis for the third breast cancer minus time of diagnosis for the second breast cancer. The features of these groups are summarized in Table 4.5.

Table 4.5 Number of breast cancer cases by time to event groups created in the first round. BC: Breast cancer, TE: Time to event or time to breast cancer recurrence

Time To Event Group	All BC Cases	Cases with TE=0
Time to second BC	97,744	20,555
Time to third BC	4,252	681
Time to fourth BC	233	42
Time to fifth BC	13	4
Total	102,242	21,282

Approximately 20% of the records with recurrence had TE equal to zero, which is unusual

since cancer usually recurs after a year if treated and more than 90% of SEER BC cases were treated with surgery. One of the reasons for a large number of zeros is sometimes a patient is diagnosed with multiple BC tumors at the same year, e.g., if a DCIS and an IBC are detected in the same time, they are recorded in separate rows in SEER database. When we were calculating BC rank field, one of the two tumors is assigned as case 1 and the other case 2; however, the two cases were diagnosed at the same time therefore neither is the recurrence of the other.

In the second round, we eliminated early recurrences, i.e., time to recurrence less than one year, to avoid cases that might not be recurrences. We re-created BC rank for records in order of occurrence and incremented BC rank if the time between that tumor record and the previous tumor record for the same patient is at least 12 months. This assumption corresponds to the definition of recurrence, i.e., detection of subsequent cancer after a period of time during which cancer could not be detected" [80] and existing literature [81] which defines recurrence as the cases detected one year after the original cancer was found. In the case of two tumors detected at the same time (invasive and in-situ), we kept the invasive case. If cases have the same behavioral code (both invasive or both in-situ), we used two approaches to determine the time to recurrence (Both approaches are shown in Figure 4.1):

- Max-Max: For both the earlier breast cancer and the next breast cancer, we chose the case with the maximum date field among the cases with the same BC rank. We called the time to recurrences created this way, Max-Max TE.

- Min-Max: For earlier breast cancer, we chose the one with the earliest date and for the subsequent breast cancer we chose the one with the latest date among the cases with the same BC rank. We called the time to recurrences created this way, Min-Max

TE.

Figure 4.1 Time to recurrence calculation by Min-Max and Max-Max methods for a patient with 4 breast tumors. Red line means the time between the two BC ranks was less than 12 months

For both of these approaches, we divided records by BC rank, which ranged from one to four. Next, we divided the time to recurrence files even further based on the type of prior breast cancer, i.e., DCIS vs. IBC. Since the number of cases with time to fourth cancer was small (61 overall), we merged the time to third and fourth breast cancer into one group. The description of the groups created is presented in Table 4.6.

Table 4.6 Number of breast cancer cases for time to event groups created in the second round. BC: Breast Cancer, IBC: Invasive Breast Cancer, TE: Time to Event or Time to Breast Cancer Recurrence

Time to Event Groups	**All BC Cases**	**Unknown if Surgery was done**
Time to second BC starting from IBC	45,656	26,979
Time to third/fourth BC starting from IBC	1,247	433
Time to second BC starting from DCIS	10,674	4,834
Time to third/fourth BC starting from DCIS	524	160
Total	58,101	32,406

4.1.3 Distribution Fitting

Breast cancer patients are at risk of cancer recurrence following treatment for breast cancer. We used two methods to quantify this risk: fitting distribution to the recurrence times, and fitting survival models to the data. In this section, we introduce the distribution fitting method for the SEER breast cancer data. We fit the lognormal, exponential, Weibull, gamma, and beta distributions to each time to event groups of breast cancer cases (first recurrence) calculated using two approaches, Max-Max and Min-Max. We divided records further to improve the distribution fits by histological types for DCIS based on ICD-O-3 coding (described in Appendix B), for invasive breast cancer cases, we used the American Joint Committee on Cancer (AJCC) 6th Edition staging system [82] for cases from 1988-2012 (refer to Appendix B). We also used grading codes explained in Appendix B for both DCIS and IBC cases as another grouping. Set of codes used for DCIS and IBC grouping are shown in Table 4.7. Furthermore we divided each of the groups into two groups of patients who were known to have received treatment, i.e., radiation or surgery, called a treatment group, and the group with no treatment or missing information about treatment called a no-treatment group.

The goodness-of-fit tests are based on empirical distribution function (EDF). Some EDF tests are not supported by SAS when certain combinations of the parameters of a specified distribution are estimated. In our analysis the gamma, beta and exponential distributions did not always have goodness-of-fit results. In the SAS documentation, the goodness-of-fit is available for these three distributions only under certain conditions for their parameters presented in Table 4.8.

SAS Enterprise Guide version 6.1 was used for all data analysis and goodness-of-fit tests. Proc univariate was run for the goodness-of-fit tests in SAS. We shifted all values of time to

Table 4.7 Histology and grade codes used for grouping DCIS cases and stage and grade codes used for grouping IBC cases for distribution fitting. The N/A category is used where grade was not determined or unknown.

DCIS		**IBC**	
Histology	Grade	Stage	Grade
8201	1	10	1
8230	2	21	2
8500	3	22	3
8501	4	31	4
8503	N/A	32	N/A
8507		40	
8522		90	

Table 4.8 Availability of Empirical Distribution Function Tests in SAS

Distribution	**Parameters Threshold**	**Scale**	**Shape**	**Tests Available**
Beta	θ pre-specified	σ pre-specified	α , β pre-specified	all
	θ pre-specified	σ pre-specified	α , β <5 estimated	all
exponential	θ pre-specified	σ pre-specified		all
	θ pre-specified	σ estimated		all
	θ estimated	σ pre-specified		all
	θ estimated	σ estimated		all
gamma	θ pre-specified	σ pre-specified	α pre-specified	all
	θ pre-specified	σ estimated	α pre-specified	all
	θ pre-specified	σ pre-specified	α estimated	all
	θ pre-specified	σ estimated	α >1 estimated	all
	θ estimated	σ pre-specified	α >1 pre-specified	all
	θ estimated	σ estimated	α >1 pre-specified	all
	θ estimated	σ pre-specified	α >1 estimated	all
	θ estimated	σ estimated	α >1 estimated	all

event so the minimum for TE is 0.5 (by subtracting 11.5 months from TE), then set the SAS parameters threshold or $\theta = 0$ and scale or $\sigma = \text{Maximum(TE)} + 5$ for all distributions. We tested numbers from 0,1, 2, . . . ,10 for adding to maximum in the scale parameter and 5 gave the best fit for our test case, which was DCIS with cribriform (8201) histology code group. Gamma and beta distributions fitted to the DCIS with 8201 histology code are shown in Figure 4.2. The complete results of the goodness-of-fit tests are presented in Appendix A for all of DCIS and IBC subgroups. In all tables, "R" means all P-values were less than or equal to 0.01 for all the goodness-of-fit tests performed by SAS, in other words, it means all goodness-of-fit tests run by SAS are rejected at significance levels less than or equal to 0.01. In case of at least one of the tests having P-value greater than 0.01, the three numbers represent the P-values for the Kolmogorov-Smirnov (KS), Cramer-von Mises (CM), and Anderson-Darling (AD) tests, respectively, for the lognormal, exponential, and gamma distributions, and the two numbers represent P-values for CM and AD respectively for the Weibull distribution. For DCIS grouped by histology codes, the beta distribution produced the best fit for both Max-Max and Min-Max approaches for all groups except for DCIS subgroup with 8500 histology code which is a category for DCIS cases with unknown histology code. For both DCIS and IBC, each no-treatment group had a better fit compared to its treatment group counterpart; however, the number of patients in each no-treatment group was significantly smaller than its treatment group counterpart. The beta distribution produced the best fit in about half of the IBC cases grouped by stage, but it did not perform well in IBC cases grouped by grade.

For simulating the patient's lifetime and measuring the expected quality of life under different treatment strategies, there were two caveats to using the fitted distributions for predicting recurrences: (i) Although we reached good fits for most of the breast cancer groups, we were unable to get a good fit for the IBC stage groups with codes 10, 21, 22,

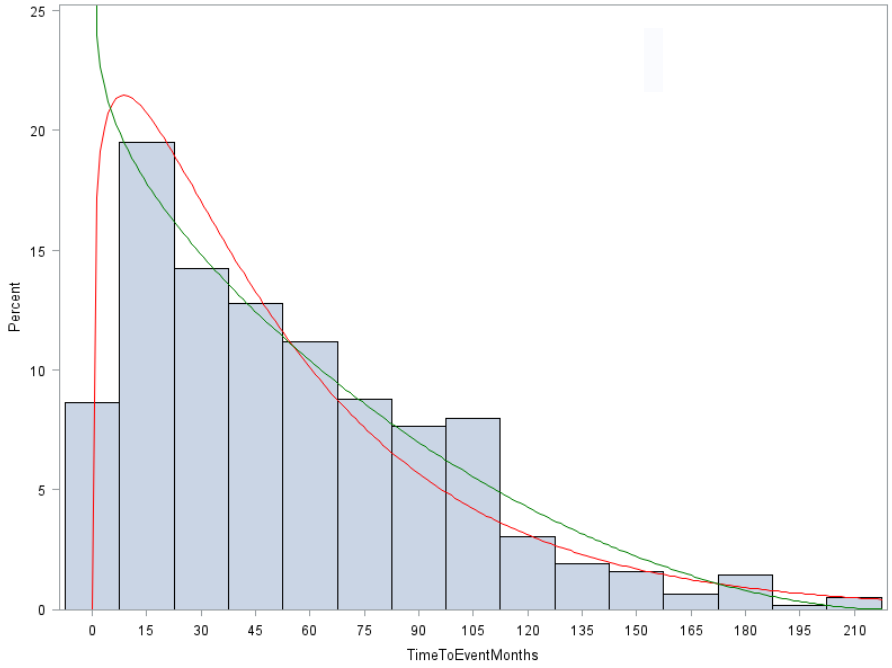

Figure 4.2 A histogram of TE in months for DCIS with cribriform (8201) histology code, fitted gamma and beta distributions are shown in red and green colors respectively

and 32 for the Max-Max approach and Stage groups 10, 32, 53, 54, and 70 for the Min-Max approach. The DCIS group with histology code 8500 did not have good fit in both approaches, and grouping by grades did not create good fits for all cases, either. (ii) We were fitting the distributions for cases that did have a recurrence, this way we were ignoring the effect of cases that were excluded due to no further follow-up or death and hence not having a recurrence, i.e., censored cases. These two issues prompted us to fit survival models which consider cases that were censored due to death or no further follow up and also take into account the effect of other prognostic factors such as age at diagnosis, race, etc.

4.2 Recurrence Prediction

In this section, we discuss some of the methods used in the literature to predict breast cancer recurrence, introduce survival analysis methods used in predicting recurrence, and recurrence prediction model we used in the simulation.

4.2.1 Breast Cancer Recurrence Prediction

After breast cancer treatment there is always a chance of breast cancer recurrence, therefore the oncologist is faced with the dilemma of whether to put the patient through a systemic treatment after surgery to reduce the risk of recurrence. Risk prediction models (RPMs) have been developed to aid both the oncologist and the patient in this decision. RPMs typically use different prognostic factors to predict the probability of recurrence for subgroups of patients within a certain period of time (usually 5-year or 10-year periods). RPMs are divided into two groups based on what type of predictive factors they use as inputs: (i) RPMs that include only clinical prognostic factors like tumor size, lymph node involvement, ER status, PR status, HER2 status, etc. (ii) RPMs that also include biomolecular profiles in addition to clinical prognostic factors or only biomolecular profiles,e.g., proteins that are not usually measured in regular clinical practice.

Engelhardt et al. [83] reviewed 20 RPMs, six of which used only clinical variables as inputs. Three of these RPMs are based on the U.S. population: Adjuvant! [84], BC Nomogram [85], and CancerMath [86].

Adjuvant!, which is one of the most commonly used tools by clinicians, was developed using the SEER data and the efficacy of adjuvant therapy estimates from 1998 overviews of randomized trials of adjuvant therapy. It takes age at diagnosis, comorbidities (simultaneous

presence of two chronic diseases or conditions in a patient), cancer grade, tumor size, nodal status, and effectiveness of systemic therapy as inputs to predict overall survival, recurrence-free survival, and systemic treatment benefits for breast cancer patients in a 10-year period.

BC Nomogram was created to estimate the 15-year breast cancer-specific survival for patients with no prior breast cancer who did not receive any adjuvant therapy. It is built on Memorial Sloan-Kettering Cancer Center (New York, NY) data to improve the Nottingham Prognostic Index (NPI) model, which was built on the UK population in 1982 [87]. NPI was constructed based on lymph node stage, tumor size and pathological grade using the Cox proportional hazards model. BC Nomogram inputs include age at diagnosis, if cancer is ductal or lobular, and tumor size.

CancerMath predicts overall survival (probability of death) and systemic treatment benefits for breast cancer patients in each year after breast cancer diagnosis up to 15 years. It uses the SNAP (Size + Nodes + Prognostic Markers) method (a method used to integrate information on tumor characteristics using a series of equations) to estimate the risk of death from cancer for each patient. CancerMath inputs include age at diagnosis, tumor morphology, cancer grade, tumor size (CancerMath only includes tumors with size less than 5 cm), nodal status, ER and HER2 status for the patient.

There are also numerous studies aimed at identifying clinical attributes associated with breast cancer recurrence. Subhedar et al. [88] used Cox proportional hazards models based on Memorial Sloan Kettering Cancer Center data from 1978-2010 to examine breast cancer recurrence after different DCIS treatments such as breast conserving surgery and mastectomy, and they showed that the hazard rate of breast cancer recurrence declines in later years for breast conserving surgery compared to earlier years. Colleoni et al. [89] published the results of a 24-year follow-up of breast cancer patients from the International Breast Cancer Study Group (IBCSG) clinical trials. They show that the annualized hazard

of recurrence is highest during the first five years. During the first five years, ER-positive tumors have a lower annualized hazard compared to ER-negative ones. However, beyond five years, patients with the ER-positive disease have higher hazards. Braunstein et al. [74] sought to identify risk factors for breast cancer recurrence after breast conserving therapy for early stage invasive breast cancer using multi-institutional cohort data from the period 1998–2007. Their Cox proportional hazards model demonstrates that younger age and lymph node involvement are associated with higher risk of local recurrence.

4.2.2 Survival Analysis

Traditional methods such as logistic and linear regression are not able to include both the event and time aspect as the outcome in the model. Traditional regression methods also are not equipped to handle censoring, a special type of missing data that occurs in time-to-event analyses when subjects do not experience the event of interest during the follow-up time. Hence, in the presence of censoring, the true time to the event might be underestimated [90]. Therefore a group of methods used to analyze data with time to an event as the outcome of interest (dependent variable) in the presence of censoring are utilized which are called survival analysis, also known as reliability theory (analysis) in engineering. The book *Survival Analysis: Techniques for Censored and Truncated Data* [91] was used to introduce the survival analysis concepts in this section and as a reference for the analyses needed.

Survival data is usually collected by following subjects for a period of time to collect survival times. The length of time that is measured from the time origin to the time that the event of interest happens is called survival time. One of the distinguishing features of survival data is censoring. Censoring occurs when there is incomplete information about

survival time, e.g., in a 20-year follow-up breast cancer recurrence study, survival time of a patient is censored if she does not have a breast cancer recurrence during the 20-year follow-up period after her diagnosis. This is because there is incomplete information on the time to cancer recurrence for her, in other words, we only know that recurrence did not happen during the 20-year period and have no more information. This type of censoring is called right censoring. Right censoring happens when we have information on the start but not the end of survival time for the subject. Right censoring is the most common censoring scheme in survival analysis.

Non-survival methods such as linear regression do not deal with censoring specifically, that is why in many fields such as health care survival analysis is used to analyze time to event data. Survival analysis methods are divided into parametric, semi-parametric and non-parametric methods. Parametric methods assume a specific distribution or structure for survival time, non-parametric methods do not have any assumption on the survival time structure. For example, Kaplan-Meier estimate is a non-parametric survival method which is a step function at the observed event times with no underlying assumption for survival function. One of the most commonly used methods in survival analysis is the Cox proportional hazards (PH) model which does not assume any distribution for survival time but assumes that the effect of covariates stays the same through time (proportional hazard property). The Cox proportional hazards model is grouped with semi-parametric methods because of its additional proportional hazard (PH) assumption.

4.2.2.1 Definitions of Common Terms in Survival Analysis

There are several terms and functions we will use in our analysis that we introduce here.
Event: Cancer recurrence, death, failure of machine or any event or experience of interest. In this thesis, we assumed recurrence as the event of interest.

Time or Study Time: The time from beginning of an observation or follow-up to (i) the event; (ii) the end of the study; or (iii) loss of contact or withdrawal from study. In this dissertation we assumed the time origin to be the time that the first cancer was diagnosed.
Censoring / Censored Observation: An observation is called censored when we only have the information that subject did not experience the event during a certain period of time. One of the censoring schemes is right censoring where we only know that from a known origin of time to a certain point in time (censoring time) the subject did not experience the event, the subject may or may not experience the event after censoring time but we do not know about it. The SEER data used in this dissertation is right-censored.
Survival Function S(t) : The probability that subject experiences an event after time t is called survival at time t.

$$S(t) = P(T > t)$$

The survival function is called the reliability function in reliability analysis.
Hazard Function h(t): The hazard function which is also known as the hazard rate (HR) or conditional rate of failure in reliability analysis is defined as below:

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T \leq t + \Delta t | T \geq t)}{\Delta t}$$

A related quantity is the cumulative hazard function $H(x)$, defined by

$$H(t) = \int_0^t h(u)\,\mathrm{d}u = -\ln[S(t)]$$

Covariate: A covariate, also called an independent variable or explanatory variable, is a variable that possibly has predicting ability for the outcome of interest (dependent variable).

We also use the term prognostic factor for covariates.

Covariates fall into two groups: continuous variables and categorical variables. In our study age is a continuous measurement whereas variables such as surgery type that take discrete values from a limited number of categories fall into categorical or nominal variables group. We need to represent categorical variables in a quantitative form to use them in statistical models. The common way to code the categorical variables is "treatment" coding which uses binary variables called "dummy" variables which take values 0 or 1. If a nominal variable has g levels we use one level of g as reference level and we create $g-1$ dummy variables to code the variable in our model. Assuming that all these g levels are mutually exclusive, only one of the $g-1$ variables can take value 1 at each observation and the reference group is represented by setting all these $g-1$ dummy variables to zero. For each categorical variable, we chose the level that had the highest frequency and was not equal to "unknown" or "other" or "missing" to be the reference group so comparison would be more meaningful. For more information on different coding schemes including treatment coding, reader is referred to the book *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences* by Cohen et al. [92].

4.2.2.2 Cox Proportional Hazard (PH) Model

The Cox proportional hazards (PH) model is one of the methods used in survival analysis for predicting survival time when multiple covariates $(x_1, x_2, \ldots, x_p)$ affect survival time(t). The Cox PH model does not assume any underlying distribution for the time to event(t) but it assumes that the hazard function follows the structure below:

$$h(t|x) = h_0(t)e^{(\beta_1 x_1 + \beta_1 x_1 + \ldots + \beta_p x_p)} = h_0(t)e^{(\beta x)}.$$

If we consider two subjects with two different set of covariates x and x', then the ratio of their hazard rate (hazard ratio-HR) is as below:

$$HR = \frac{h(t|x)}{h(t|x')} = \frac{h_0(t)e^{(\sum_{i=1}^{p}\beta_i x_i)}}{h_0(t)e^{(\sum_{i=1}^{p}\beta_i x_i')}} = e^{(\sum_{i=1}^{p}\beta_i(x_i - x_i'))}$$

As seen above in the Cox PH model, HRs are proportional and the HRs are time independent; therefore the model has "proportional hazard" in its name. If the hazard rates are time dependent, then the Cox PH is not a good fit.

There are several methods to test if a model satisfies the proportionality assumption such as the graphical method. In this dissertation, we added time-dependent covariates to the Cox PH model and tested if the coefficients of these covariates are equal to zero. This is done by creating time-dependent covariates equal to the interactions of the predictors and a function of survival time and including them in the model. For example, if the predictor of interest is x_j , then we create a time-dependent covariate $x_j(t) = x_j g(t)$, where $g(t)$ is a function of time, e.g., t or $\ln t$. The model assessing proportional hazard assumption for x_j adjusted for other covariates is

$$h(t, x(t)) = h_0(t)e^{[\beta_1 x_1 + \beta_2 x_2 + ... + \beta_p x_p + \delta x_j g(t)]}$$

where $x(t) = (x_1, x_2, \ldots x_p, x_j(t))'$ is the vector of explanatory variables for a particular individual. The null hypothesis to check proportionality is that $\delta = 0$. The test statistic can be carried out using either a Wald test or a likelihood ratio test [91]. In the Wald test, the test statistic is $W = (\hat{\delta}/se(\hat{\delta}))^2$. The likelihood ratio (LR) test calculates the likelihood under null hypothesis, L_0, and the likelihood under the alternative hypothesis,L_α. The LR statistic is then $LR = -2\ln(L_0/L_\alpha) = -2(l_0 - l_\alpha)$, where $l_0 = \ln(L_0)$, $l_\alpha = \ln(L_a)$. The statistic has approx-

imately a chi-square distribution with one degree of freedom under the null hypothesis, provided the sample size is large enough. If the time-dependent covariate is significant, i.e., the null hypothesis is rejected, then the predictor is not proportional. In the same way, we can also assess the PH assumption for several predictors simultaneously. For our models we used $g(t) = \ln(t)$ for all variables included in the model and we used the Wald test to check if the coefficients are equal to zero, the statistic for which is automatically estimated by SAS software.

If the assumption of PH is violated, the results from a PH model will be difficult to generalize to situations where the length of follow-up is different from the data used in the analyses. The accelerated failure time (AFT) approach is an alternative strategy for the analysis of time-to-event data and can be suitable even when hazards are not proportional, and this family of models contains a certain form of PH as a special case (when we use Weibull as the baseline distribution it also satisfies the proportional hazards assumption). The framework can allow for different forms of the hazard function and may provide a closer description of the data in certain circumstances. In addition, the results of the AFT model may be easier to interpret and more relevant to clinicians, as they can be directly translated into expected reduction or increase of the median time to event, unlike the hazard ratio which only deals with the proportion of subjects not experiencing the event.[93]

4.2.2.3 Accelerated Failure Time (AFT) Model

Accelerated failure time (AFT) models are a set of parametric survival models where the survival function of a subject with covariates $X = (x_1, x_2, \ldots, x_p)$ at time t, $S(t|X)$, is the same as the survival function of a subject with baseline survival, S_0, at time $t\, e^{(-\theta^\tau X)}$, where τ indicates transpose of a vector or a matrix, $\theta^\tau = (\theta_1, \theta_2, \ldots, \theta_p)$ is a vector of regression coefficients, and $e^{(-\theta^\tau X)}$ is called acceleration factor, which shows how a change in covariate

values changes the time scale from the baseline time scale. In other words:

$$S(t|X) = S_0[t.e^{(-\theta^\tau X)}] \text{ for all } t$$

A second implication is that the median time to the event with covariate vector X is the baseline median time to event divided by the acceleration factor.

The second representation of the relationship between covariate values and survival is the linear relationship between log(time) and the covariate values. Here, the usual linear model for log time is assumed, namely,

$$\ln T = \mu + \gamma^\tau X + \sigma W$$

where γ is a vector of regression coefficients and W is the error distribution. The interpretation of $\gamma^\tau = (\gamma_1, \gamma_2, \ldots, \gamma_p)$ is very similar to a linear regression model. When $|\gamma_k|$ is small, it can be interpreted as the percentage increase if $\gamma_k > 0$, or percentage decrease if $\gamma_k < 0$ in the average survival time and/or median survival time when we increase the covariate value of x_k by one unit. The two representations explained above are closely related. If we let $S_0(t)$ be the survival function of the random variable $e^{(\mu+\sigma W)}$, then, the linear log-time model is equivalent to the accelerated failure-time model with $\theta = \gamma$. In AFT models, a probability distribution is specified for $\ln(T)$, e.g., log-logistic, log-normal, and Weibull distribution. Some of the distributions considered for $\ln T$ in AFT models with their corresponding error distributions in AFT are shown in Table 4.9.

Table 4.9 lnT and Error Distribution- Φ() is the standard normal cumulative distribution function

lnT Distribution	**Baseline Survival Function** ($S_0(t)$)	**Error Distribution** (W)
Exponential	$e^{(-\lambda t)}$	Standard Extreme Value (min)
Weibull	$e^{(-\lambda t^{\alpha})}$	Extreme Value
Log-logistic	$\frac{1}{1+\lambda t^{\alpha}}$	Standard Logistic
Lognormal	$1-\Phi(\frac{[\log(t)-\mu]}{\sigma})$	Standard Normal
Gamma	No closed-form expression	Generalized Extreme Value

4.2.2.4 Cox Proportional Hazards Model and Accelerated Failure Time Model

An obvious way to choose between the two model types (semi parametric and parametric) is to fit the one that fits the data better. If the AFT model clearly fits the data better than the Cox PH model, or vice versa, this model may be adopted as being the more appropriate. The main drawback of parametric models is the need to specify the distribution that most appropriately mirrors the distribution of the actual survival times. This is an important requirement that needs to be verified, and an appropriate distribution may be difficult to identify because of the presence of censoring. Where a suitable distribution can be found, however, the parametric model is more informative than the Cox PH model. It is straightforward to derive the hazard function and to obtain predicted survival times when using a parametric model, which is not the case in the Cox PH framework. Additionally, the appropriate use of these models offers the advantage of being slightly more efficient; they yield more precise estimates (i.e. smaller standard errors). In this dissertation we fit both types of model to the data, checked the underlying assumption and looked at their fit based on the Akaike information criterion (AIC) and residuals graphs. Partial likelihood is used to calculate the AIC in semi-parametric models whereas likelihood is used in AIC calculation for parametric models [91]. In partial likelihood we are interested in the observed rankings

in the data (T1 > T2 > ...) without specifying the baseline hazard [94].

4.2.3 Survival Models for SEER Data

4.2.3.1 Data Preparation

Two sets of records are considered censored in our data: records of patients who did not have a recurrence due to death before breast cancer relapse and patients who did not have a recurrence before last follow-up day (Dec 31st, 2012 for our data). First, we eliminated the records with no recurrence and no follow-up information, i.e., death date or last follow-up was unknown as well as the patients who were in the study for less than one month, i.e., patients with study time equal to zero (TE=0). Then we calculated the TE for the remaining censored cases (months from last diagnosis to death or months from last diagnosis to the cut-off date of 12/31/2012), and added them to the data we created for the cases with the first breast cancer recurrence using the Max-Max approach in Section 4.1.2 to prepare the data for survival analysis. Next, we divided the breast cancer population into four groups based on race and type of initial breast cancer: white patients with initial DCIS (DCIS W), African American patients with initial DCIS (DCIS AA), white patients with initial IBC (IBC W), and African American patients with initial IBC (IBC AA). The information for these four groups is shown in Table 4.10. We ran Cox PH and AFT models with 7 different distributions on each of these groups.

Originally we had the following covariates included as inputs to the models (codes for each of the categorical variables are described in Appendix B): age at diagnosis (a numerical variable which has values over 35), and the following categorical variables: ethnicity, histology type with ICD-O-3 coding, grade codes, ER status, PR status, HER2 status, surgery codes, radiation codes, tumor size, and stage codes based on AJCC 6th

Table 4.10 Recurrence and vital status for survival data subgroups- (%): Shows the percentage from the subpopulation in each row, W: white, AA: African American

Subgroup	Had a Recurrence	Died Before Recurrence	Alive with No Recurrence	Total
DCIS W	8,481 (7.81%)	13,890 (12.75%)	86,507 (79.43%)	108,155 (100%)
DCIS AA	1,146 (8.59%)	2,087 (15.64%)	10,110 (75.77%)	13,343 (100%)
IBC W	37,982 (4.78%)	249,232 (31.39%)	506,722 (63.82%)	793,936 (100%)
IBC AA	4,454 (4.64%)	37,088 (38.68%)	54,350 (56.68%)	95,892 (100%)

edition [82]. Although HER2 status is recognized as one of the covariates affecting breast cancer survival in the literature, we did not include it in our models. This was due to the fact that HER2 was only collected in 2010-2012 (less than 13% of records has HER2 status values in all survival data created) and for all other years, HER2 status is missing.

4.2.3.2 Model Selection

With the exception of the Weibull and lognormal distribution, it is difficult to use a formal statistical test to discriminate between parametric models because the models are not nested in a larger model. One way of selecting an appropriate model is to base the decision on minimum Akaikie information criterion (AIC).

For a model $f(X|a)$ with the set of covariate coefficients (a) and the set of observations (X), the maximum likelihood estimate $a(x)$ is defined as the value of a that maximizes the likelihood $f(x|a)$ for a given observation x. The value of $\log f(x|a(x))$ shows an upward bias as an estimate of $\log f(X|a)$. Thus to use $\log f(x|a(x))$ as the measure of the goodness of the model $f(X|a)$, it must be corrected for the expected bias.

The expected bias is equal the dimension, or the number of parameters, for the set of covariate coefficients a. Thus the relative goodness of a model determined by the maximum likelihood estimate is given by

AIC = -2*(log maximum likelihood - number of parameters) or

AIC = -2*(log maximum likelihood) + 2($p+k$).

Here the log denotes natural logarithm. The coefficient -2 is used to make the quantity similar to the familiar chi-square statistic in the test of the dimensionality of the parameter space. p denotes the number of explanatory variables and k is the number of parameters for the chosen distribution, e.g., $k=2$ if we used Weibull distribution for the AFT model and $k=0$ for Cox PH model [95]. We used AIC to evaluate the relative quality of the statistical models (smaller AIC is better). Although other goodness-of-fit tests exist in the literature, AIC was the common goodness-of-fit test that was available from SAS in all the AFT and Cox PH models, and by including the number of parameters and covariates in the formula we try to avoid over-fitting.

We used proc lifereg and proc phreg to run AFT and Cox PH models in SAS, respectively. We used stepwise selection to choose the variables for Cox PH model. Stepwise selection is a method that allows moves in either direction, dropping or adding variables at the various steps. For AFT models none of the selection methods (backward, forward, and stepwise selection) were available in the software so we started with all the possible covariates in the model then manually eliminated covariates to reach convergence for the model and get the lowest AIC possible when all the variables had P-values less than 0.05 (for type III analysis). In the next sections, we discuss the resulting models.

In our survival models, all the covariates except for age are categorical variables. For each variable, two types of variable analysis are produced: type III analysis of effects and analysis of maximum likelihood parameter estimates. Type III analysis of effects for AFT and Cox PH models is testing the effect of adding each variable to the model using the likelihood ratio test format. For each variable like v the following is computed: $s=-2[l(\hat{\beta})-l(\tilde{\beta})]$ where l represents the loglikelihood, $l(\hat{\beta})$ represents loglikelihood of the model with all the selected variables but variable v (called reduced model) and $l(\tilde{\beta})$ represents loglikelihood of the

model with all the selected variables including the variable v (called the full model). The resulting test statistic is distributed as a chi-squared variate, with degrees of freedom equal to the number of parameters that are constrained (here, the number of variables removed from the model). The type III analysis tests if the increase in the likelihood by adding variable v is statistically different from zero. For continuous variables, type III analysis and analysis of maximum likelihood parameter estimates are the same. On the other hand, the analysis of maximum likelihood estimates for categorical variables compares each level of a categorical variable to the reference level (also called baseline class), to check if the effect of each level compared to the reference level is statistically significant. The degrees of freedom are the number of parameters in the full model (all the selected variables) minus the number of parameters in the reduced model (all the selected variables except the specific variable).

4.2.3.3 Cox PH Results

We first ran the Cox PH model for the four groups in Table 4.10 using stepwise selection for variable selection. We included time dependent variables for each of the variables in the model, to check the proportionality assumption, by multiplying each of them by log(TE), e.g., the time dependent variable for age is age*log(TE) . Then we added a joint hypothesis test to check if the coefficients of these time dependent variables were equal to zero, called the proportionality test. After building the models using stepwise variable selection, if at least one time dependent variable remained in the model with P-value less than 0.05, it would cause proportionality test rejection at significant level at least 0.05, which means the proportionality assumption was not valid. All groups except for the African American DCIS group had at least one time dependent variable in their final models. For the African American DCIS group none of the time dependent variables had coefficients that were

Table 4.11 Cox Proportional Hazard Models Details for Four Groups of SEER Data Using Stepwise Selection- AA: African American, W: white, IBC: Invasive breast cancer, AIC: Akaike information criterion, -: None of the time dependent variables not in the model

Group	Variable(s)	Stratified by Decade	AIC	Proportionality Test P-value
DCIS AA	Surgery	No	19746	-
DCIS W	Age, Surgery, Surgery*log(TE), PR Status, Radiation*log(TE), Radiation, Histology	No	183504	<.0001
IBC AA	Age*log(TE), Surgery, Surgery*log(TE), PR Status, ER Status, Radiation*log(TE) , Stage, Stage*log(TE)	No	90043	<.0001
IBC W	Age, Age*log(TE), Surgery, Surgery*log(TE), Histology*log(TE), ER Status, Radiation*log(TE), Radiation, Stage, Stage*log(TE), Ethnicity, Grade	No	923012	<.0001
DCIS AA	Surgery, PR Status	Yes	17794	-
DCIS W	Age, Surgery, Surgery*log(TE), PR Status, Radiation*log(TE), Radiation, Histology	Yes	167934	<.0001
IBC AA	Age*log(TE), Surgery, Surgery*log(TE), PR Status, ER Status, Radiation*log(TE) , Stage, Stage*log(TE)	Yes	80778	<.0001
IBC W	Age, Age*log(TE), Surgery, Surgery*log(TE), Histology*log(TE), ER Status, Radiation*log(TE), Radiation, Stage, Stage*log(TE), Ethnicity, Grade	Yes	837937	<.0001

statistically different from zero. We suspected that the significance of time variables might be avoided if we used stratification. Next, we created a new variable called decade which captures the decade in which the patient was diagnosed with the initial breast cancer. When we added the stratification on decade to the remaining three models, the proportionality test was still rejected. The summary of these models with their corresponding AIC statistics are presented in Table 4.11. All the variables included in the model had P-value less than 0.0001 for their type III analysis.

4.2.3.4 AFT Results

Accelerated failure time models are fitted using the exponential, Weibull, logistic, normal, log-logistic, lognormal, and generalized gamma distributions. The generalized gamma is a 3-parameter distribution with parameters k. The survival function for this form of the generalized gamma distribution is given by:

$$s(w) = \begin{cases} 1 - \frac{\Gamma(\delta^{-2},\delta^{-2})\exp(\delta * \frac{w-\mu}{\sigma}))}{\Gamma(\delta^{-2})} & \text{if} \quad \delta > 0 \\ \frac{\Gamma(\delta^{-2},\delta^{-2})\exp(\delta * \frac{w-\mu}{\sigma}))}{\Gamma(\delta^{-2})} & \text{if} \quad \delta < 0 \end{cases}$$

where μ denotes the location parameter, σ denotes the scale parameter, $\Gamma(a)$ denotes the complete gamma function, $\Gamma(a,z)$ denotes the incomplete gamma function, and δ is a free shape parameter. For more information on the generalized gamma distribution, the reader is referred to the book *Statistical Models and Methods for Lifetime Data* [96]. The generalized gamma distribution includes the Weibull, exponential, and the lognormal models as limiting cases. However, the other parametric models (logistic, normal, log-logistic) are not nested in the generalized gamma distribution, and it is difficult to use a statistical test to discriminate between them. That is why we use AIC for model selection. Also the generalized gamma model is most commonly used as a tool for picking an appropriate parametric model for survival data but, rarely, as the final parametric model, that is why we chose the next best model instead, if gamma distribution had the lowest AIC [90]. For the parametric models, the AIC is given by AIC=-2*log(Likelihood)+2*(p+k), where k=1 for the exponential model, k=2 for the Weibull, log-logistic, and lognormal models and k=3 for the generalized gamma model. For each model, we first include all the variables in the models, if the model building process converged then we used backward elimination for variable selection eliminating the variable with higher P-value until we are left with variables with

P-values less than 0.05. If the model did not converge in the beginning, which is usually caused by no statistical difference among different levels of a categorical variable that is in the model, we checked the P-value for different levels of each variable and we chose to eliminate the variable with more levels with high P-value to see if it results in convergence. We also checked to see if elimination of other variables results in model convergence; but for our dataset there were certain variables that needed to be eliminated for model convergence. The models fitted to the four groups in SEER data with their corresponding AIC statistics can be seen in Table 4.12.

From the Table 4.12 we can see for DCIS AA, DCIS W, and IBC W groups the AFT with lognormal distribution has the lowest AIC. For IBC AA group AFT with gamma distribution has the lowest AIC but AFT with the lognormal distribution is a close second; and since we prefer to choose simpler models, we use lognormal distribution to model it in the simulation. The final selected models chosen for each group, selected variables with P-values for type III analysis of each, and each models' AIC statistics are shown in Table 4.13. For each variable included in the model, there are two variables in the table. First is degrees of freedom, which equals 1 for continuous variables and number of variable levels minus 1 for categorical variables, e.g. there are 5 distinct values (number of levels=5) possible for grade variable in IBC W group which results in degrees of freedom of 4 for grade in the model. The other value shows the P-value which is used to test the null hypothesis that including that variable results in no likelihood increase. A low P-value (usually < 0.05) indicates that you can reject the null hypothesis that the increase in the likelihood by adding the variable to the model is not statistically significant. If there is no value in front of a covariate, that covariate was not selected in the final model.

We checked the overall fit of parametric models using Cox-Snell residuals. The Cox-Snell residual, r_j, equals to the negative of the natural log of the survival probability for each

Table 4.12 AIC of Fitted Parametric Models to the Four Groups of SEER Data- AA: African American, W: white, IBC: Invasive breast cancer, AIC: Akaike information criterion

	DCIS AA	DCIS W	IBC AA	IBC W
Exponential	8649	67466	36630	314124
Gamma	8537	66520	35704	309048
Log-logistic	8498	66899	35979	311464
Lognormal	8435	66360	35741	308452
Logistic	13264	103612	55555	482420
Normal	13048	101796	54497	472429
Weibull	8515	67338	36089	311957

Table 4.13 Type III analysis for variables included in selected AFT models- AA: African American, W: white, IBC: Invasive breast cancer, DF: Degrees of freedom, , AIC: Akaike information criterion.

	DCIS AA		DCIS W		IBC AA		IBC W	
	DF	**P-value**	**DF**	**P-value**	**DF**	**P-value**	**DF**	**P-value**
ER Status	4	<0.001	4	<0.001	3	<0.001	4	<0.001
Age			1	0.0018	1	<0.001	1	<0.001
Surgery			12	<0.001	11	<0.001	12	<0.001
Stage					10	<0.001	10	<0.001
Radiation			9	<0.001			9	<0.001
Histology			6	<0.001				
PR Status					3	0.0068		
Ethnicity							1	<0.001
Grade							4	<0.001
Distribution	Lognormal		Lognormal		Lognormal		Lognormal	
AIC	8435		66360		35741		308452	

observation. It is also defined by $r_j = \hat{H}(T_j|Z_j)$, where $\hat{H}$ is the cumulative hazard rate of the fitted model, $Z_j = (Z_{j1}, \ldots, Z_{jp})$ is the vector of covariates for observation j, and T_j is the study time for observation j. If the model fits the data then the r_j's should follow a standard (distribution parameter (rate) $\lambda = 1$) exponential distribution, so that a hazard plot of r_j versus the Nelson-Aalen estimator of the cumulative hazard of the r_j's should be a straight line with slope 1. Nelson-Aalen is a nonparametric estimator of the cumulative hazard rate based on right-censored data, where estimation of the cumulative hazard at time t is $\hat{H}(t) = \Sigma_{t_i<t} \frac{d_i}{n_i}$ with d_i the number of events at t_i and n_i the total number of individuals at risk at t_i. The Cox-Snell residuals for some of the AFT models are:

Exponential: $\hat{\lambda} T_j e^{(\hat{\beta}^t Z_j)}$ (λ is the rate of exponential distribution)

Weibull: $\hat{\lambda} T_j^{\hat{\alpha}} e^{(\hat{\beta}^t Z_j)}$ (λ is the inverse of scale and α is the shape parameter of the distribution)

Log-logistic: $\ln\left(\frac{1}{1+\hat{\lambda} T_j^{\hat{\alpha}} \exp(\hat{\beta}^t Z_j)}\right)$ (λ is the inverse of scale and α is the shape parameter of the distribution)

lognormal: $\ln\left[1 - \Phi\left(\frac{\ln T_j - \hat{\mu} - \hat{\gamma} Z_j}{\hat{\sigma}}\right)\right]$ (μ is the mean and σ is the standard deviation of the distribution).

We do the following to check the model fit using the Cox-Snell residuals:

(i) Estimate cumulative hazard function of the Cox-Snell residuals. Denote the estimates by $\hat{H}_r(r)$.

(ii) Plot $\hat{H}_r(r)$ against r_j. Check whether the plot is linear through the origin with a slope 1. If yes, the fitted model is adequate.

Here is a note of caution about Cox-Snell residuals: "The Cox-Snell residuals should be used with some caution. The exponential distribution for the residuals holds only when the actual parameter values for the models are used. When the estimates of these quantities are used to compute the residuals, as we do here, departures from the exponential distribution

may be partly due to the uncertainty in estimating the parameters. This uncertainty is the largest in the right-hand tail of the distribution and for small samples [91]."

The four cumulative hazard plots for the Cox-Snell residuals for the final models in Table 4.13 for four groups, DCIS AA, DCIS W, IBC AA, and IBC AA are shown in Figures 4.3, 4.4, 4.5, and 4.6, respectively. We see from these plots that lognormal AFT gives reasonable fits to the the four groups of data. The Cox-Snell residuals follow the 45 degree line closely for IBC AA shown in Figure 4.5. For the remaining three groups, we see some departure from the 45 degree line on the right hand side but they still have reasonable fits if we compare them to the accepted examples in the literature [91].

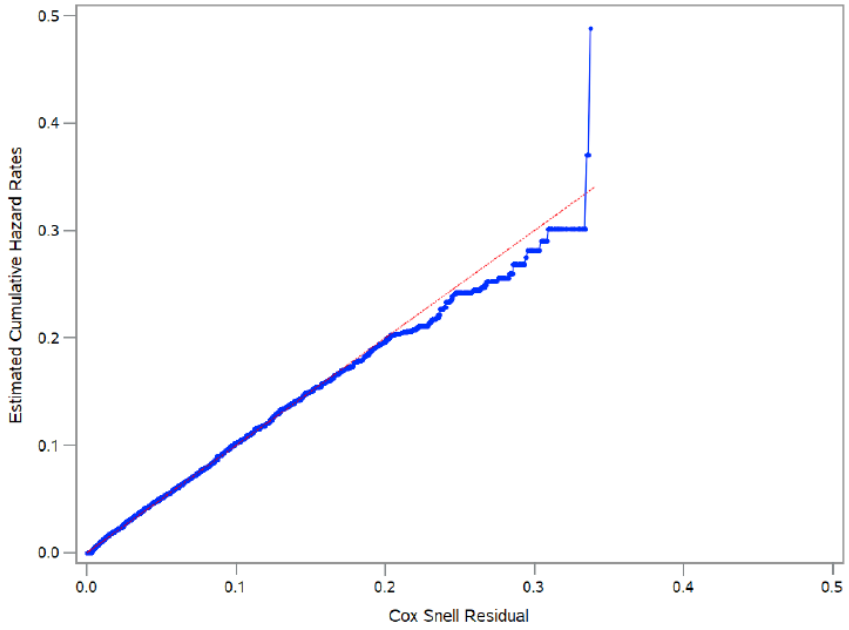

Figure 4.3 Cox-Snell residuals to assess the fit of the lognormal regression model for the DCIS AA group- AA: African American.

The estimates for four groups: DCIS AA, DCIS W, IBC AA, and IBC W are summarized in

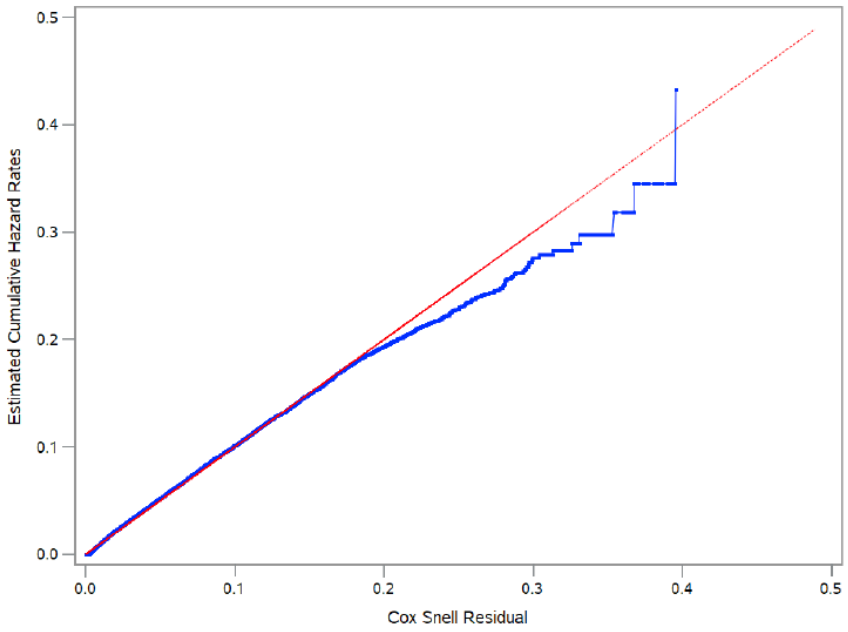

Figure 4.4 Cox-Snell residuals to assess the fit of the lognormal regression model for the DCIS W group- W: white.

Tables 4.14, 4.15, 4.16, and 4.17, respectively. The variables and the estimated coefficients are shown in the first and second columns in each of the Tables. Age is the only numerical variable, and it has a positive coefficient in the model for African American IBC group meaning as the age of diagnosis for the first IBC in African American patients increases, the mean time to recurrence increases, as well. Dummy coding was used to quantify categorical variable. For each group of categorical variable group, the baseline is the variable with DF and coefficient estimate equal to zero. The coefficients can be interpreted as explained in Section 4.2.2.3: The estimate for each coefficient shows the change in log(recurrence time) with the condition present compared to baseline class while holding other covariates fixed. For example grade is one of the categorical variables in white IBC group. Grade-I was chosen as baseline, because it has the highest frequency among the grade groups. All other Grade levels have negative coefficients which means they all have smaller median time to

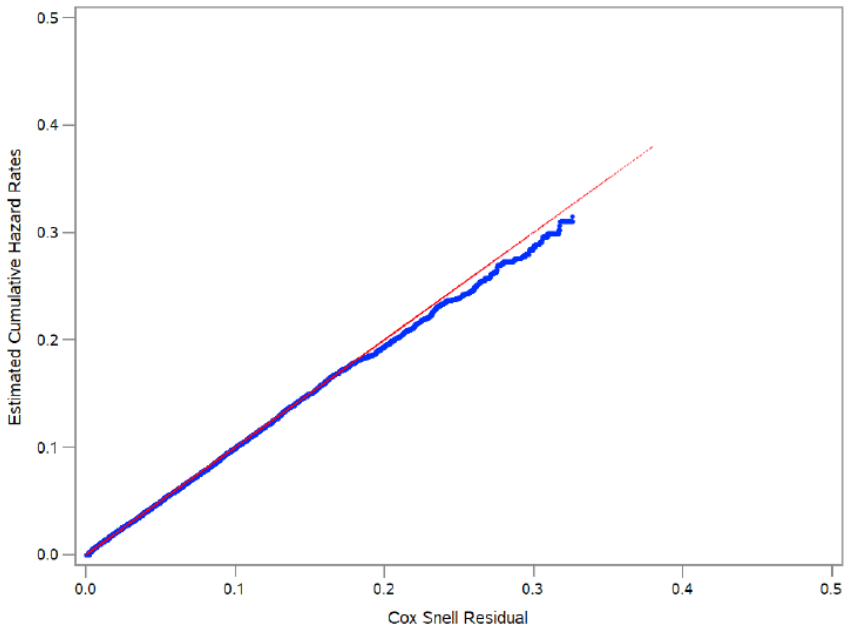

Figure 4.5 Cox-Snell residuals to assess the fit of the lognormal regression model for the IBC AA group- AA: African American, IBC: Invasive breast cancer.

event compared to that of the Grade-I when all the other variables are fixed. The summary of SEER coding used for categorical variables is presented in Appendix B. Although all groups included in the models are significant in type III analysis shown in Table 4.13 some of the values for the categorical variables are not significant compared to the baseline class. One solution for this issue may be grouping some of these values together based on a breast cancer expert knowledge in the future. We used the lognormal AFT models in this chapter presented in Tables 4.14, 4.15, 4.16, and 4.17 to assign expected recurrence time in the simulation model in Chapter 5.

In this chapter, we analyzed the publicly available cancer screening data called SEER for breast cancer patients. Survival analysis models were used to predict breast cancer recurrence using patient's demographic information and her breast cancer tumor attributes. These recurrence models were used to predict expected recurrence time in the simulation

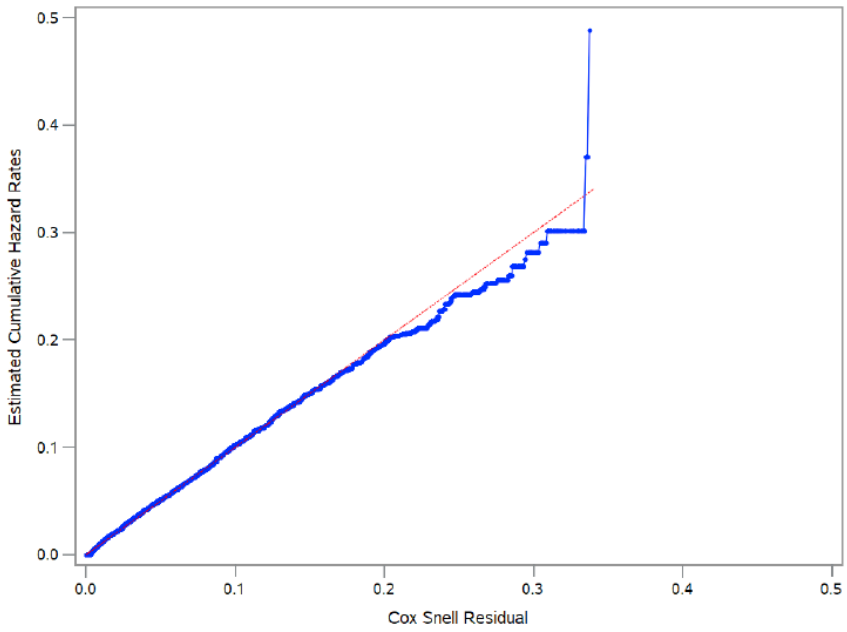

Figure 4.6 Cox-Snell residuals to assess the fit of the lognormal regression model for the IBC W group- W: white, IBC: Invasive breast cancer.

model in Chapter 5.

Table 4.14 Analysis of maximum likelihood parameter estimates for African American patients with DCIS using accelerated failure time model with lognormal distribution

Parameter	Estimate	Standard Error	95% Confidence Limits		Pr >ChiSq
Intercept	4.1289	0.0722	3.9873	4.2704	<.0001
ER Status-Negative	-0.1232	0.1075	-0.3340	0.0875	0.2517
ER Status-Borderline	0.5510	0.6999	-0.8207	1.9227	0.4311
ER Status-Unknown	-0.1871	0.0566	-0.2981	-0.0762	0.0009
ER Status-Not 1990+	0.3363	0.1070	0.1266	0.5460	0.0017
ER Status-Positive	0.0000	.	.	.	.
Scale	1.4551	0.0336	1.3907	1.5224	

Table 4.15 Analysis of maximum likelihood parameter estimates for white patients with DCIS using accelerated failure time model with lognormal distribution

Parameter	Estimate	Standard Error	95% Confidence Limits		P-value
Intercept	4.5723	0.0572	4.4603	4.6844	<.0001
Age	-0.0018	0.0006	-0.0030	-0.0007	0.0018
Histology-8201	0.1341	0.0443	0.0473	0.2209	0.0025
Histology-8230	-0.0800	0.0515	-0.1808	0.0209	0.1202
Histology-8500	0.0630	0.0265	0.0111	0.1149	0.0174
Histology-8503	-0.0214	0.0494	-0.1182	0.0754	0.6641
Histology-8507	-0.0109	0.0691	-0.1464	0.1246	0.8743
Histology-8522	-0.2735	0.0453	-0.3623	-0.1846	<.0001
Histology-comedocarcinoma	0.0000	.	.	.	.
ER Status-Negative	-0.0785	0.0445	-0.1657	0.0087	0.0777
ER Status-Borderline	-0.1910	0.2587	-0.6980	0.3161	0.4604
ER Status-Unknown	-0.0997	0.0246	-0.1479	-0.0515	<.0001
ER Status-Not 1990+	0.1861	0.0423	0.1032	0.2691	<.0001
ER Status-Positive	0.0000	.	.	.	.
Surgery-0	-0.2200	0.0707	-0.3586	-0.0814	0.0019
Surgery-Missing	-0.1033	0.0286	-0.1594	-0.0473	0.0003
Surgery-19	-0.2975	0.9771	-2.2125	1.6175	0.7607
Surgery-20	-0.0260	0.0273	-0.0796	0.0275	0.3407
Surgery-30	1.0449	0.4169	0.2278	1.8619	0.0122
Surgery-40	0.5143	0.0390	0.4379	0.5906	<.0001

Table 4.15 continued from previous page

Parameter	Estimate	Standard Error	95% Confidence Limits		P-value
Surgery-50	0.5070	0.0548	0.3996	0.6143	<.0001
Surgery-60	0.2368	0.3552	-0.4593	0.9329	0.5050
Surgery-80	0.6106	0.4101	-0.1931	1.4144	0.1365
Surgery-90	0.2819	0.3390	-0.3826	0.9463	0.4057
Surgery-99	0.1445	0.3406	-0.5230	0.8120	0.6713
Surgery-Lumpectomy	0.0000	.	.	.	.
Radiation-1	0.0728	0.0223	0.0290	0.1166	0.0011
Radiation-2	0.0331	0.1041	-0.1709	0.2371	0.7505
Radiation-3	-0.5727	0.5010	-1.5547	0.4093	0.2530
Radiation-4	-0.0462	0.1665	-0.3724	0.2801	0.7814
Radiation-5	0.1473	0.1761	-0.1979	0.4924	0.4029
Radiation-6	-0.5697	0.6716	-1.8861	0.7466	0.3963
Radiation-7	-0.4623	0.0786	-0.6163	-0.3083	<.0001
Radiation-8	0.0400	0.0964	-0.1490	0.2290	0.6786
Radiation-9	-0.1566	0.1263	-0.4042	0.0911	0.2153
Radiation-None	0.0000	.	.	.	.
Scale	1.6417	0.0145	1.6134	1.6704	

Table 4.16 Analysis of maximum likelihood parameter estimates for African American patients with IBC using accelerated failure time model with lognormal distribution

Parameter	Estimate	Standard Error	95% Confidence Limits		P-value
Intercept	4.2736	0.0666	4.1431	4.4041	<.0001
Age	0.0048	0.0009	0.0030	0.0066	<.0001
ER Status-Negative	-0.1541	0.0422	-0.2368	-0.0713	0.0003
ER Status-Borderline	0.1548	0.2144	-0.2655	0.5750	0.4703
ER Status-Unknown	0.2164	0.0902	0.0396	0.3931	0.0164
ER Status-Not 1990+	-0.0878	0.0717	-0.2284	0.0528	0.2209
ER Status-Positive	0.0000	.	.	.	.
PR Status-Negative	-0.0009	0.0412	-0.0818	0.0799	0.9820
PR Status-Borderline	-0.0332	0.1630	-0.3527	0.2863	0.8385
PR Status-Unknown	-0.2990	0.0867	-0.4689	-0.1292	0.0006
PR Status-Not 1990+	0.0000	.	.	.	.
PR Status-Positive	0.0000	.	.	.	.
Surgery-0	0.0706	0.0734	-0.0733	0.2146	0.3362
Surgery-Missing	0.0244	0.0380	-0.0501	0.0988	0.5211
Surgery-19	6.3096	1897.623	-3712.96	3725.582	0.9973
Surgery-20	-0.0158	0.0406	-0.0955	0.0639	0.6975
Surgery-30	0.4050	0.4974	-0.5699	1.3800	0.4155
Surgery-40	0.3312	0.0604	0.2128	0.4496	<.0001
Surgery-50	0.2118	0.0404	0.1326	0.2910	<.0001
Surgery-60	0.1962	0.2609	-0.3151	0.7075	0.4521
Surgery-80	0.1808	0.2838	-0.3755	0.7371	0.5242

Table 4.16 continued from previous page

Parameter	Estimate	Standard Error	95% Confidence Limits		P-value
Surgery-90	0.0559	0.3495	-0.6292	0.7409	0.8730
Surgery-99	0.1947	0.3382	-0.4682	0.8576	0.5648
Surgery-Lumpectomy	0.0000	.	.	.	.
Stage-Missing	0.0325	0.0745	-0.1136	0.1786	0.6630
Stage-IIA	0.0545	0.0337	-0.0115	0.1205	0.1053
Stage-IIB	-0.0590	0.0431	-0.1435	0.0254	0.1706
Stage-III NOS	-0.0511	0.1805	-0.4049	0.3027	0.7771
Stage-IIIA	-0.0914	0.0517	-0.1927	0.0100	0.0772
Stage-IIIB	-0.4204	0.0800	-0.5771	-0.2637	<.0001
Stage-IIIC	-0.2490	0.0715	-0.3891	-0.1088	0.0005
Stage-IV	-0.0494	0.0954	-0.2363	0.1375	0.6046
Stage-N/A	0.9773	0.5538	-0.1082	2.0628	0.0776
Stage-Unknown	-0.1601	0.0499	-0.2580	-0.0623	0.0013
Stage-I	0.0000	.	.	.	.
Scale	1.5451	0.0176	1.5109	1.5801	

Table 4.17 Analysis of maximum likelihood parameter estimates for white patients with IBC using accelerated failure time model with lognormal distribution

Parameter	Estimate	Standard Error	95% Confidence Limits		Pr >ChiSq
Intercept	5.2581	0.0277	5.2038	5.3125	<.0001
Age	-0.0033	0.0003	-0.0038	-0.0027	<.0001
Ethnicity-Hispanic	0.0440	0.0161	0.0123	0.0756	0.0065
Ethnicity-Non Hispanic	0.0000	.	.	.	.
Grade-II	-0.0175	0.0138	-0.0446	0.0097	0.2068
Grade-III	-0.0619	0.0154	-0.0921	-0.0317	<.0001
Grade-IV	-0.1940	0.0341	-0.2610	-0.1271	<.0001
Grade-NA	-0.0380	0.0163	-0.0699	-0.0061	0.0195
Grade-I	0.0000	.	.	.	.
ER Status-Negative	-0.2093	0.0140	-0.2367	-0.1819	<.0001
ER Status-Borderline	-0.0550	0.0783	-0.2084	0.0984	0.4822
ER Status-Unknown	-0.0778	0.0148	-0.1068	-0.0487	<.0001
ER Status-Not 1990+	-0.0781	0.0239	-0.1249	-0.0312	0.0011
ER Status-Positive	0.0000	.	.	.	.
Radiation-1	-0.1273	0.0102	-0.1474	-0.1073	<.0001
Radiation-2	-0.2451	0.0483	-0.3399	-0.1504	<.0001
Radiation-3	-0.1814	0.2332	-0.6384	0.2756	0.4366
Radiation-4	-0.3380	0.0477	-0.4315	-0.2444	<.0001
Radiation-5	-0.1050	0.0657	-0.2337	0.0237	0.1098
Radiation-6	-0.4066	0.2006	-0.7997	-0.0135	0.0426
Radiation-7	-0.5322	0.0438	-0.6180	-0.4464	<.0001

Table 4.17 continued from previous page

Parameter	Estimate	Standard Error	95% Confidence Limits		Pr >ChiSq
Radiation-8	-0.0174	0.0336	-0.0833	0.0485	0.6051
Radiation-9	-0.0558	0.0596	-0.1727	0.0612	0.3499
Radiation-None	0.0000	.	.	.	.
Stage-Missing	-0.1333	0.0241	-0.1806	-0.0860	<.0001
Stage-IIA	0.0562	0.0127	0.0313	0.0810	<.0001
Stage-IIB	0.0238	0.0189	-0.0132	0.0609	0.2078
Stage-III NOS	-0.2925	0.0712	-0.4321	-0.1530	<.0001
Stage-IIIA	0.0284	0.0224	-0.0156	0.0724	0.2062
Stage-IIIB	-0.0855	0.0429	-0.1696	-0.0014	0.0463
Stage-IIIC	-0.2086	0.0302	-0.2678	-0.1495	<.0001
Stage-IV	-0.1601	0.0425	-0.2434	-0.0769	0.0002
Stage-N/A	-0.1107	0.1466	-0.3979	0.1765	0.4500
Stage-Unknown	-0.0796	0.0194	-0.1176	-0.0415	<.0001
Stage-I	0.0000	.	.	.	.
Surgery-0	0.0983	0.0381	0.0237	0.1730	0.0099
Surgery-Missing	-0.1448	0.0145	-0.1733	-0.1164	<.0001
Surgery-19	6.1807	805.8733	-1573.30	1585.663	0.9939
Surgery-20	-0.0092	0.0152	-0.0390	0.0207	0.5470
Surgery-30	0.0568	0.2006	-0.3364	0.4500	0.7770
Surgery-40	0.1760	0.0224	0.1320	0.2200	<.0001
Surgery-50	0.1790	0.0174	0.1448	0.2131	<.0001
Surgery-60	0.3175	0.1215	0.0793	0.5557	0.0090

Table 4.17 continued from previous page

Parameter	Estimate	Standard Error	95% Confidence Limits		Pr >ChiSq
Surgery-80	-0.0469	0.1137	-0.2697	0.1760	0.6801
Surgery-90	0.0906	0.1503	-0.2040	0.3851	0.5467
Surgery-99	0.2457	0.1651	-0.0779	0.5694	0.1367
Surgery-Lumpectomy	0.0000	.	.	.	.
Scale	1.6482	0.0067	1.6351	1.6614	

CHAPTER

5

BREAST CANCER SIMULATION MODEL

5.1 Existing Models

5.1.1 Simulation in Health Care

Simulation, one of the most commonly used tools in Operations Research (OR), has been used since the 1960s for modeling OR problems in health care settings [97]. Simulation allows the user to model dynamic, complex systems with uncertainty, ask "What if?" questions and design new systems. There are four simulation categories used in OR: Monte Carlo (MC), discrete-event simulation (DES), system dynamics (SD) and agent-based simulation (ABS). Some researchers use a hybrid of these methods to simulate a system, one common hybrid simulation example is SD and DES used together to capture a system both at the individual and population level, e.g., breast cancer simulation model built by Tejada et al. [98] combines DES and SD to simulate breast cancer occurrence and screening in women aged 65 and older.

Monte Carlo: MC is defined by Fishman [99] as performing statistical sampling experiments to get approximate solutions to mathematical problems. MC can be used for solving deterministic (e.g., estimating the area of a circle) and stochastic problems. For simulation, MC is used to create variable distributions to simulate the system uncertainty. MC simulates different scenarios and produces forecasts as outputs, usually in the form of relevant means and probabilities, e.g. , Akkerman and Knip [100] used MC to simulate patients' length of stay in a hospital following a cardiac surgery to estimate unused bed capacity under different bed allocation scenarios. Jacobson and Sewell [101] used MC with integer programming to evaluate the economic value of combination vaccines for children.

Discrete Event Simulation: DES models a system as a discrete sequence of well-defined events happening in an orderly fashion where an event is defined as a change in a sys-

tem's state at a particular point in time. A specific type of DES is a micro-simulation in which the effect of a policy on an agent (individual or household) is simulated [102]. In DES, components of the system are called entities, they go through the model and can engage in processes, seize resources, consume materials, create queues, etc. In health care simulations, entities are usually individual patients who can seize resources like hospital beds and go through processes like surgery. For example, Toro-Diaz et al. [103] used DES to simulate patients in need of liver transplants and the donated organs to predict trends in the liver transplant process through the year 2030.

System Dynamics: SD models flows around networks instead of modeling the individual behavior of entities. In SD, three main objects are considered: stocks, flows, and delays. Stocks are basic stores of objects, e.g., the number of patients in a hospital department. Flows define the movement of items between different stocks in the system as well as in and out of the system itself. Delays are the delay between the system measuring something and the system then acting upon that measurement. [104]

Agent Based Simulation: ABS allows the modeler to simulate objects called agents who interact with each other as well as with the system, move to different geographic locations, remember the state of the system and their histories, and have different attributes and behavior depending on location and time. For disease modeling, ABS has been used in chronic disease and infectious disease, e.g., Lee et al. [105] use ABS to simulate the H1N1 influenza pandemic in Washington DC area.

Simulation models can also be classified by their applications in health care into three groups of disease models, operational or tactical models, and strategic models. Disease models are often used for studying the clinical effectiveness or cost-effectiveness of a particular intervention (e. g. , a screening policy) in a population but they can also be used to simulate at the organ or cellular level. Operational or tactical models are used for

capacity planning, resource allocation, and process redesign, e. g. , simulating a hospital to estimate bed utilization under different bed allocation strategies. Strategic models are usually system-wide models that do not focus on individual patients but more on how different parts of the system interact. Usually, DES is used for disease and operational models and SD is more commonly utilized for strategic models.

The type of model chosen depends on the problem at hand, level of abstraction needed, and the outcome of interest. If the difference in the individual elements and their outcomes are of interest and the model is used for tactical and operational decisions, then DES and ABS are preferred, both of which are capable of modeling individuals with different attributes, although DES is the more process-focused model of the pair. In DES entities or agents (as are called in ABS) are more passive, i.e., they cannot interact with each other directly except for sharing resources in some instances, but in ABS, agents can interact and influence each others' behavior directly. A DES model can also be presented by an ABS model, however, the simulation run time on the computer might be longer. SD is mainly used for strategic planning, simulating continuous processes, where a high level abstraction is done rather than focusing on individual differences. If agents are defined as higher level components, e.g. companies versus companies' employees, ABS can also be used for higher level abstraction and simulating some processes typically simulated by SD. DES and ABS use probability distributions to simulate stochastic process whereas SD usually takes a deterministic approach using average rates for creating stocks and flows [104]. For a detailed comparison among the three major simulation paradigms, the reader is refereed to Borshchev and Filippov 2004 paper [106].

5.1.2 Breast Cancer Simulation Models

Simulation has been used to assess different breast cancer screening strategies in the literature. De Koning et al. [107] extended the MIcrosimulation Screening Analysis (MISCAN) computer simulation package (first developed for all diseases by Habbema et al. [108] and later developed for breast cancer by Van Oortmarssen et al. [109]) to evaluate different screening policies. They assumed six discrete stages for breast cancer, starting in a disease-free stage and assuming time spent in each of the stages follows an exponential distribution. This was followed by a series of models developed under the Cancer Intervention and Surveillance Modeling Network (CISNET) program from 2000, to evaluate the impact of screening policies and adjuvant therapy for breast cancer. These models although using different approaches have some common inputs which include: adjuvant treatment dissemination and efficacy, mortality from causes other than breast cancer, changes in underlying risk of developing breast cancer, dissemination of mammography screening, prevalence of breast cancer in 1975, prescreening/preadjuvant therapy survival, stage distribution, and mortality rates where most of these inputs come from the Breast Cancer Surveillance Consortium (BCSC). The CISNET program comprises seven models: Dana-Farber Cancer Center (D), Erasmus University Rotterdam (E), Georgetown University Medical Center (G), University of Texas M. D. Anderson Cancer Center (M), Stanford University (S), University of Rochester (R), and University of Wisconsin-Madison (W). The CISNET models evaluate the impact of adjuvant therapy and screening policies on the U.S. population under different scenarios. Four models use simulation (E, M, G, and W), one model takes an analytical approach (D), and the remaining two models are hybrids of analytical and simulation approaches (S and R) [110]. Four groups (M, D, G, and R) model breast cancer in stages, but three (models E, S, and W) use tumor size and tumor growth. Models E, W, and G

model DCIS explicitly and assume three different types of pre-clinical DCIS: regressive DCIS, DCIS that is diagnosed clinically, and DCIS that progresses to invasive disease. The Wisconsin model (Wisconsin breast cancer epidemiology simulation model, UWBCS, W) by Fryback et al. [111] uses DES to model breast cancer progression, where tumors grow according to a Gompertz distribution, in the population of the state of Wisconsin. The Erasmus University Rotterdam model developed by Tan et al. [69] used the MISCAN-Fadia model for predicting and comparing different screening policies in a dynamic population. The DES model generates independent individual life histories including events like birth, initiation of a breast cancer tumor, clinical diagnosis of the tumor, death from breast cancer, and death from other causes. The Georgetown University Medical Center model (G) is a microsimulation of breast cancer in the U.S. population, where the impact of screening and treatment are managed by creating "parallel universes", whereby the same life history is subjected to different screening or treatment strategies and the varying results are directly compared [110].

For a detailed review of all CISNET models, their inputs, assumptions, and outcomes and other breast cancer models, the reader is referred to the paper by Koleva-Kolarova et al. [112]. In addition to these models, Tejada et al. [98] developed a hybrid DES/SD simulation model to simulate breast cancer natural history and evaluate different screening strategies for the U.S. women 65 and older. DCIS incidence was modeled but the progression of DCIS to IBC was not included.

In this dissertation, we have built a simulation with both progressive and non-progressive DCIS to evaluate treatment timing for DCIS patients. We can also use this simulation to estimate cumulative quality-adjusted life years (QALYs) to be used as rewards/penalties for the POMDP model in Chapter 3.

5.2 DCIS Treatment Simulation

We built a breast cancer simulation model to evaluate DCIS treatment policies. This model is used to evaluate the effect of DCIS treatment policy on the population level. In this model, patients start in the simulation in healthy state with no prior breast cancer history. The simulation model does not model screening or tumor growth explicitly. Instead, the breast cancer incidence rates from the literature are used, to explore the effect of DCIS treatment policy under current breast cancer screening practice. When a patient is diagnosed with IBC, the stage is assigned based on the IBC stage distribution of SEER patients of the similar demographic group (same five-year age group, race, and ethnicity), e.g., if a 42-year-old non-Hispanic white female is diagnosed with IBC in the simulation model then the stage and other attributes of her breast cancer is randomly assigned from the IBC tumors diagnosed in 40-45 year-old non-Hispanic white female patients in SEER data base.

Population Simulation Model Description

We built a population level DES model with individuals at risk represented by entities to explore the effect of different DCIS treatment strategies in a female population age 35-75 with African American or white race in 1978 to 2013.

State Transition: In the simulation model, patients start from no breast cancer (BC) with no prior BC history in the first chain (Figure 5.1.A), where they are at risk of IBC and DCIS. After being diagnosed with BC (either a stage of IBC or DCIS) and receiving treatment for it, they are transfered to the second chain shown in Figure 5.1.B, which shows state transitions for women with BC history who might have breast cancer recurrence (either DCIS-R or a stage of IBC-R). There are three stages of IBC in the model: local, regional, and distant based on the extent of invasive breast cancer progression which are assumed to be completely observable.

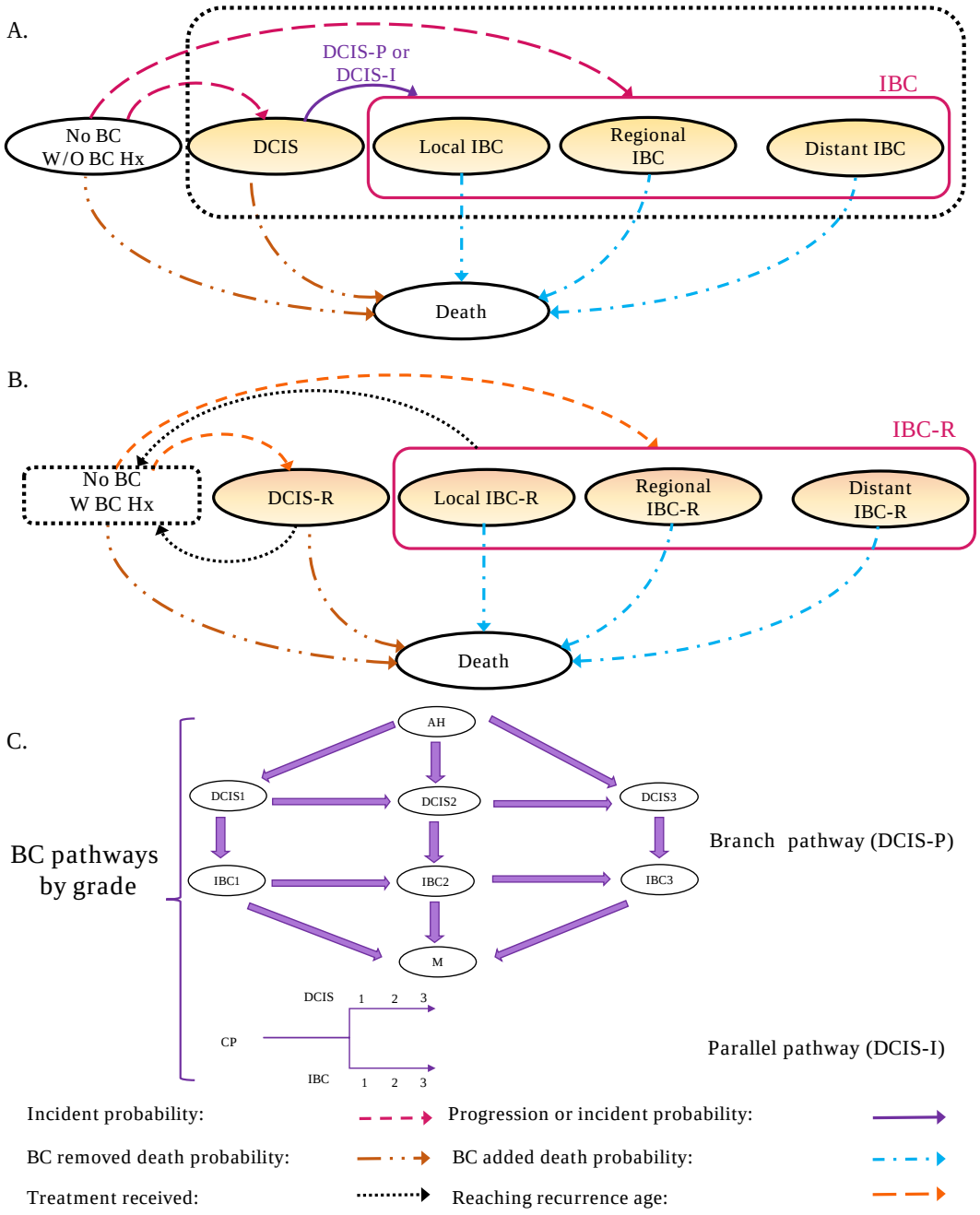

Figure 5.1 State transition for patient's states in simulation model: A. State transition for patients without BC history. B. State transition for patients with BC history. C. BC pathways corresponding to DCIS-P and DCIS-I.
After treatment, the dotted rectangle in the top figure is transformed into the "No BC w BC Hx" state in the bottom figure if the patient survives and continues in the next period.
BC: breast cancer, W/O: without, W: with, Hx: history, R: recurrence, AH: atypical hyperplasia , CP: common progenitor, M: metastasis or distant cancer, grades of low, intermediate and high for both DCIS and IBC are indicated by 1, 2, and 3, respectively.

If a patient is diagnosed with both IBC and DCIS, she would be in the IBC state in the model and there is no difference between that and an IBC diagnosed alone. We classify and model two types of DCIS diagnosed based on the potential of DCIS to progress to IBC: progressive DCIS or DCIS-P and non-progressive DCIS or DCIS-I. The type of DCIS diagnosed (both for first DCIS case and DCIS diagnosed in patients with BC history or DCIS-R) is known in the model but is partially observable by the decision maker for making treatment decisions, i.e., the decision maker knows the DCIS grade, histology, etc. at the time of diagnosis but does not know if it is the type that progresses to IBC. The decision maker can decide not to treat and instead update her belief about the DCIS type before considering possible treatments. If she observes a change, it means the observations suggest progression of DCIS to IBC, such as observing more comedo necrosis in the biopsy or an increase in size of the tumor compared to no change, which suggests that DCIS is not progressing. The DCIS treatment decision is driven by a threshold for DCIS-P belief in the simulation model, i.e., if the decision maker has the belief probability higher than the pre-specified threshold in the model, the patient is treated in that period; otherwise patient is not treated and another observation is taken in the next six months. The decision maker forms a belief for what type of DCIS the patient might have based on observations which correspond to the Bayesian belief probability of DCIS-P in the POMDP model in Chapter 3. The two DCIS types (DCIS-P and DCIS-I) are embedded in the DCIS states shown in the two top diagrams in Figure 5.1 and DCIS state is labeled as DCIS (for patients with no BC history) and DCIS-R (for patient with BC history) in Figure 5.1.A and Figure 5.1.B, respectively. Figure 5.1.C shows the two BC pathways that inspired the definition of non-progressive DCIS (DCIS-I) and progressive DCIS (DCIS-P). Transition to IBC state in DCIS-I chain (parallel pathway) is independent of DCIS and has a lower probability compared to the DCIS-P progression to IBC, i.e., it is assumed that patients with DCIS-I who are

under watchful waiting have the same IBC risk as patients with no prior BC history. The pathways are not explicitly modeled because the rates for both pathways are not available and the change and no change observations are inspired by the transitions suggested by these pathways. The transitions from different IBC stages to higher stages are not modeled because it is assumed IBC cases are treated immediately after diagnosis, preventing them from progressing further.

In the population model, individuals enter the model with no breast cancer and each year they are at risk of IBC estimated by the U.S. incidence rate (Section 5.2.2). When an individual is diagnosed with breast cancer, the stage at diagnosis is assigned to the tumor based on SEER data distribution (Section 5.2.3), i.e. the diagnosed tumor may be at the local, regional, or distant stages based on the data. After BC diagnosis and receiving treatment, cancer-free patients with BC history are still at risk of BC recurrence. Next breast cancer age is predicted by the survival models in Chapter 4 by adding the expected years to next breast cancer to the current age of the patient. After BC treatment, first it is determined whether the next breast cancer is DCIS or IBC (with probability 0.55 IBC [88]); then a random number generator creates a random number, which is the expected years to next BC, using the survival models in Chapter 4 based on the patient and her tumor characteristics. This number is then added to the patient's current age and rounded up to the nearest 0.5 to calculate the next BC age. Breast cancer death is assumed to be only possible from invasive disease (IBC) [113] but it is not explicitly modeled, instead relative survival is used to estimate probability of death for women with BC history up to ten years after BC diagnosis (Section 5.2.7). Death for women without BC history and women with a history of breast cancer ten years after diagnosis, occur based on probabilities from US life tables with BC removed as cause of death based on age and birth year (Section 5.2.6).

Time step: The simulation time step is six months, but a patient with no BC history or

with DCIS-I under watchful waiting has a probability of being diagnosed with a new breast cancer each year because annual breast cancer risks for breast cancer diagnosis are used, and it is less likely that patient is screened for breast cancer more frequently than every year with no BC history. Also, we determine if the patient dies and calculate cumulative QALYs annually. Six months is used as the time step because after DCIS diagnosis if the patient chooses watchful waiting, it is assumed they will be under close observation to quickly detect progression of DCIS to IBC. For recurrence, we check if the patient reached the recurrence age every six months.

Simulation model overview: A schematic representation of the population simulation model is shown in Figure 5.2. The simulation starts with population initialization, the size of the population, race, and ethnicity distribution are inputs to the simulation in the ”Initialize Population” module. For each patient, the patient's race (white or African American), ethnicity (Hispanic or non-Hispanic), and age are randomly generated based on the U.S. female population distribution in the ”Assign Patient's Attribute” module (a complete table for the population distributions can be found in Appendix C) (Section 5.2.1). Each year, DCIS and IBC risks are assigned to individuals who had no prior breast cancer based on their age group, race, and ethnicity, in the ”Assign DCIS and IBC Risk” module. In the event of a breast cancer (DCIS or IBC) detection, determined in the ”IBC Diagnosis and DCIS Diagnosis” modules, breast cancer attributes such as stage, grade, ER or PR status, treatment received, etc., are assigned randomly to patients based on age at diagnosis, race, ethnicity and type of breast cancer (DCIS or IBC) from the SEER database in the ”Assign IBC Attributes” and the ”Assign DCIS Attributes” modules.

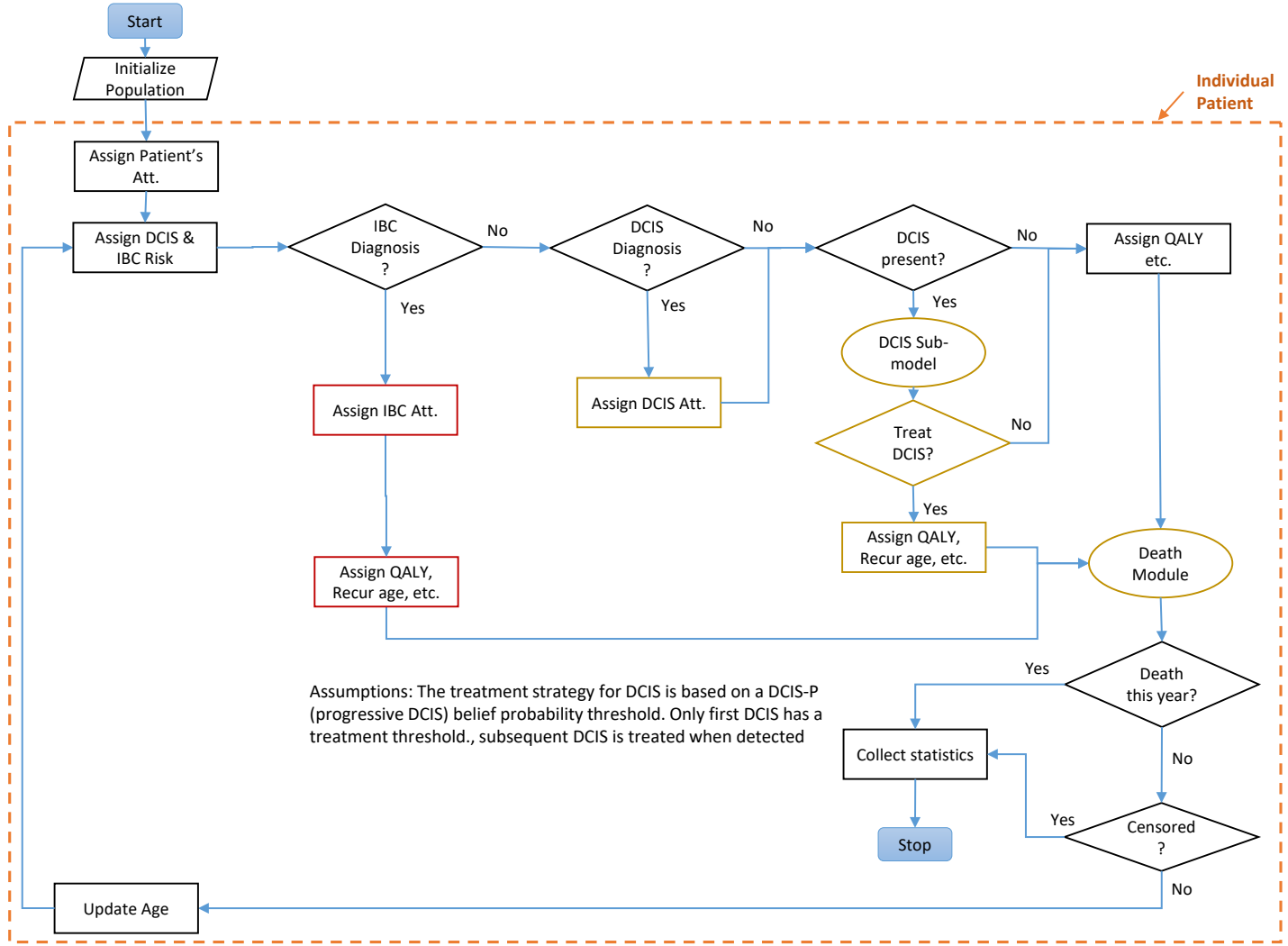

Figure 5.2 Population Breast Cancer Simulation- Att.: Attributes, QALY: Quality adjusted life years, IBC: Invasive breast cancer

In addition, for DCIS cases, the simulation randomly assigns the case to be a progressive DCIS (DCIS-P) corresponding to DCIS branch pathway or a non-progressive DCIS (DCIS-I) corresponding to DCIS parallel pathway based on the age at diagnosis and tumor grade [114], in the "Assign DCIS Attributes" module. After breast cancer treatment, the BC recurrence age at diagnosis is assigned to patients based on the survival model fitted to the SEER data in Chapter 4 in "Assign QALY, Recur Age, etc." module shown in Figure 5.2 . Approximately, half of these recurrent cases are IBC and the other half are DCIS [88]. As seen in Chapter 4, there are four survival models for predicting age of recurrence after breast cancer:

1. Survival model after DCIS treatment in African American patients;
2. Survival model after IBC treatment in African American patients;
3. Survival model after DCIS treatment in white patients;
4. Survival model after IBC treatment in white patients.

IBC cases are treated after detection; however, it is possible to delay DCIS treatment after detection. The decision to initiate DCIS treatment depends on the DCIS-P belief and a DCIS treatment threshold. If the current DCIS-P belief is greater than the threshold, DCIS will be treated; otherwise it is assumed the treatment decision will be deferred to the next period. If DCIS treatment is delayed, the DCIS-P belief is updated based on the observation during that period. It is assumed that the next period will be six months after the current observation (Section 5.2.4). The formulas introduced in Chapter 3, are used to update DCIS-P belief in "DCIS Sub-model" module. There are two observations possible: change or no change in the tumor and the probability of these events happening depends on DCIS being progressive, i.e. , Prob(change|DCIS-P) is different from Prob(change|DCIS-I). Change in this context means change for the worse, e.g., change from DCIS1 (low grade) to

DCIS2 (Intermediate grade DCIS). Changes like this exist in both the parallel and branch pathways (as seen in Figure 5.1.C) therefore the decision maker cannot be 100% sure which type of DCIS is detected (DCIS-P versus DCIS-I). We assume the change is more likely to be an indicator of a DCIS-P than a DCIS-I, in other words, Prob(change|DCIS-P) > Prob(change|DCIS-I). The threshold strategy is only applied to first DCIS diagnosed (which is also the first breast cancer) in patients over the age of 40 because due to the lower chance of screening before age 40, DCIS diagnosed before this age is more likely to be clinically symptomatic (it is more likely found with physical exam) which suggests its more aggressive nature; as a result, the DCIS tumors found before age 40 and recurrent DCIS tumors are treated when detected in the simulation model. After each year, accumulated QALYs are calculated based on the events in that year (refer to Section 5.2.5). Every year the model checks if the patient dies. In the case of BC history, every six months after being diagnosed with BC, the model checks if the patient has reached the recurrence age. If the patient survives, and her age is not equal to the stop age, her age is updated in the "Update Age and Risk" module and if she has no BC history her BC risk is updated in the same module, then she goes through the process again.

We use the cumulative QALYs, the number of breast cancer incidence, and the number of deaths to evaluate different DCIS strategies in the population. DCIS strategies are defined by the DCIS treatment threshold for different groups in the population. Next, the simulation components are explained in more detail and the data sources for simulation model are introduced.

5.2.1 Population

African American and white women age between 35 and 75 are considered for simulation. The U.S. Preventive Services Task Force (USPSTF) recommends biennial breast screening starting at age 50 or age 40 for women who put more value on benefits of screening compared to its harm [1]. Women under ages 40 have a lower rate of DCIS because they are not typically screened by mammogram, and the sensitivity of a mammogram is low in this population due to the increased density of a young woman's breasts. Also tumors found in women younger than 40 are usually found at later stages and have poorer prognosis and they should be treated immediately [115]. Women start at 35 in the model to capture their breast cancer history and all the DCIS patients younger than 40 are treated according the current practice (almost all are treated) but for DCIS found in women older than 40 there is the option of watchful waiting. The stopping age was chosen at 75 because the USPSTF concludes "current evidence is insufficient to assess the balance of benefits and harms of screening mammography in women age 75 years or older", and we were focusing more on breast cancers found by screening. Model focus is on women who are white or African American with Hispanic or non-Hispanic ethnicity because the majority of the U.S. female population age 35–75 fall into this race and ethnicity group (around 92% of the U.S. population for 2014).

It is assumed the ratio of African American to white women stayed the same during these 35 years which is approximately 1 to 14 and is the same as this ratio in 2014. The simulation starts with a population of women age 35–75 in 1978 (approximately 39% of total population used in simulation), each year women aged 35 are added to the model, and all the women age through the simulation after entering until they exit the model. Women older than 35 are not added to the model after 1978 since it would be hard to know this

population's breast cancer history for model validation later. Women grow old in the model, regardless of the year they entered the model, until they exit the model because: they reach age 75, they reached year 2013, or they die. The population dynamic in the simulation model is shown in Figure 5.3.

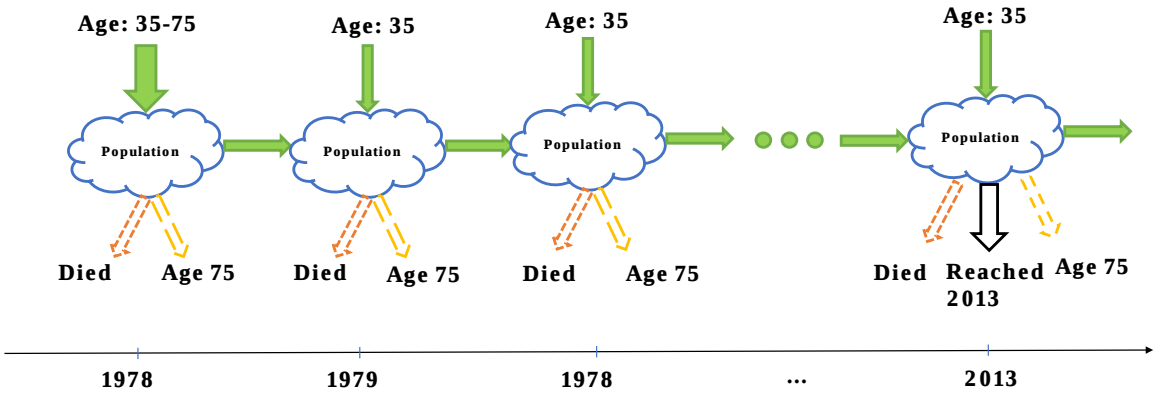

Figure 5.3 Population dynamics in breast cancer population simulation model through the years. The individuals leaving the model because of reaching age 75 or year 2013 are censored.

The number of women age 35–75 in 1978 and women age 35 each year from 1979–2013 was taken from World Development Indicator data [116]; then the distribution of women entering each year was calculated and shown in Table 5.1. For 1978 the age distribution of women for each race was taken from Center for Disease Control data [117], which is shown in Table 5.2 . It is assumed there is a uniform distribution for five year age groups, e.g., if a patient is in 55–59 age group, then with probability 0.2 she could be 55, 56, 57, 58, or 59 .

5.2.2 Breast Cancer Incidence

Some of the previous screening models such as Tejada et al.[98] have used patients' attributes such as their breast density, menopause status, age, etc., to estimate their breast

Table 5.1 Distribution of Female Population Used for Population Model by Year

Year 1-9									
Year	1978	1979	1980	1981	1982	1983	1984	1985	1986
Age	35-75	35	35	35	35	35	35	35	35
Population	44,248,992	1,355,170	1,416,153	1,487,579	1,563,717	1,638,765	1,707,390	1,769,605	1,832,050
Percent	38.97%	1.19%	1.25%	1.31%	1.38%	1.44%	1.50%	1.56%	1.61%
Year 10-18									
Year	1987	1988	1989	1990	1991	1992	1993	1994	1995
Age	35	35	35	35	35	35	35	35	35
Population	1,884,706	1,927,873	1,966,609	2,009,534	2,059,710	2,113,899	2,164,020	2,203,719	2,232,722
Percent	1.66%	1.70%	1.73%	1.77%	1.81%	1.86%	1.91%	1.94%	1.97%
Year 19-27									
Year	1996	1997	1998	1999	2000	2001	2002	2003	2004
Age	35	35	35	35	35	35	35	35	35
Population	2,246,725	2,254,866	2,255,010	2,246,767	2,229,814	2,204,295	2,168,007	2,126,685	2,090,838
Percent	1.98%	1.99%	1.99%	1.98%	1.96%	1.94%	1.91%	1.87%	1.84%
Year 28-36									
Year	2005	2006	2007	2008	2009	2010	2011	2012	2013
Age	35	35	35	35	35	35	35	35	35
Population	2,063,085	2,036,785	2,019,971	2,011,323	2,006,086	2,002,511	1,997,650	1,996,317	1,998,095
Percent	1.82%	1.79%	1.78%	1.77%	1.77%	1.76%	1.76%	1.76%	1.76%

Table 5.2 Population Distribution by Race and Age in 1978- AA: African American, W: white.

Age Group	**AA Population**	**Percent of AA Population**	**W Population**	**Percent of W Population**
Ages 35-39	755	16.88%	5,746	14.54%
Ages 40-44	669	14.95%	4,982	12.61%
Ages 45-49	631	14.10%	5,091	12.88%
Ages 50-54	611	13.66%	5,447	13.78%
Ages 55-59	565	12.63%	5,381	13.62%
Ages 60-64	454	10.15%	4,681	11.84%
Ages 65-69	452	10.10%	4,312	10.91%
Ages 70-74	291	6.50%	3,369	8.52%
Age 75	46	1.03%	512	1.29%
Total	4474	100.00%	3,9521	100.00%

cancer risk each year (it is assumed these patients have no prior breast cancer history in these models). In this dissertation, breast cancer incidence in the U.S. female population based on age, race, and year is used and the screening is not modeled explicitly. The aim is to evaluate the effect of different DCIS treatment strategies,i.e., DCIS-P treatment threshold, in current screening practice. Modeling the screening can be an extension for future work. Both IBC and DCIS incidence rates have changed during the last four decades for each age group in US African American and white female population. The DCIS rates for African American and white women are shown in Figure 5.4 and Figures 5.5 [118] and 5.6 [119], including the IBC rates by year for African American and white women, respectively. A line was fitted to each age group for each race and the incidence rate for each year was estimated using these fitted lines in the simulation. IBC and DCIS rate formulas are presented in Tables 5.4 and 5.3. These rates apply to women with no prior breast cancer [120] or patients with current DCIS-I who chose watchful waiting. It is assumed that DCIS-I patients who choose not to treat are still at risk of IBC independent of their DCIS (parallel pathway) so they have the same IBC risk as individuals with no breast cancer history that are shown in Table 5.4. DCIS-P turns into IBC with a higher probability than the IBC risk shown in Table 5.4 and it will be discussed in Section 5.2.4. For patients with breast cancer history we use the four survival models described in Chapter 4 to estimate the age of recurrence and every six months the model checks if they have reached the age of recurrence.

5.2.3 Assigning Tumor's Attributes

After a patient is diagnosed with DCIS or IBC, tumor attributes are assigned based on the SEER data. These attributes include: stage, size, grade, histology, ER status, PR status, HER2 status, type of surgery, and type of radiology received. The SEER data is divided into smaller

Table 5.3 DCIS incidence rates for race and age groups, United States, Rates are per 100,000. Year $\in \{1978, 1979, \ldots, 2013\}$- AA: African American, W: white

Group	Formula	R^2
W Females, Ages Below 50	0.373655761002*Year + 735.80065433784	0.94
W Females, Ages Over 50	2.812401793467*Year+ 5550.3240299833	0.92
AA Females, Ages Below 50	0.293293576734*Year+ 577.557324652986	0.90
AA Females, Ages Over 50	3.006134153836*Year+ 5939.16948134518	0.95

Table 5.4 Female invasive breast cancer incidence rates race and age groups, United States, Rates are per 100,000. Year $\in \{1978, 1979, \ldots, 2013\}$- AA: African American, W: white

Group	Formula	R^2
W Females, Ages 20-49	-0.5103+0.0005*Year-1.2737*10^{-7}*$Year^2$	0.6353
W Females, Ages 50-64	-8.1719+0.0082*Year-2.04677*10^{-6}*$Year^2$	0.8152
W Females, Ages 65-74	-12.3224+0.0123*Year-3.08060*10^{-6}*$Year^2$	0.8583
W Females, Ages 75+	-12.2283+0.0122*Year-3.0661*10^{-6}*$Year^2$	0.782
AA Females, Ages 20-49	-0.0279*$Year^2$ + 111.55*Year- 111412	0.4001
AA Females, Ages 50-64	-0.1473*$Year^2$ + 590.62*Year - 591745	0.8383
AA Females, Ages 65-74	-0.1378*$Year^2$ + 555.07*Year - 558651	0.8304
AA Females, Ages 75+	3.4097*Year - 6421.9	0.5164

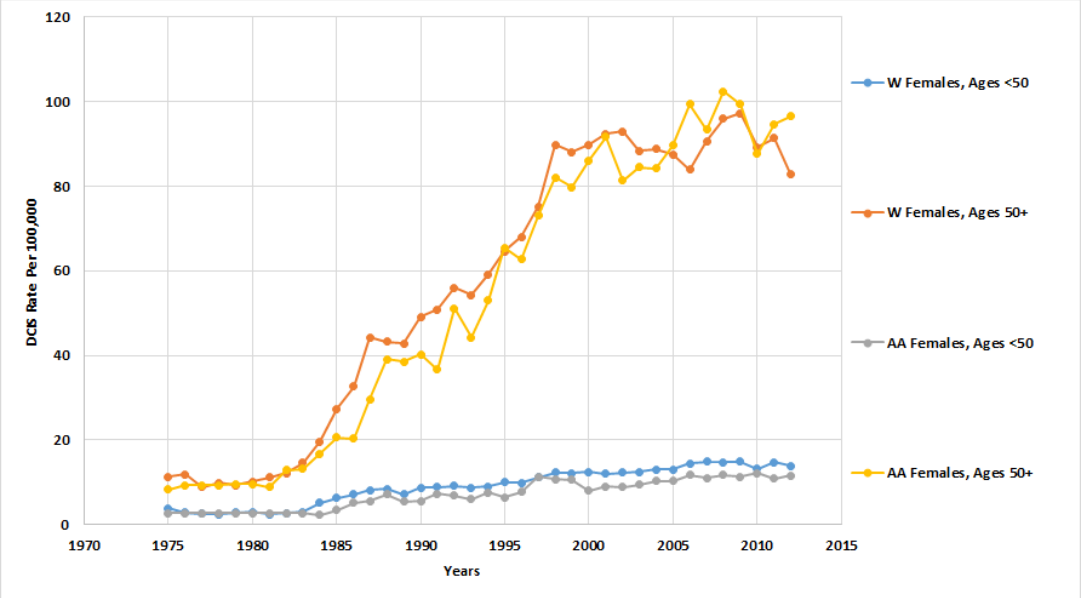

Figure 5.4 DCIS rate per 100,000 through the years for white and African American Women in US by year-AA: African American W: white

groups of patients based on their breast cancer type (DCIS or IBC), race, ethnicity and age at diagnosis to use them as surrogates for breast cancer patients in the simulation model. When a patient is diagnosed with breast cancer, using her age at diagnosis, race and ethnicity, the model randomly (using a uniform distribution) chooses a tumor from her age-race-ethnicity-breast cancer type group and assigns its attributes to the diagnosed tumor in simulation, e.g., if a non-Hispanic white patient is diagnosed with IBC at age 47, the model uses a uniform distribution to choose a tumor record from the non-Hispanic white 45–49 IBC age group and assigns that record's attribute to the IBC tumor detected in the simulation for the patient. The distribution of groups for DCIS and IBC are shown in Tables 5.5 and 5.6, respectively. We did not divide the Hispanic African American patients diagnosed with DCIS into groups by age because of the small number of patients in this group (about 0.6% of the population belong to Hispanic African American group).

Table 5.5 DCIS grouped by age, race and ethnicity- * Hispanic African American group is not divided further by age because of small size of the sample

Age Group/ Race Ethnicity	Non-Hispanic white	Hispanic white	Non-Hispanic African American	Hispanic African American
35-39	2,858	377	485	*
40-44	8,889	1,298	1,276	*
45-49	13,758	1,670	1,813	*
50-54	15,437	1,716	2,070	*
55-59	15,284	1,456	2,071	*
60-64	14,611	1,223	1,913	*
65-69	14,117	1,140	1,791	*
70-74	12,010	866	1,432	*
75-79	9,755	570	1,016	*
80-84	5,883	270	523	*
85+	2,879	125	295	*
Total	115,481	10,711	14,877	192

Table 5.6 IBC grouped by age at diagnosis, race and ethnicity

Age Group/ Race Ethnicity	Non-Hispanic white	Hispanic white	Non-Hispanic African American	Hispanic African American
35-39	25,100	5,034	5,404	94
40-44	51,051	8,802	9,377	159
45-49	79,092	11,366	12,514	210
50-54	91,557	10,933	13,256	163
55-59	98,933	10,050	13,147	153
60-64	104,625	8,910	11,997	138
65-69	103,381	7,982	10,602	127
70-74	94,835	6,352	8,845	83
75-79	85,960	4,917	7,058	72
80-84	64,350	2,978	4,723	42
85+	54,599	2,213	4,072	26
Total	853,483	79,537	100,995	1,267

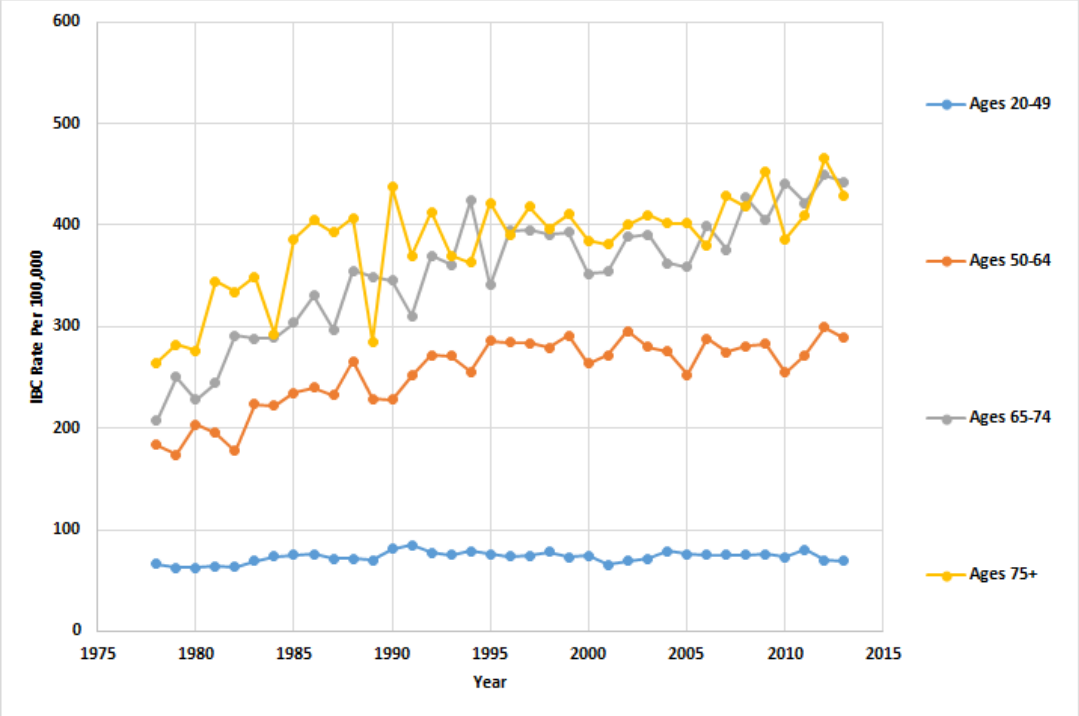

Figure 5.5 IBC rate per 100,000 through the years for African American Women in US by year of diagnosis.

5.2.4 DCIS Progression

When a patient is diagnosed with DCIS, the DCIS tumor may be progressive (DCIS-P) or non-progressive (DCIS-I). If the tumor is DCIS-P, then it has the potential to turn into IBC, whereas DCIS-I will never turn to IBC; but the patient might get IBC independent of having a DCIS with the same probability as a patient with no BC history. Patients with DCIS-I, corresponding to a parallel pathway, might still be diagnosed with IBC but their IBC incidence rate is the same as the IBC incidence rate for the population with no breast cancer history. In the simulation, the threshold policy is only applied to the first DCIS which was also the first breast cancer in that patient and subsequent DCIS is treated when detected. This means that if at a certain decision epoch the DCIS-P belief probability

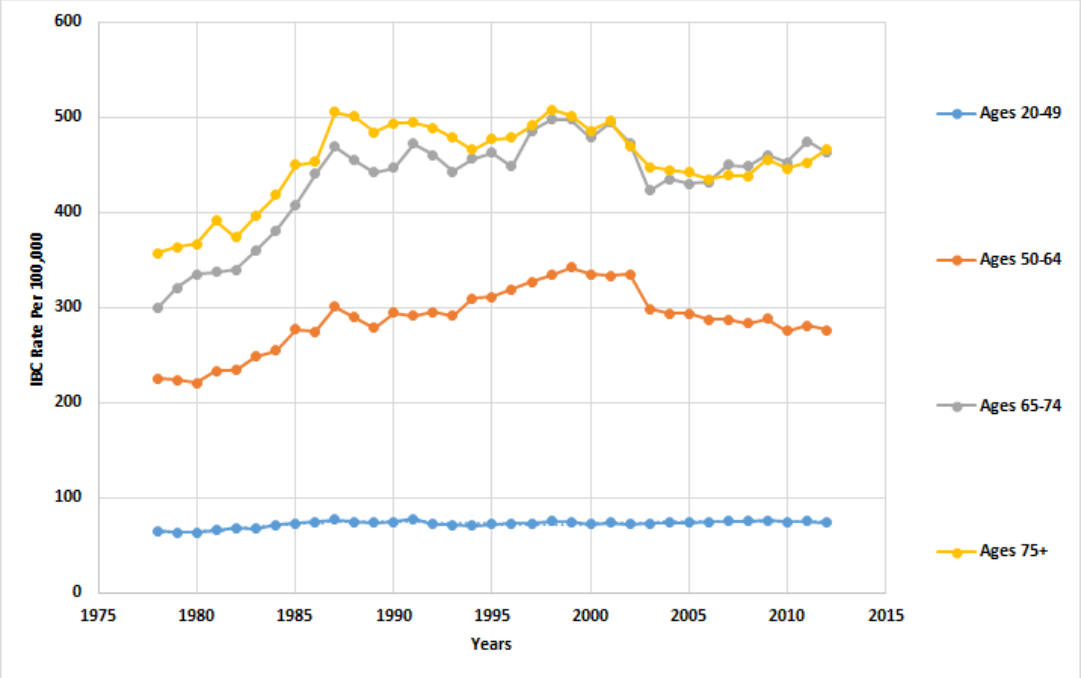

Figure 5.6 IBC rate per 100,000 through the years for white Women in US by year of diagnosis.

($W_n(2,\cdot)$ in Chapter 3) is more than the specified treatment threshold, then the DCIS is treated; otherwise patient waits for another epoch, if the DCIS is the first BC diagnosed in the patient, . In the simulation, there is no decision horizon defined, which means the watchful waiting continues as long as the patient is alive and is not diagnosed with IBC and the DCIS-P belief remains below the defined threshold.

The probabilities of DCIS-P and DCIS-I are from Van Luijt et al. [114] and are functions of the age at diagnosis and the initial DCIS grade as shown in Table 5.7. It is assumed the probability for unknown grade is the weighted average of the low, intermediate, and high grades with weights based on the percent of each detected in mass screening (16.4%, 31.6%, 52.0% for low, intermediate, and high grade, respectively). Breast cancer tends to be more aggressive in younger women [28]; and assuming that DCIS is more aggressive in younger ages, the maximum probability of each grade was used as the probabilities of DCIS-P for

Table 5.7 DCIS-P Probability by Age and Grade

Age Group	Low Grade	Intermediate Grade	High Grade	Unknown Grade
35-50	0.51	0.54	0.79	0.67
50-55	0.42	0.54	0.79	0.65
55-60	0.38	0.45	0.71	0.57
60-65	0.34	0.36	0.50	0.43
65-70	0.51	0.48	0.39	0.44
70-75	0.46	0.42	0.34	0.38

age 35–49 and grades which were missing from from Van Luijt et al. The DCIS-P progression to IBC probability in six months is estimated to be 0.043 from Tan et al. [71].

5.2.5 Quality Adjusted Life Years

A Quality Adjusted Life Years (QALYs) is a measure which was originally developed to do cost-effectiveness analyses to guide health resource allocation. QALY is the value associated with a health state and is usually between 0 and 1, death has a QALY of 0, and 1 represents a perfect health state (it is possible to have health states worse than death that have negative QALYs) [121]. We extended the method used by Schousboe et al. [122] to calculate multipliers for different breast cancer states using the health-related quality of life study by Lidgren et al. [123]. Lidgren et al. calculated the HQ-5D index for primary and recurrent breast cancers. They did not differentiate between DCIS, local IBC, and regional IBC. In our model it is assumed that for both primary and recurrent cancers the HQ-5D lower limit for the 95% confidence interval, the mean, and the upper limit of the 95% confidence interval correspond to regional IBC, local IBC, and DCIS multipliers, respectively. For each health state at each age group, the multipliers were multiplied by the QALYs of healthy individuals at that age group to calculate the estimated QALYs. The QALY values by age and state are

Table 5.8 QALY by age and health state for female population

State/Age	30-39	40-49	50-59	60-69	70-79	80-89
Healthy	0.89	0.86	0.84	0.81	0.77	0.72
In Situ 1st Year	0.8	0.78	0.75	0.73	0.69	0.65
In Situ Later Years	0.89	0.86	0.84	0.81	0.77	0.72
In Situ Recurrence	0.88	0.85	0.83	0.8	0.76	0.72
Local 1st Year	0.76	0.73	0.71	0.69	0.66	0.62
Local Later Years	0.88	0.85	0.82	0.79	0.76	0.71
Local Recurrence	0.85	0.82	0.8	0.77	0.73	0.69
Regional/Unknown 1st Year	0.67	0.65	0.63	0.61	0.58	0.54
Regional/Unknown Later Years	0.85	0.82	0.8	0.77	0.73	0.69
Regional/Unknown Recurrence	0. 83	0. 8	0. 78	0. 75	0. 72	0. 67
Distant 1st Year	0. 67	0. 65	0. 63	0. 61	0. 58	0. 54
Distant Later Years	0.74	0.72	0.69	0.67	0.64	0.6
Distant Recurrence	0.67	0.65	0.63	0.61	0.58	0.54

presented in Table 5.8, the healthy QALYs are taken from Hanmer et al. [124]. The multipliers and their sources are summarized in Table C.1 in Appendix C. At the end of each year for each patient, the QALYs of that year based on the breast cancer events or the patient's history in case of no breast cancer event are added to the accumulated QALY sfor that patient. If the patient died in that year half the QALYs of that year are added to the accumulated QALYs of the patient.

5.2.6 Death for Patients without Breast Cancer History

Life tables with breast cancer removed were used for assigning the probability of death from causes other than breast cancer from Rosenberg [72]. Annual other cause death probabilities were assigned to patients by their age and birth year. Examples of the death from other causes probabilities for the female cohort born in 1950 for different ages are shown in Table 5.9, e.g., a woman aged 45 born in the year 1950 has a chance of 0.001897 of dying from

Table 5.9 Probability for death from other causes breast cancer removed for different ages

Birth Year	Age	Probability of Death from Other Causes
1950	35	0.000852
1950	36	0.000894
1950	37	0.001015
1950	38	0.001089
1950	39	0.00113
1950	40	0.001178
1950	41	0.001266
1950	42	0.001445
1950	43	0.001594
1950	44	0.001742
1950	45	0.001897
...	...	...
1950	100	0.24225

other causes before her next birthday.

5.2.7 Death for Breast Cancer Patients

We assumed DCIS cancers do not cause any difference in survival for breast cancer patients before progressing to IBC, in other words the probability of death for DCIS patients is the same as probability of death for women without breast cancer history. Norod at al. [113] showed that the probability of dying from breast cancer for women diagnosed with DCIS, without an IBC recurrence, in 20 years is less than 0.5%. The cause of death information from death certificates are unreliable due to subjectivity, misclassification error, and sometimes unavailability; therefore in the literature relative survival is used to compare survival of cancer patients to patients without cancer instead [125]. The relative survival is defined as the ratio of observed survival to expected survival where the expected survival is the survival

of a cohort similar to the study population from the general population which is obtained from life tables . The probability of death for breast cancer patients is assigned using the SEER five-year breast cancer relative survival by age, race, and breast cancer stage [126]. Life tables provide the survival probability by year so the probabilities have a discrete format. The death probability for ten years after diagnosis is estimated using formulas as below. R_i is the relative survival after i years, $P_{BC}(T > t+i|T > t)$ is the probability of dying after $t+i$ given that she survived t years for a patient with breast cancer, and $P_G(T > t+i|T > t)$ is the probability for the general population (population without breast cancer) to survive beyond time $t+i$ given that they survived t years.

$$P_{BC}(T = t+i|T > t) = \frac{R_{i-1}P_G(T > t+i-1) - R_i P_G(T > t+i)}{P_G(T > t)} \quad i \in \{1,2,\ldots,10\},$$

$$R_i = \frac{P_{BC}(T > t+i|T > t)}{P_G(T > t+i|T > t)}$$

$$P_G(T > t+i|T > t) = \frac{1 - \sum_{j=0}^{j=t+i} P(T = j)}{1 - \sum_{j=0}^{j=t} P(T = j)}$$

We assumed that R_i is the average relative survival, and the survival for a patient each year after diagnosis at age t is calculated by first calculating $P_G(T < t+i|T > t)$ from life tables without breast cancer as cause of death as explained in Section 5.2.6; and then multiplying it by the corresponding R_i based on age group, race, and breast cancer stage. The relative survival after five years was found by fitting linear and polynomial curves to the five-year relative survival. From the models, we chose the one with maximum R^2 with a simpler form, i.e., if both linear and polynomial model had approximately the same R^2, we would choose the linear model. If the number estimated by regression model was negative, then we assume the relative survival would be equal to the last non-negative value. The formulas

for fitted curves are summarized in Table 5.10; and in the formulas x represents years from breast cancer diagnosis, e. g., the relative survival for a breast cancer patient within six years for a 60-year-old African American patient born in 1935 diagnosed with regional breast cancer is calculated with formula $-0.0489x + 1.0089 = 0.7155$. The probability of survival beyond six years for a a 60-year-old woman without BC history is 0.9412345509823. Then the probability of survival for the patient is $0.9412345509823 * 0.7155 = 0.673453$. The relative survival for breast cancer patients in five years from the SEER and the fitted curves are shown in Figures 5.7, 5.8, 5.9, and 5.10 for white patients age 0-64, African American patients age 0-64, white patients over the age of 65,and African American patients over the age of 65 respectively by stage. We can see from these diagrams that the more advanced the breast cancer, the lower the relative survival for breast cancer patients. SEER BC cases are classified as local, regional, distant and unknown stages based on the following definitions [120]. Stages considered in each of the categories are based on the definition given by the SEER for local, regional, distant and the 6th staging definition in the TNM staging system from the American Joint Committee of Cancer (AJCC) manual [127]. The TNM system classifies tumors based on tumor size and how far it has spread within the breast and to adjacent tissues (T), the extent of spread to the nearby lymph nodes (N), and the presence or absence of distant metastases (spread to distant organs) (M).

- Localized cancer is cancer that is limited to the organ in which it began, without evidence of spread (no lymph node involvement). Localized cancer includes the stages: I, INOS, IA, IA1, IA2, IB, IB1, IB2, IC, IS, IEA, IEB, IE, ISA, ISB, and IIA.

- Regional cancer is cancer that has spread beyond the original (primary) site to nearby lymph nodes or organs and tissues (lymph node involvement but no metastasis). Regional cancer includes stages : II, IINOS, IIB, IIC, IIEA, IIEB, IIE, IISA, IISB, IIS,

Table 5.10 Models fitted to breast cancer death by stage, race, and age group with their corresponding R^2- x represent year(s) after treatment. $x \in \{1,2,\ldots,10\}$

	Model	$\mathbf{R}^2$
white 00-64		
Localized	$-0.0041x+1.002$	0.9647
Regional	$-0.0245x+1.0082$	0.9858
Distant	$-0.0023x^3+0.0343x^2-0.2495x+0.9979$	0.9996
Unknown/unstaged	$-0.0009x^3+0.0133x^2-0.1067x+0.9977$	0.9973
African American 00-64		
Localized	$-0.012x+1.004$	0.9859
Regional	$-0.0489x+1.0089$	0.9912
Distant	$-0.0037x^3+0.0609x^2-0.3727x+0.9987$	0.9999
Unknown/Unstaged	$-0.0821x+0.9751$	0.9808
white 65+		
Localized	1	
Regional	$-0.0361x+0.999$	0.9965
Distant	$-0.0117x^3+0.1243x^2-0.4858x+0.9905$	0.9946
Unknown/unstaged	$-0.0097x^3+0.1034x^2-0.3967x+0.9918$	0.9934
African American 65+		
Localized	$-0.0015x^2-0.0013x+0.9993$	0.9952
Regional	$-0.0569x+0.9944$	0.995
Distant	$-0.015x^3+0.1547x^2-0.5711x+0.9875$	0.9921
Unknown/unstaged	$-0.0072x^3+0.0756x^2-0.3212x+0.9941$	0.9964

IIESA, IIESB, IIES, III, IIINOS, IIIA, IIIB, IIIC, IIIEA, IIIEB, IIIE, IIISA, IIISB, IIIS, IIIESA, IIIESB, and IIIES.

- Distant cancer is cancer that has spread from the primary site to distant organs or distant lymph nodes (metastasis). Distant cancer includes stages: IV, IVNOS, IVA, IVB, IVC, and occult.

- Unstaged cancer is cancer for which there is not enough information to indicate a stage. Unstaged cancer includes stage categories: N/A, Unknown Stage, and Missing.

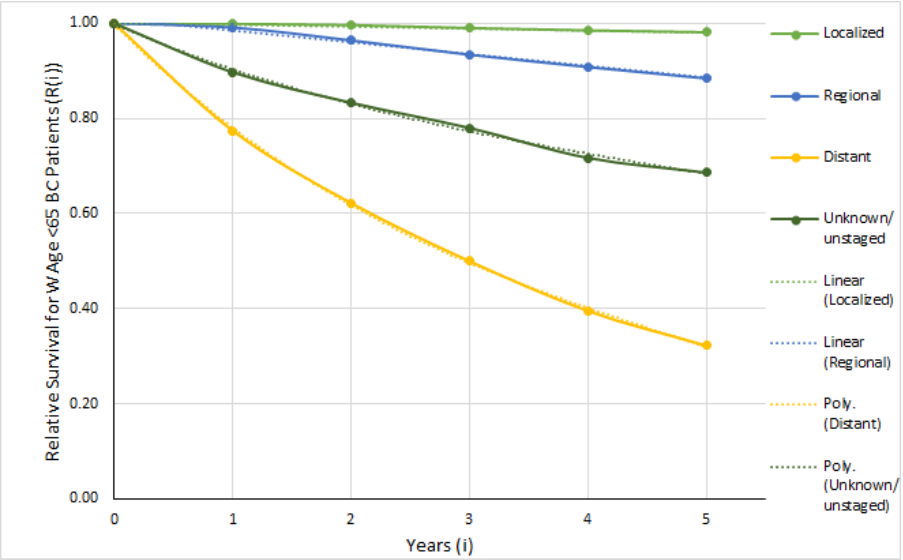

Figure 5.7 Relative survival for breast cancer patients for first five years by stage for white women age 0-64

5.3 Simulation Model Validation

The model is tested against breast cancer cases diagnosed in 2013 from SEER data, which was not used in developing the simulation or any of the survival models. The simulation is run for 35 years from 1978 to 2013 with women entering the model without history of breast cancer and being diagnosed with breast cancer as they age through the model. The simulation model under current practice, treating almost all DCIS cases, was validated using three measurements: breast cancer age, recurrence time, and 10-year relative survival. Simulation model was run for 999,126 (88% of the population) white females and 136,244 (12% of the population) African Americans, corresponding to 1% of the selected US female population, each with 10 replications. Breast-cancer-free women enter the model in 1978 at age 35–75 or in later years at age 35 and continue in the model until they reach age 75, reach 2013 or die.

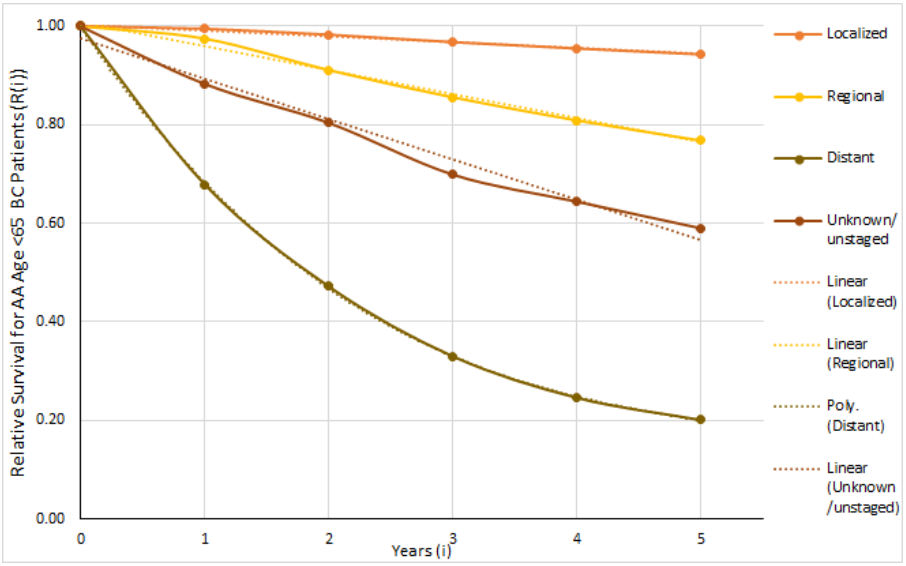

Figure 5.8 Relative survival for breast cancer patients for first five years by stage for African American women age 0-64

Age of first BC in 2013: First breast cancer cases diagnosed in patients with age 35–75 in 2013 in simulation and SEER were used to calculate the statistics shown in Table 5.11. First BC age distributions for African American and white Patients for the simulation and the SEER data in 2013 are shown in Figures 5.11 and 5.12. We can see in the charts and the statistics that the first breast cancer age does not follow a normal distribution so confidence intervals for the first BC age mean , calculated assuming normal distribution, are not very reliable to compare the two distributions, however, the mean, median, and the quantiles are reasonably close. In the charts, there is a relatively large gap between SEER and simulation distribution for ages 40-50 and we suspect that is because of the form of BC rate input to the simulation model. The IBC and DCIS rates for SEER data from 1978–2012 were aggregated for ages below 50 and the lower rates for ages below 40 brought the overall average rate for ages below 50 down and that is why the model underestimate BC rate for ages 40–50.

Years to BC recurrence in 2013: The breast cancer cases diagnosed in 2013 which were

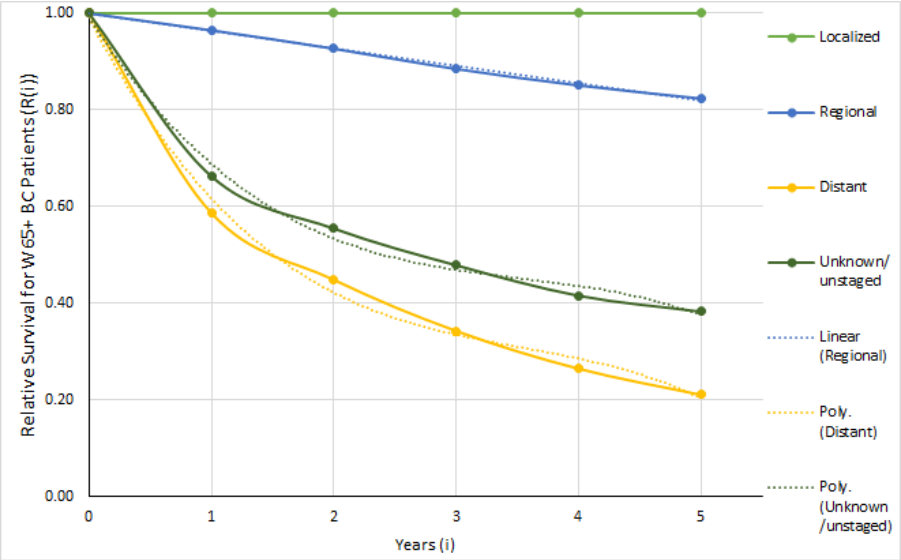

Figure 5.9 Relative survival for breast cancer patients for first five years by stage for white women age 65+

the second breast cancer diagnosed in women age 35–75 at the first and second breast cancer were chosen from SEER and simulation output data. The time between first BC and the second BC were calculated in years and the ones which were less than a year were dropped from the analysis. The statistics for time to second BC for simulation and SEER data are shown in Table 5.12. The distributions of time from first breast cancer diagnosis with IBC and DCIS as first breast cancer are shown in Figures 5.13 and 5.14, respectively. The distribution for years to second breast cancer for African American and white patients can be seen in Figures 5.15 and 5.16, respectively. The time to first recurrence does not follow a normal distribution so we used Wilcox Rank test which is a non-parametric test based solely on the order in which the observations from the two samples fall. There were four groups to test and the Wilcox Rank test comparing them to the SEER data has P-values higher than 0.05 for three of them. The four groups with P-values in parenthesis are: African American patients with IBC as first breast cancer (P-value= 0.0776), African American patients with

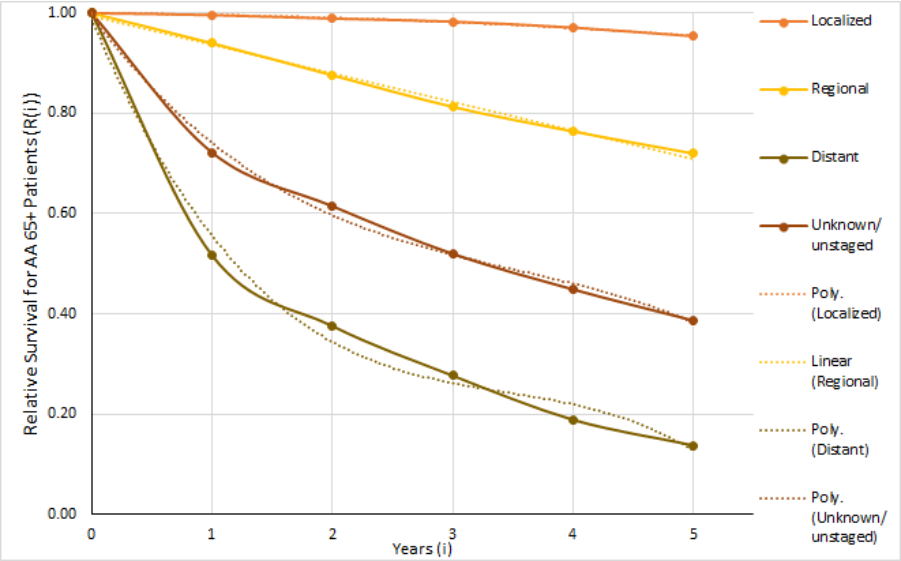

Figure 5.10 Relative survival for breast cancer patients for first five years by stage for African American women age 65+

DCIS as first BC (P-value= 0.2536), white patients with IBC as first BC (P-value= 0.5343), and white patients with DCIS as first BC (P-value= 0.0017). Generally, the distribution of time to second breast cancer has a heavier tail compared to the SEER data, and this might be because of the max-max approach used for the data building the survival model in Chapter 4 as explained in Section 4.1.2. This problem might be resolved by eliminating the recurrences happening less than a year from the initial breast cancer in the simulation data versus shifting them to the ones happening later in the SEER data.

10-year relative survival for IBC patients: In the simulation, the patients leave the model when they reach 2013 or their age reaches 75 so the simulation data for the survival after IBC is right censored. Life table method was used to estimate 10-year survival for each race, IBC diagnosis age group, and IBC stage from the simulation data. The life tables with BC removed as cause of death [72] were used to estimate 10-year survival for each diagnosis age and birth year group. For each race and age group a weighted average of 10-year survival

Table 5.11 Statistics for first breast cancer diagnosis age in SEER versus simulation in 2013

	SEER First BC Age in 2013	Simulation First BC Age in 2013
Number of Observations	58,635	37,646
Mean	57.9124073	58.2341816
Mode	65	51
Standard Deviation	10.0447307	9.86847
Skewness	-0.2064342	-0.2741102
Kurtosis	-0.9025903	-0.6620091
25% Quantile	50	52
Median	59	58
75% Quantile	66	66
Confidence Interval Limits Assuming Normality for Mean		
Lower Limit	57.8311	58.13449
Upper Limit	57.99371	58.33387

Table 5.12 Statistics for years to second breast cancer cases diagnosed in 2013 in SEER versus simulation

	SEER Years to Second BC in 2013	Simulation Years to Second BC in 2013
Number of Observations	3,407	662
Mean	9.19826827	10.1132931
Mode	1	3
Standard Deviation	5.59408	9.86847
Skewness	0.94106204	0.88219864
Kurtosis	1.04683667	0.2473752
25% Quantile	5.08333	5
Median	8.33333	9
75% Quantile	12.33333	14
Confidence Interval Limits Assuming Normality for Mean		
Lower Limit	9.01036	9.59159
Upper Limit	9.38618	10.635

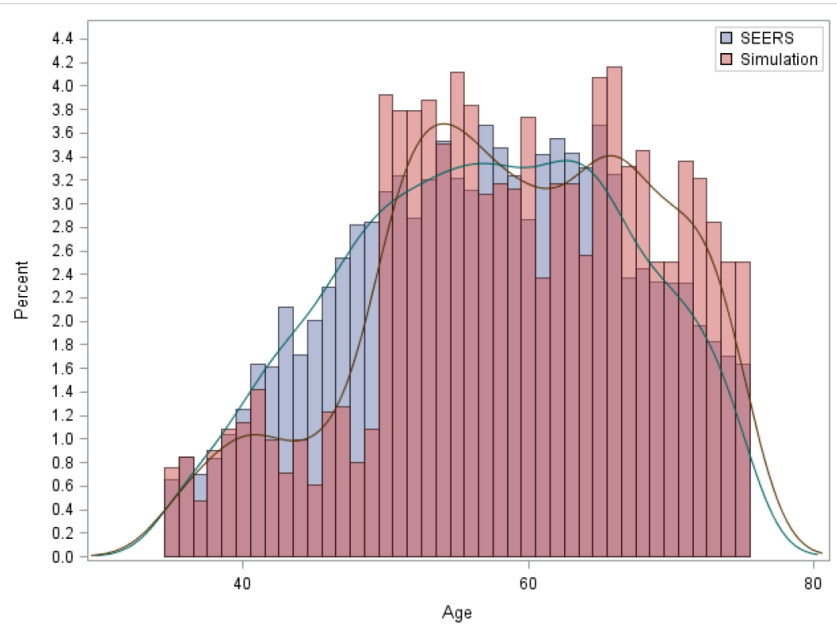

Figure 5.11 Distribution of age of first breast cancer in African American patients in 2013

with BC removed cause of death life tables was calculated with the weights corresponding to the distribution of age and birth year in the similar race and age group from the simulation. The 10-year relative survival was calculated by dividing 10-year survival of BC patients over 10-year survival of women without BC for IBC patients in the simulation and is compared to the 10-year relative survival estimated by the SEER group calculated from 2000–2013 data [119] by race, IBC diagnosis age group, and IBC stage as shown in Table 5.13. The age groups available in SEER are less than 65 and more than 65; and since the simulation right censors the data at age 75, the simulation data for ages above 65 is mostly censored and the estimations for these age groups are inaccurate . However, the estimated confidence intervals for most of the groups coincide, but the simulation seems to be overestimating survival for distant breast cancers.

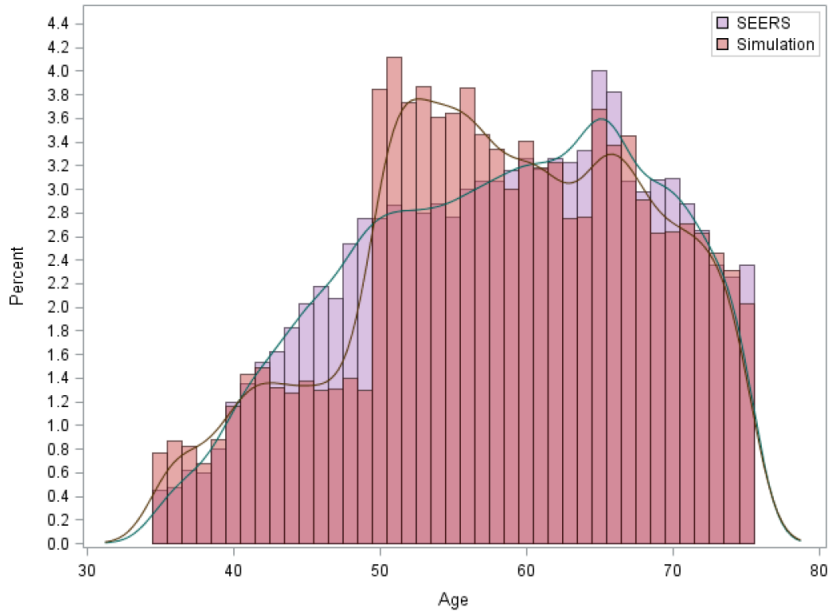

Figure 5.12 Distribution of age of first breast cancer in white patients in 2013

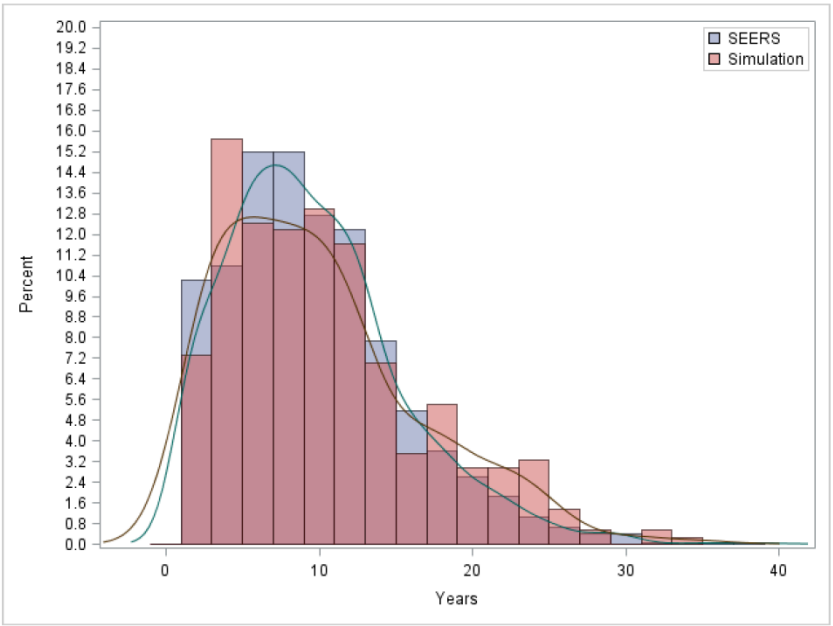

Figure 5.13 Distribution of years to second breast cancer diagnosed in 2013- first BC is IBC

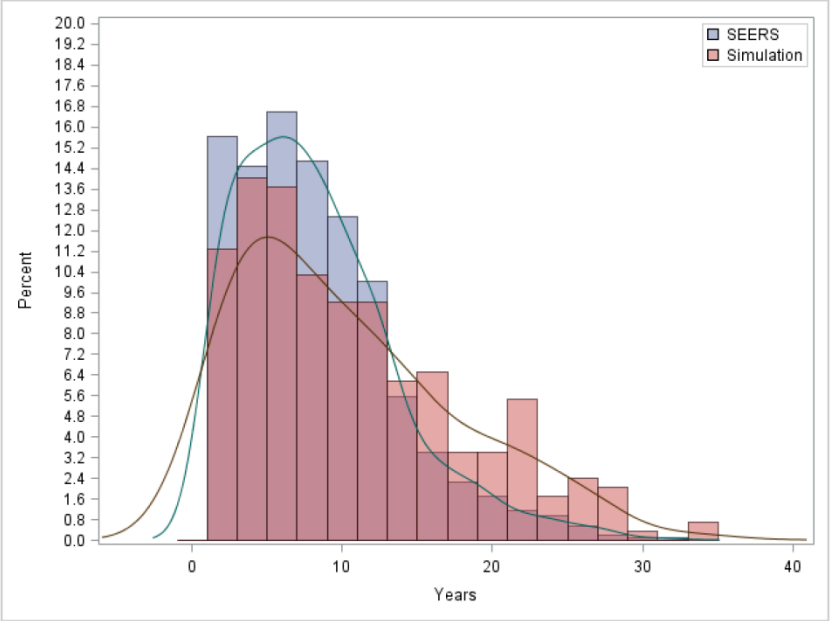

Figure 5.14 Distribution of years to second breast cancer diagnosed in 2013- first BC is DCIS

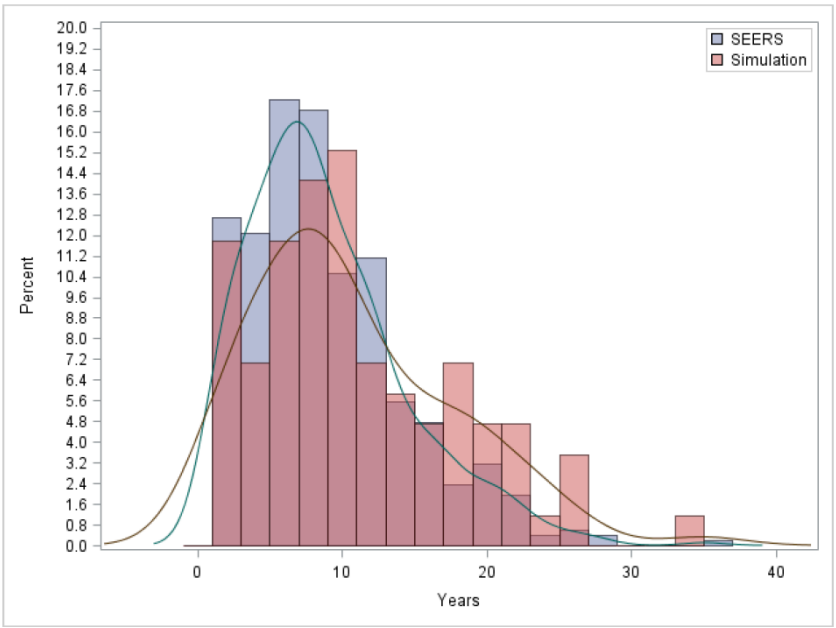

Figure 5.15 Distribution of years to second breast cancer diagnosed in 2013 for African American patients

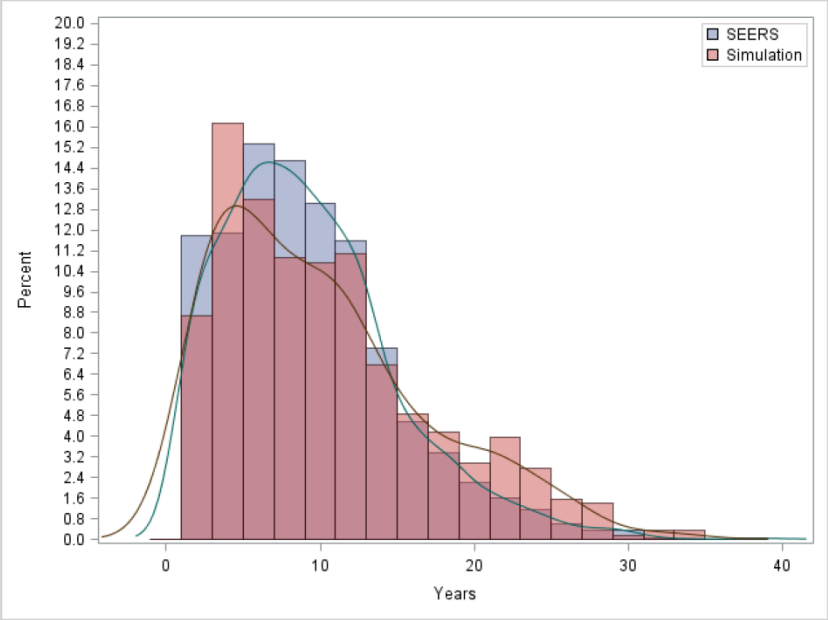

Figure 5.16 Distribution of years to second breast cancer diagnosed in 2013 for white patients

Table 5.13 Relative survival for simulation and SEER data- AA: African American, W: white, S(10): Average 10-year survival probability, RS: Relative survival, LL: Lower limit, UL: Upper limit

Age	Race	Stage	S(10) for IBC Patients	S(10) for Women without BC	LL Simulation 10-Year RS	Simulation 10-Year RS	UL Simulation 10-Year RS	LL SEER 10-Year RS	SEER 10-Year RS	UL SEER 10-Year RS
<65	**W**	**Localized**	0.8835	0.9253	0.9527	0.9548	0.9568	0.953	0.955	0.9568
<65	**W**	**Regional**	0.7432	0.9253	0.7984	0.8031	0.8078	0.7776	0.7811	0.7845
<65	**W**	**Distant**	0.3378	0.9253	0.3533	0.365	0.3768	0.1449	0.1534	0.1621
<65	**W**	**Unstaged**	0.5005	0.9253	0.5356	0.5409	0.5461	0.5723	0.5911	0.6095
65+	**W**	**Localized**	0.9945	0.7366	1.349	1.3502	1.3513	0.9803	0.9878	0.9925
65+	**W**	**Regional**	0.5647	0.7366	0.7525	0.7667	0.7807	0.6866	0.6955	0.7043
65+	**W**	**Distant**	0.245	0.7366	0.3115	0.3327	0.3542	0.0789	0.0884	0.0986
65+	**W**	**Unstaged**	0.3254	0.7366	0.4321	0.4417	0.4514	0.3118	0.3343	0.3569
<65	**AA**	**Localized**	0.818	0.9248	0.8773	0.8846	0.8916	0.872	0.8796	0.8867
<65	**AA**	**Regional**	0.5922	0.9248	0.6278	0.6404	0.6528	0.6232	0.6329	0.6425
<65	**AA**	**Distant**	0.3017	0.9248	0.3039	0.3262	0.3487	0.0904	0.1043	0.1192
<65	**AA**	**Unstaged**	0.3974	0.9248	0.414	0.4297	0.4455	0.4116	0.4555	0.4983
65+	**AA**	**Localized**	0.6937	0.7398	0.9183	0.9378	0.9566	0.8601	0.8834	0.903
65+	**AA**	**Regional**	0.4687	0.7398	0.601	0.6336	0.6657	0.5315	0.5572	0.582
65+	**AA**	**Distant**	0.0117	0.7398	0.0026	0.0159	0.0577	0.0375	0.0547	0.0764
65+	**AA**	**Unstaged**	0.3417	0.7398	0.4323	0.462	0.4918	0.1557	0.2096	0.2691

5.4 Results

The simulation model is run for 10 replications for each race separately for DCIS-P belief treatment threshold in 0.5-1 range with population size 240,000 and 120,000 for the white and African American populations, respectively. It is assumed that initial DCIS-P belief is 0.5 for all DCIS cases and the QALYs when not treating DCIS at active surveillance are the same as the first year after DCIS-recurrence, which is 0.99 multiplied by the QALYs of a healthy person of that age.

5.4.1 DCIS Treatment

Around 53% of first DCIS cases in both African American and white simulation population are DCIS-P and the proportion of DCIS-P and DCIS-I treated depends on the DCIS-P treatment threshold, if the DCIS-P belief probability is above the DCIS-P treatment threshold the DCIS is treated, otherwise the patient waits another six months. The treatment timing depends on the updated DCIS-P belief probability, which itself depends on the observation taken every six months where the probability of each observation, i.e., change versus no change, depends on the type of DCIS (DCIS-P vs DCIS-I), where P(change|DCIS-P)= 0.9 and P(change|DCIS-I)= 0.2. The percentage of first DCIS-I treated decreases more sharply by increasing the DCIS-P treatment threshold compared to the percentage of first DCIS-P treated when the treatment threshold changes from 0.5 to 0.55 as shown in Figure 5.17 and Table 5.14 which corresponds to changing the treatment policy from treating all DCIS cases to only the ones with DCIS-P belief probability higher than the specified threshold. For both African American and white population changing the threshold from 0.5 to 0.55 means decreasing the overtreatment by 70% while increasing under-treatment by 10%.

Table 5.14 Percentage of first DCIS-P and first DCIS-I treated for African American and white patients by DCIS-P treatment threshold- AA: African American, W: white

DCIS-P Treatment Threshold	Percent of DCIS-I Treated AA	Percent of DCIS-P Treated AA	Percent of DCIS-I Treated W	Percent of DCIS-P Treated W
0.5	99.26%	98.91%	99.16%	98.31%
0.55	29.10%	87.12%	27.37%	86.55%
0.6	29.10%	86.93%	27.25%	86.55%
0.65	23.57%	85.56%	21.25%	84.53%
0.7	23.57%	85.56%	21.25%	84.53%
0.75	23.57%	85.56%	21.25%	84.53%
0.8	22.64%	84.90%	20.05%	84.09%
0.85	22.39%	84.72%	19.93%	83.97%
0.9	16.75%	80.57%	13.48%	79.26%
0.95	15.97%	79.04%	12.51%	77.91%
1	14.64%	19.08%	10.98%	15.68%

Changing the treatment threshold from 0.55 to just below 1 decreases the overtreatment and increases under-treatment gradually, however, at the treatment threshold equal to 1 there is a significant decrease in percentage of DCIS-P treated which corresponds to the policy of not treating any of the first DCIS cases, which are also first BC diagnosed in the patient. Notice that the percentage of first DCIS-P and DCIS-I treated never reaches zero since only the cases that are also first BC diagnosed in each patient are considered for the active surveillance option and the rest of first DCIS cases are treated right away. While the number of DCIS cases that are treated decreases as the treatment threshold increases, the average rate of first IBC starts to increase slightly from DCIS-P cases turning to IBC; and at the end increasing the threshold from 0.95 to 1 increases the average IBC rate even more corresponding to around 2% and 2.6% average increase in African American and white population, respectively. On the other hand, the average rates of first DCIS and BC recurrence stay the same for treatment threshold 0.5 to 1.

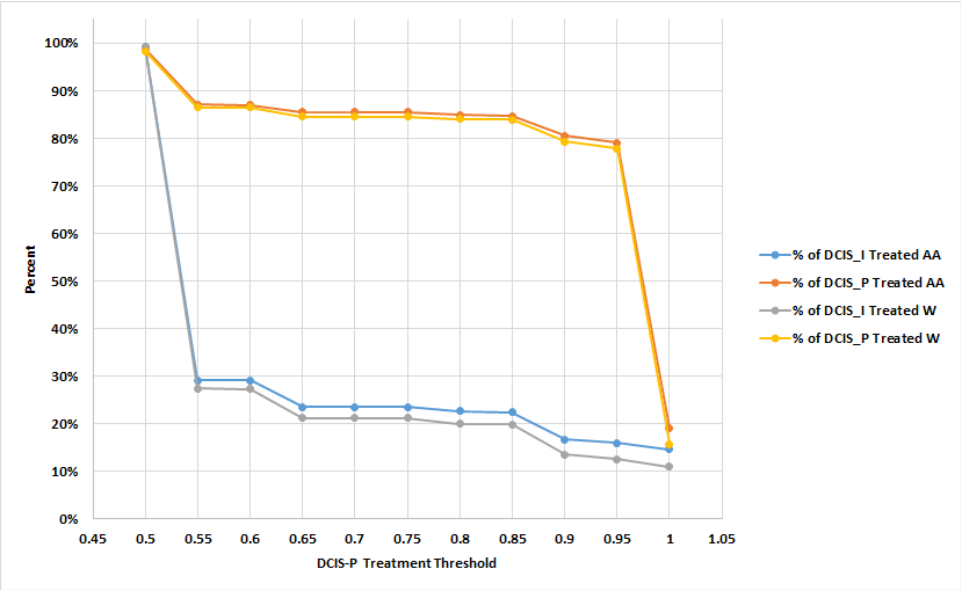

Figure 5.17 Percentage of first DCIS-P and first DCIS-I treated for African American and white patients by DCIS-P treatment threshold- AA: African American, W: white

5.4.2 DCIS and IBC Diagnosed Together

If the patient decides to wait and not treat DCIS based on the DCIS-P belief probability and the pre-specified threshold, there is a chance that DCIS-P progresses to IBC or IBC tumors develop independently in patients with DCIS-I, which results in diagnosis of IBC later at one of the observations taken every six months. From a patient point of view, with no information on which IBC resulted from waiting (IBC developed from DCIS-P) and which one is independent of the active surveillance decision, IBC observation has an added negative implication because it might have been prevented if the DCIS was treated right away. The percentage of first DCIS-I and DCIS-P which are later found with IBC while doing watchful waiting of DCIS by treatment threshold are shown in Figure 5.18 and Table 5.15. After the initial increase when changing DCIS-P treatment threshold from 0.5 to 0.55, the percentage of DCIS-I found with IBC remains the same matching the independence

of probability of developing IBC from having DCIS-I. Increasing the treatment threshold results in increasing the percentage of DCIS-P progressing to IBC while waiting, with a large jump from treatment threshold equal to 0.95 to 1 at the end. In the beginning of the DCIS-P treatment threshold range, the percentage of DCIS-I and DCIS-P found with IBC are very close, with difference less than 1% but the gap between them starts to increase after 0.60.

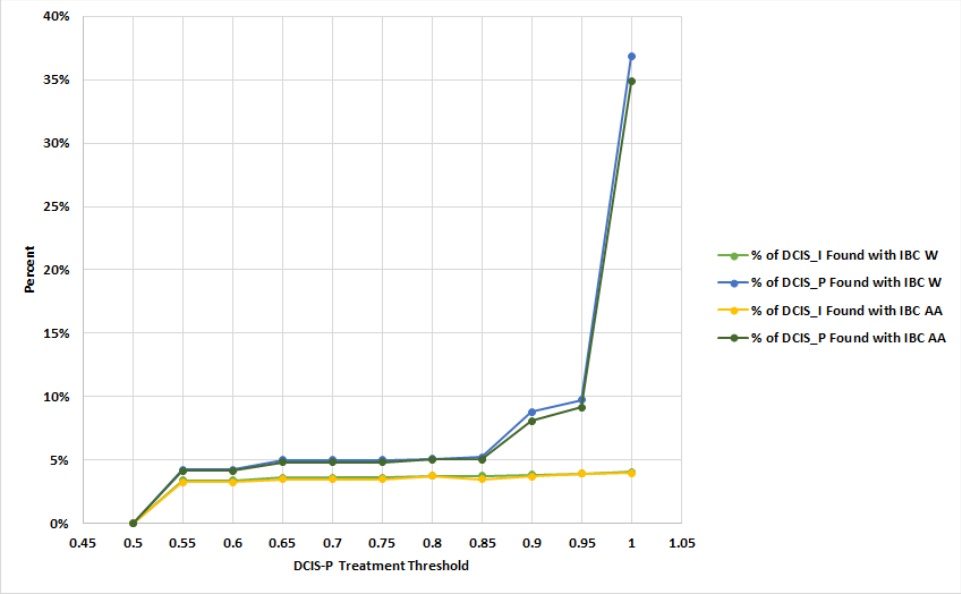

Figure 5.18 Percentage of first DCIS-P and first DCIS-I which had an IBC diagnosis while in active surveillance for African American and white patients by DCIS-P treatment threshold- AA: African American, W: white

5.4.3 Years Spent in Active Surveillance

The number of years spent in active surveillance while having DCIS was evaluated for patients at different points: the first DCIS treatment, being diagnosed with IBC while waiting with DCIS, dying, and leaving the simulation when reaching age 75 or reaching

Table 5.15 Percentage of first DCIS-P and first DCIS-I which had an IBC diagnosis while in active surveillance for African American and white patients by DCIS-P treatment threshold- AA: African American, W: white

DCIS-P Treatment Threshold	Percent of DCIS-I Found with IBC- AA	Percent of DCIS-P Found with IBC-AA	Percent of DCIS-I Found with IBC W	Percent of DCIS-P Found with IBC W
0.5	0.00%	0.00%	0.00%	0.00%
0.55	3.23%	4.15%	3.36%	4.24%
0.6	3.23%	4.14%	3.36%	4.24%
0.65	3.47%	4.81%	3.60%	4.98%
0.7	3.47%	4.81%	3.60%	4.98%
0.75	3.47%	4.81%	3.60%	4.98%
0.8	3.73%	5.03%	3.72%	5.09%
0.85	3.48%	5.02%	3.72%	5.20%
0.9	3.69%	8.08%	3.82%	8.78%
0.95	3.93%	9.17%	3.93%	9.73%
1	3.97%	34.87%	4.06%	36.86%

2013 (called censored from here on) for DCIS-I and DCIS-P for each patient. The average number of years when reaching each of these for different DCIS-P threshold values are shown in Figures 5.19,5.21, 5.20, and 5.22 and Tables 5.16 and 5.17 for African American and white patients. The number of years spent with DCIS increase with increase in treatment threshold for all types of DCIS at all points except for average number of years waiting on DCIS-I just before treating it. The years spent with DCIS-I before treatment decrease as the number of first DCIS-I treated is reduced dramatically to almost 20% shown in Figure 5.17 and the average is affected more by the cases that are treated right away with years spent with DCIS equal to zero, i.e., the first DCIS-I cases that are recurrences of an initial IBC.

Table 5.16 Average number of years spent at active surveillance for the first DCIS, measured at IBC diagnosis, DCIS treatment, death, and exiting the model by reaching age 75 or 2013 (censored) for African American patients by DCIS-P treatment threshold- AA: African American

DCIS-P Treatment Threshold	DCIS-I Year(s) at Treatment AA	DCIS-I Year(s) at Death AA	DCIS-I Year(s) When Censored AA	DCIS-I Year(s) at DCIS-I & IBC AA	DCIS-P Year(s) at Treatment AA	DCIS-P Year(s) at Death AA	DCIS-P Year(s) When Censored AA	DCIS-P Year(s) at DCIS-P & IBC AA
0.5	0.425	0.407	0.424	0	0.436	0.415	0.434	0
0.55	0.66	4.561	5.235	7.17	0.972	0.874	0.928	0.748
0.6	0.645	4.573	5.235	7.141	0.974	0.874	0.93	0.774
0.65	0.473	5.019	5.601	7.3	1.038	0.945	0.994	0.878
0.7	0.464	5.013	5.602	7.3	1.039	0.961	0.993	0.878
0.75	0.461	5.013	5.602	7.3	1.039	0.961	0.993	0.878
0.8	0.383	5.086	5.705	7.39	1.054	0.947	1.017	0.955
0.85	0.364	5.08	5.71	7.428	1.054	0.953	1.024	1.031
0.9	0.215	5.667	6.125	7.357	1.488	1.247	1.399	1.082
0.95	0.139	5.724	6.182	7.42	1.59	1.348	1.49	1.193
1	0	5.658	6.257	7.533	4.396	4.233	4.501	4.397

Table 5.17 Average number of years spent at active surveillance for the first DCIS, measured at IBC diagnosis, DCIS treatment, death, and exiting the model by reaching age 75 or 2013 (censored) for white patients by DCIS-P treatment threshold- W:white

DCIS-P Treatment Threshold	DCIS-I Year(s) at Treatment W	DCIS-I Year(s) at Death W	DCIS-I Year(s) When Censored W	DCIS-I Year(s) at DCIS-I & IBC W	DCIS-P Year(s) at Treatment W	DCIS-P Year(s) at Death W	DCIS-P Year(s) When Censored W	DCIS-P Year(s) at DCIS-P & IBC W
0.5	0.444	0.447	0.439	0	0.453	0.437	0.446	0
0.55	0.806	5.132	5.458	6.88	1.012	0.912	0.953	0.731
0.6	0.788	5.158	5.469	6.88	1.013	0.913	0.954	0.732
0.65	0.632	5.637	5.859	6.952	1.08	0.987	1.023	0.885
0.7	0.623	5.637	5.864	6.952	1.08	0.987	1.023	0.885
0.75	0.623	5.637	5.864	6.952	1.08	0.987	1.023	0.885
0.8	0.526	5.681	5.937	6.96	1.094	0.995	1.043	0.946
0.85	0.509	5.676	5.958	6.961	1.096	1.013	1.047	0.982
0.9	0.362	6.087	6.42	6.92	1.56	1.358	1.43	1.051
0.95	0.249	6.179	6.503	7.057	1.677	1.485	1.532	1.157
1	0	6.129	6.607	7.219	5.346	4.456	4.621	4.413

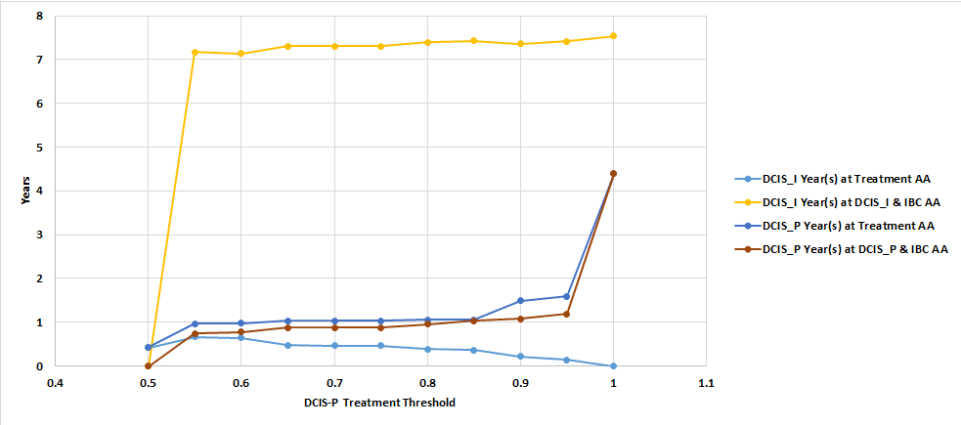

Figure 5.19 Average number of years spent at active surveillance for the first DCIS, measured at IBC diagnosis and DCIS treatment for African American patients by DCIS-P treatment threshold-AA: African American

5.4.4 Exit Mode Distribution

The distribution of DCIS patients is analyzed by first categorizing them into two groups of patients with history of DCIS but no history of IBC (Hx DCIS-No IBC) and patients with history of both IBC and DCIS (Hx DCIS-IBC) at the point of analysis . Then for each group proportions of them who died, exited because they reached age 75, and exited because they reached 2013 are calculated and are shown in Figures 5.23 and 5.24 for Hx DCIS-IBC and Hx DCIS-No IBC, respectively and in Tables 5.18 and 5.19 for African American and white patients, respectively. The distributions for each race remain the same for treatment threshold 0.5-0.95 and there is a small increase in percent death when the threshold policy is increased from 0.95 to 1 for both races if they also have a history of IBC.

5.4.5 Death Age

Initial age, age at first diagnosis of DCIS and IBC with death age for patients with history of IBC and DCIS are shown in Figures 5.25 and 5.26 and Tables 5.20 and 5.21 for African

Table 5.18 Distribution of exit mode for African American patients with history of DCIS and no history of IBC (Hx DCIS-No IBC) and patients with history of both DCIS and IBC (Hx DCIS-IBC) by DCIS-P treatment threshold- AA: African American

DCIS-P Treatment Threshold	Percent Died of Hx DCIS- No IBC AA	Percent Censored at Age 75 of Hx DCIS- No IBC AA	Percent Censored at 2013 Hx DCIS- No IBC AA	Percent Death of Hx DCIS- IBC AA	Percent Censored at Age 75 Hx DCIS- IBC AA	Percent Censored at 2013 Hx DCIS- IBC AA
0.5	10.99%	28.55%	60.46%	18.59%	37.18%	44.23%
0.55	11.57%	27.99%	60.43%	18.39%	35.63%	45.98%
0.6	11.69%	27.96%	60.35%	18.39%	35.63%	45.98%
0.65	11.62%	28.11%	60.27%	18.99%	34.64%	46.37%
0.7	11.64%	28.15%	60.22%	18.99%	34.64%	46.37%
0.75	11.64%	28.15%	60.22%	18.99%	34.64%	46.37%
0.8	11.47%	28.21%	60.32%	18.99%	34.64%	46.37%
0.85	11.49%	28.24%	60.27%	18.99%	34.64%	46.37%
0.9	11.69%	28.49%	59.81%	19.47%	34.74%	45.79%
0.95	11.96%	28.36%	59.68%	19.69%	34.72%	45.60%
1	14.42%	27.76%	57.82%	22.71%	30.17%	47.12%

Table 5.19 Distribution of exit mode for white patients with history of DCIS and no history of IBC (Hx DCIS-No IBC) and patients with history of both DCIS and IBC (Hx DCIS-IBC) by DCIS-P treatment threshold- W:white

DCIS-P Treatment Threshold	Percent Died of Hx DCIS-No IBC W	Percent Censored at Age 75 of Hx DCIS-No IBC W	Percent Censored at 2013 Hx DCIS-No IBC W	Percent Death of Hx DCIS-IBC W	Percent Censored at Age 75 Hx DCIS-IBC W	Percent Censored at 2013 Hx DCIS-IBC W
0.5	10.90%	27.24%	61.87%	14.11%	39.42%	46.47%
0.55	10.51%	27.45%	62.04%	14.49%	37.81%	47.70%
0.6	10.51%	27.52%	61.98%	14.44%	38.03%	47.54%
0.65	10.56%	27.56%	61.88%	14.78%	37.46%	47.77%
0.7	10.56%	27.56%	61.88%	14.78%	37.46%	47.77%
0.75	10.56%	27.56%	61.88%	14.78%	37.46%	47.77%
0.8	10.46%	27.57%	61.97%	14.78%	37.46%	47.77%
0.85	10.52%	27.61%	61.87%	14.73%	37.67%	47.60%
0.9	10.43%	27.67%	61.90%	14.81%	35.80%	49.38%
0.95	10.84%	27.48%	61.68%	15.02%	34.83%	50.15%
1	12.13%	27.44%	60.44%	17.14%	30.04%	52.83%

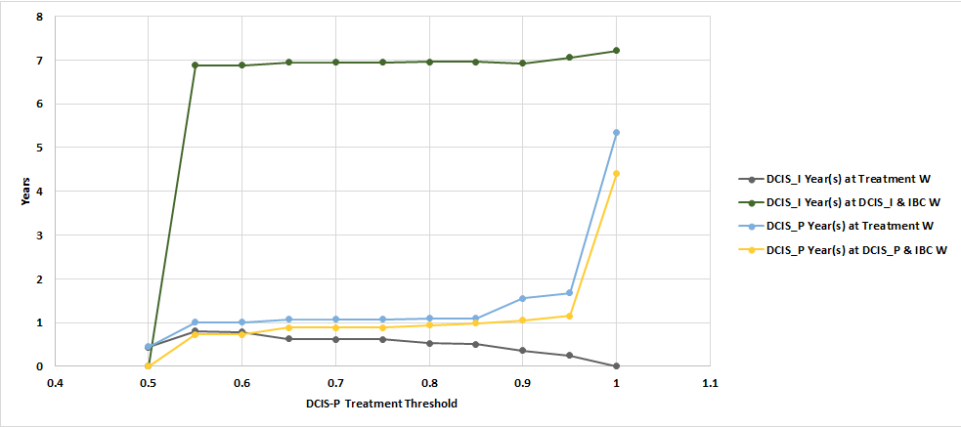

Figure 5.20 Average number of years spent at active surveillance for the first DCIS, measured at IBC diagnosis and DCIS treatment for white patients by DCIS-P treatment threshold- W: white

American and white patients, respectively. Death age for patients with an IBC history and women without BC history remains the same by changing the treatment threshold. For patients with a DCIS history there are two points a decrease in death age happens when changing the policy from treating all to treating some DCIS cases from threshold 0.5 to 0.55 and from treating some DCIS cases to treating none of them from threshold 0.95 to 1. The death age is higher for DCIS patients compared to women without breast cancer history which seems counterintuitive but according to the recent study done in Netherlands women with a history of DCIS "had lower risk of dying of all causes"[128] but in our model we suspect this is partly because DCIS patients have a higher age at diagnosis (around 58) than the average age of entry for general population (around 42) in the model which means they have already made it to the 58 to be diagnosed with DCIS and after that they still have the same survival as the general population unless they develop an IBC which less than 30% of them do.

Table 5.20 Average initial age of women without BC history, age of first diagnosis for patients with DCIS and IBC history and their death age by DCIS-P treatment threshold for African American women- AA: African American

DCIS-P Treatment Threshold	Population Initial Age AA	First DCIS Age AA	First IBC Age AA	Death Age No Hx BC AA	Death Age Hx DCIS AA	Death Age Hx IBC AA
0.5	41.549	58.734	58.837	63.203	66.552	62.609
0.55	41.556	58.691	58.88	63.203	66.546	62.604
0.6	41.556	58.685	58.88	63.203	66.552	62.609
0.65	41.555	58.707	58.879	63.206	66.474	62.606
0.7	41.555	58.709	58.879	63.206	66.464	62.604
0.75	41.554	58.711	58.879	63.205	66.464	62.604
0.8	41.554	58.702	58.877	63.201	66.503	62.6
0.85	41.555	58.703	58.877	63.201	66.502	62.604
0.9	41.555	58.747	58.877	63.212	66.304	62.623
0.95	41.558	58.74	58.877	63.209	66.247	62.639
1	41.558	58.779	58.902	63.202	65.524	62.636

Table 5.21 Average initial age of women without BC history, age of first diagnosis for patients with DCIS and IBC history and their death age by DCIS-P treatment threshold for white women- W: white

DCIS-P Treatment Threshold	Population Initial Age W	First DCIS Age W	First IBC Age W	Death Age No Hx BC W	Death Age Hx DCIS W	Death Age Hx IBC W
0.5	42.165	57.983	58.935	63.357	66.957	62.857
0.55	42.17	58.017	58.913	63.38	66.642	62.834
0.6	42.17	58.018	58.913	63.38	66.642	62.834
0.65	42.169	58.04	58.923	63.374	66.647	62.845
0.7	42.169	58.039	58.924	63.374	66.647	62.847
0.75	42.169	58.039	58.924	63.374	66.647	62.847
0.8	42.169	58.032	58.926	63.37	66.632	62.845
0.85	42.169	58.032	58.926	63.37	66.647	62.842
0.9	42.165	58.014	58.922	63.358	66.414	62.808
0.95	42.168	57.996	58.922	63.358	66.346	62.8
1	42.165	58.031	58.926	63.347	65.461	62.819

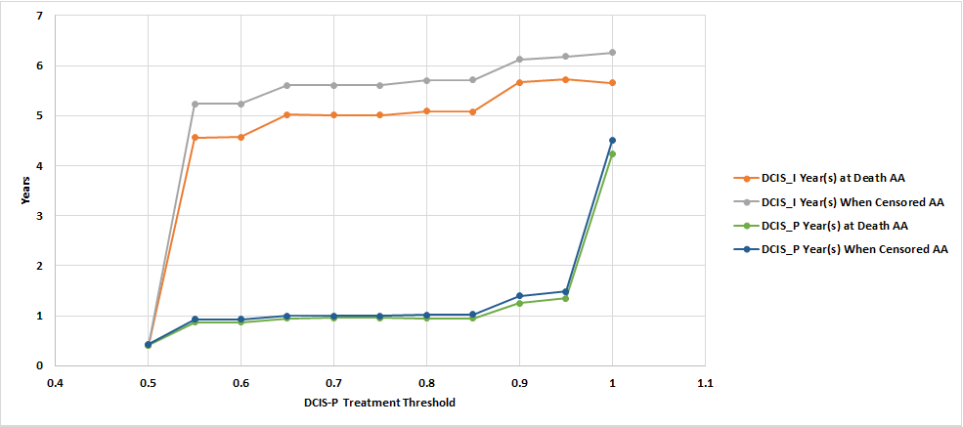

Figure 5.21 Average number of years spent at active surveillance for the first DCIS, measured at death and exiting the model by reaching age 75 or 2013 (censored) for African American patients by DCIS-P treatment threshold- AA: African American

5.4.6 QALYs

The accumulated QALYs for each individual for her time in the model is measured at death and when she exits the model due to reaching 2013 or being 75 years old (called censored). The average accumulated QALY for the whole population is not sensitive to the change in the threshold policy so the patients are grouped into three categories by their histories of BC to see the differences more clearly: patients who have history of DCIS but no history of IBC (Hx DCIS-No IBC), patients with history of both IBC and DCIS (Hx DCIS-IBC), and patients with history of IBC with or without a history of DCIS (Hx IBC), and their average accumulated QALYs at death and when they are censored are shown in Figures 5.27 and 5.28 and Tables 5.22 and 5.23 for African American and white patients, respectively. African Americans have a slightly higher QALYs for most categories driven by their younger average age entering the model allowing them to gain more QALYs before exiting the simulation but they have lower QALYs for categories that have a history of IBC at death because of their lower relative survival when having an IBC compared to the white patients. The QALY

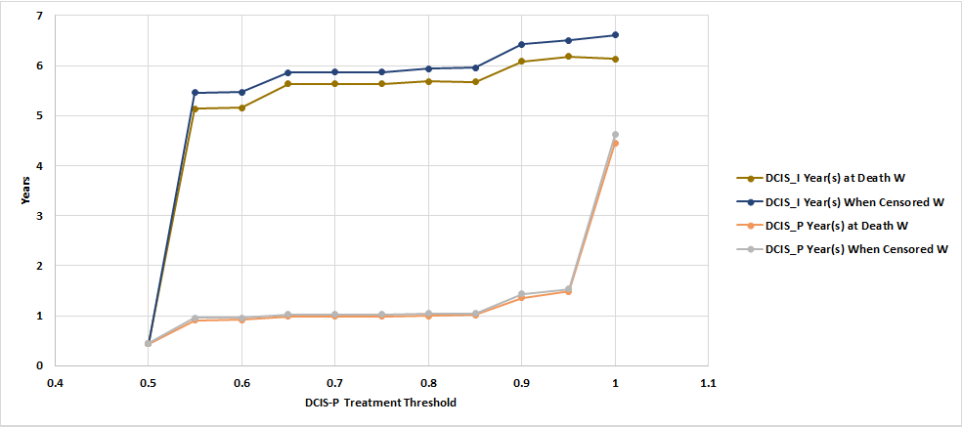

Figure 5.22 Average number of years spent at active surveillance for the first DCIS, measured at death and exiting the model by reaching age 75 or 2013 (censored) for white patients by DCIS-P treatment threshold- W: white

of patients with a history of DCIS and IBC is lower than the QALY of patients with DCIS but no history of IBC, however, in white patients the average QALY of Hx DCIS-IBC is more the Hx DCIS-No IBC at death. The average half width for white Hx DCIS-No IBC and Hx DCIS-IBC patients is 0.11 and 1.6, respectively implying that although the average QALY for patients with IBC seems to become higher because of not spending a long time with DCIS and accruing 0.99 of a healthy person QALY during active surveillance, their increased QALY is not statistically significant because their confidence interval is wide enough that they intersect from one value threshold to the other.

In this chapter, we described the breast cancer simulation model created to evaluate DCIS treatment policies in the population. The analysis of the simulation results showed that metrics such as the percentage of mortality in the population and average patients' QALY when they exit the simulation are not very sensitive to the treatment policy.

Table 5.22 Average accumulated QALY for patients with history of DCIS and no history of IBC (Hx DCIS-No IBC), patients with history of both DCIS and IBC (Hx DCIS-IBC), and patients with history of IBC (Hx IBC) at death and exiting the model by reaching age 75 or 2013 (censored) by DCIS-P treatment threshold for African American women- AA: African American, Acc: accumulated

DCIS-P Treatment Threshold	Acc QALY Hx DCIS-No IBC Death AA	Acc QALY Hx DCIS-No IBC Censored AA	Acc QALY Hx DCIS-IBC Death AA	Acc QALY Hx DCIS-IBC Censored AA	Acc QALY Hx IBC Death AA	Acc QALY Hx IBC Censored AA
0.5	20.67	22.514	19.482	23.271	15.327	20.94
0.55	20.298	22.544	19.464	23.258	15.287	20.92
0.6	20.311	22.541	19.464	23.25	15.288	20.92
0.65	20.38	22.523	19.53	23.264	15.301	20.947
0.7	20.383	22.522	19.53	23.264	15.301	20.947
0.75	20.383	22.522	19.53	23.264	15.301	20.947
0.8	20.386	22.53	19.435	23.256	15.292	20.948
0.85	20.432	22.528	19.517	23.258	15.294	20.948
0.9	20.272	22.57	19.553	23.27	15.314	20.973
0.95	20.344	22.554	19.803	23.227	15.329	20.965
1	19.895	22.438	19.691	23.295	15.393	21.019

Table 5.23 Average accumulated QALY for patients with history of DCIS and no history of IBC (Hx DCIS-No IBC), patients with history of both DCIS and IBC (Hx DCIS-IBC), and patients with history of IBC (Hx IBC) at death and exiting the model by reaching age 75 or 2013 (censored) by DCIS-P treatment threshold for white women- W: white, Acc: accumulated

DCIS-P Treatment Threshold	Acc QALY Hx DCIS-No IBC Death W	Acc QALY Hx DCIS-No IBC Censored W	Acc QALY Hx DCIS-IBC Death W	Acc QALY Hx DCIS-IBC Censored W	Acc QALY Hx IBC Death W	Acc QALY Hx IBC Censored W
0.5	20.169	22.022	19.97	22.726	15.725	20.747
0.55	20.017	21.981	19.788	22.767	15.712	20.749
0.6	20.01	21.982	19.787	22.767	15.712	20.748
0.65	20.033	21.984	19.831	22.761	15.704	20.752
0.7	20.033	21.984	19.831	22.761	15.704	20.753
0.75	20.033	21.984	19.831	22.761	15.704	20.753
0.8	19.995	21.971	19.79	22.767	15.701	20.754
0.85	20.005	21.967	19.753	22.769	15.7	20.755
0.9	19.918	21.938	20	22.827	15.693	20.765
0.95	19.815	21.927	20.012	22.834	15.703	20.772
1	19.599	21.857	19.819	22.832	15.8	20.817

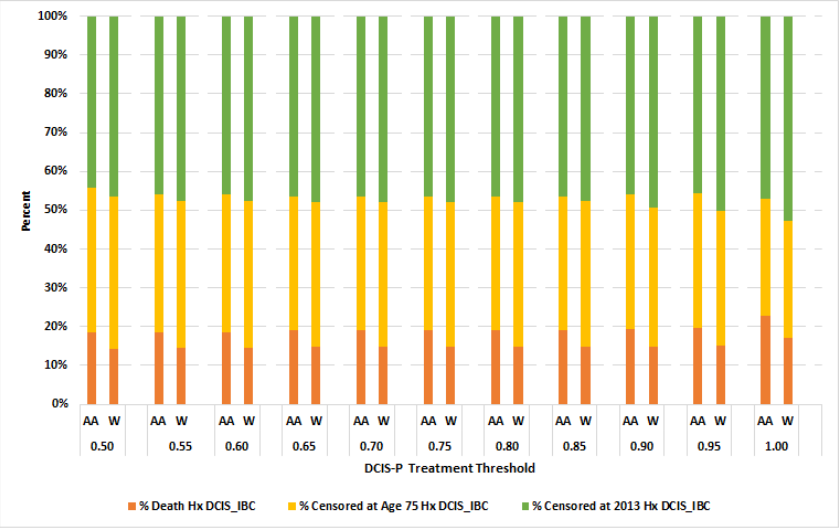

Figure 5.23 Distribution of exit mode for African American and white patients with history of both DCIS and IBC (Hx DCIS-IBC) by DCIS-P treatment threshold- AA: African American, W: white

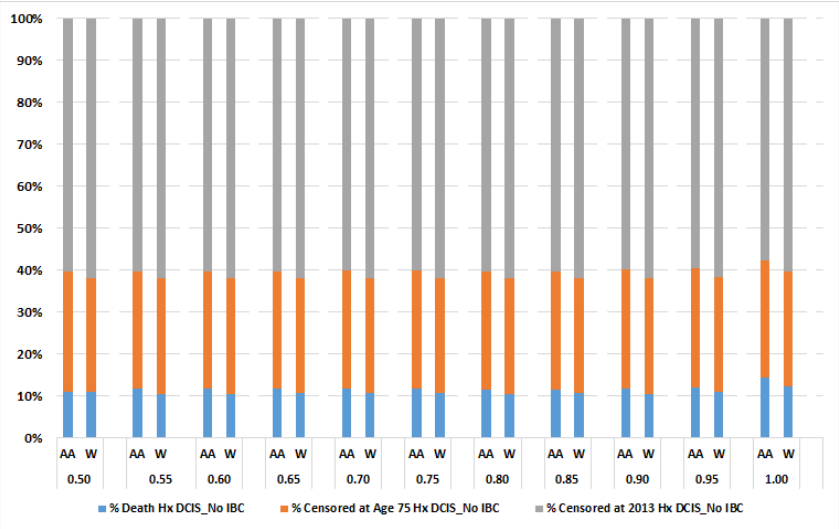

Figure 5.24 Distribution of exit mode for African American and white patients with history of DCIS and no history of IBC (Hx DCIS-No IBC) by DCIS-P treatment threshold- AA: African American, W: white

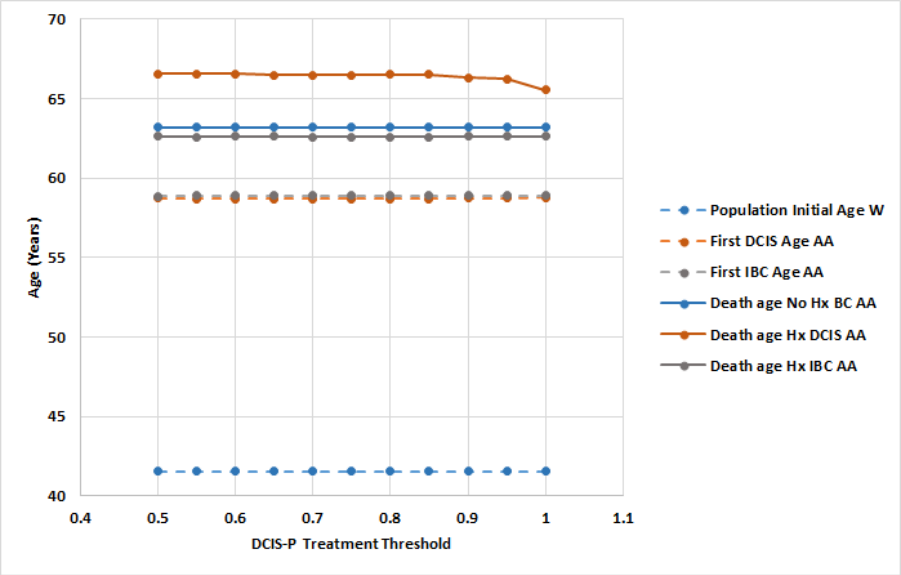

Figure 5.25 Average initial age of women without BC history, age of first diagnosis for patients with DCIS and IBC history and their death age by DCIS-P treatment threshold for African American women- AA: African American

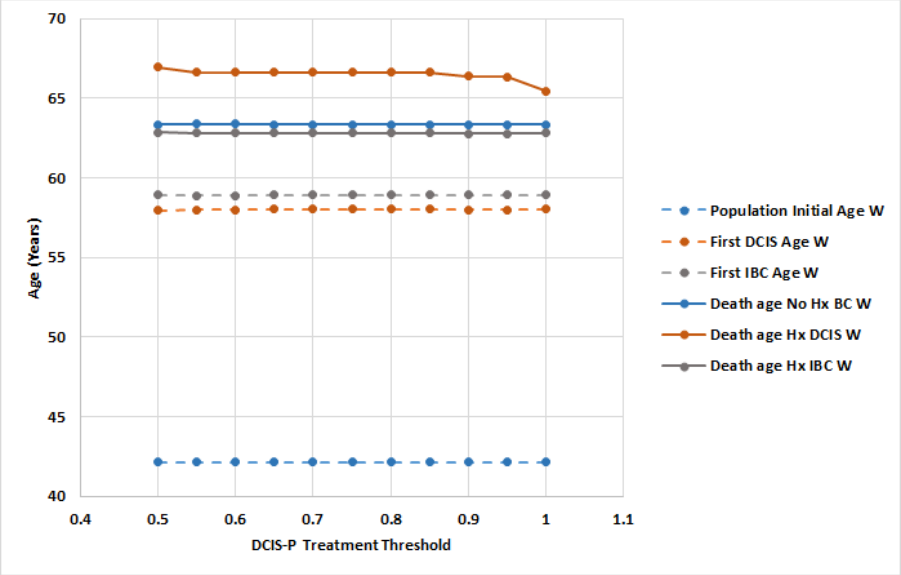

Figure 5.26 Average initial age of women without BC history, age of first diagnosis for patients with DCIS and IBC history and their death age by DCIS-P treatment threshold for white women- W: white

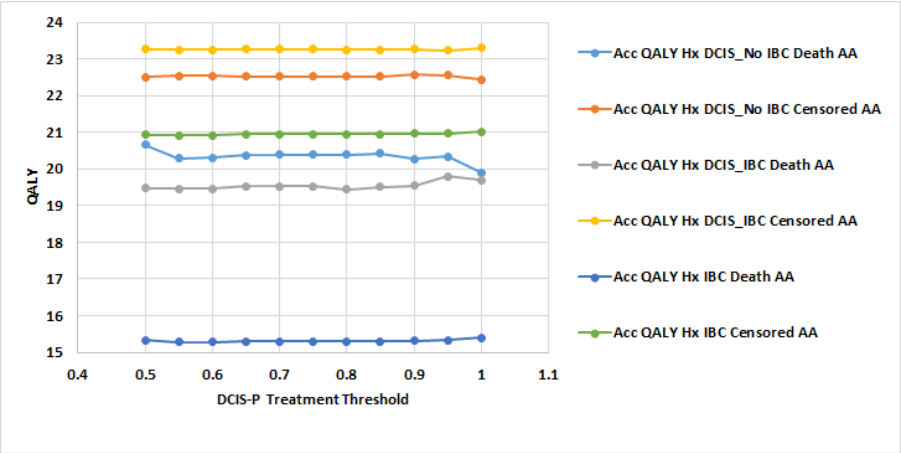

Figure 5.27 Average accumulated QALY for patients with history of DCIS and no history of IBC (Hx DCIS-No IBC), patients with history of both DCIS and IBC (Hx DCIS-IBC), and patients with history of IBC (Hx IBC) at death and exiting the model by reaching age 75 or 2013 (censored) by DCIS-P treatment threshold for African American women- AA: African American, Acc: accumulated

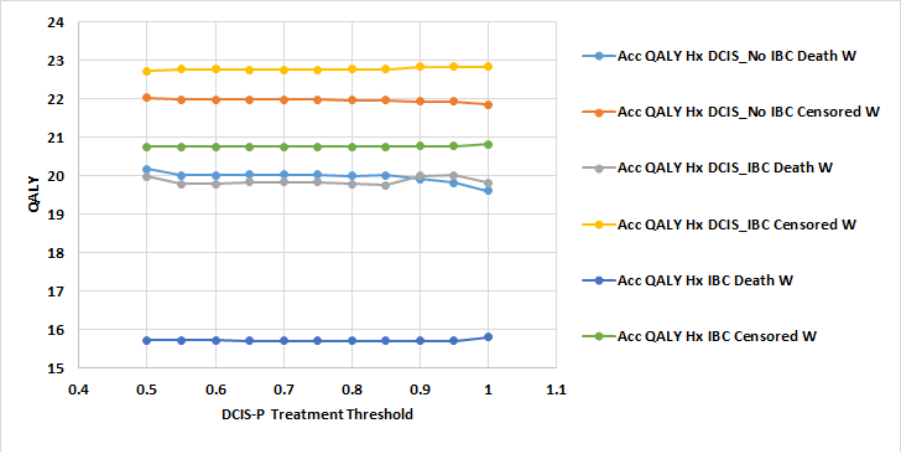

Figure 5.28 Average accumulated QALY for patients with history of DCIS and no history of IBC (Hx DCIS-No IBC), patients with history of both DCIS and IBC (Hx DCIS-IBC), and patients with history of IBC (Hx IBC) at death and exiting the model by reaching age 75 or 2013 (censored) by DCIS-P treatment threshold for white women- W: white, Acc: accumulated

CHAPTER

6

CONCLUSIONS AND FUTURE WORK

The final chapter of this dissertation is dedicated to conclusions, limitations, and future work.

6.1 Conclusion and Contribution

In this dissertation, we explored the management of ductal carcinoma in situ (DCIS) when active surveillance, i.e., taking more observations before treating the cancer, is an option. Unlike invasive breast cancer (IBC), DCIS cannot spread to the vital organs before breaking through the duct, which can give the patient and physicians time to evaluate its nature. It is assumed there are two types of DCIS based on its potential to progress to IBC by exiting the duct, where DCIS first started growing, in the patient's lifetime: progressive DCIS (DCIS-P), with potential to change to IBC; and indolent DCIS (DCIS-I), without the potential to become IBC in the future. It is assumed that observing changes in DCIS can be suggestive of its aggressive nature; however, since active surveillance has never been an option there is no data on the likelihood function for observations conditioned on each state. So we considered a likelihood function based on the idea that change is more probable in DCIS-P compared to DCIS-I.

The effect of taking observations, first on the individual level using a partially observable Markov decision process (POMDP), and then on the population level using discrete event simulation, were evaluated in this dissertation in Chapters 3 and 5, respectively. Modeling DCIS treatment as a POMDP showed that at each decision epoch there seemed to be a threshold for the DCIS-P belief probability, above which it is optimal to treat and below which it is optimal to take another observation in the next period. In the simulation, a range of threshold values were used as different DCIS treatment policies and criteria such as quality adjusted life years (QALYs), death age, and number of years before treatment for

each DCIS type were utilized to evaluate the effect of each policy.

In addition, we used recurrence prediction models to model life after treatment for breast cancer patients in the simulation model to calculate more accurately QALYs, probability of death, and the effect of treatment on each patient's life. In Chapter 4, we used the Cox proportional hazards model and accelerated failure time (AFT) models to perform survival analysis on publicly available breast cancer SEER data. The AFT model was used as an input to the simulation in Chapter 5 to predict time to breast cancer recurrence based on each patient's tumor attributes in the model.

The simulation results show that outcomes such as average death age and QALYs are not highly sensitive to changes in the threshold policy, which means exploring the option of active surveillance and reducing overtreatment should be discussed with patients and maybe become a viable option in the future at least for low-risk DCIS cases. To the best of our knowledge, there has been no similar work considering active surveillance for DCIS and evaluating policies using measures such as QALYs, mortality, and the increase in the number of breast cancer cases. Currently, there is a trial in the UK called LORIS, patients with low-risk DCIS are opting for watchful waiting or monitoring the cancer without surgery [23], which might make the data available to improve the accuracy of this analysis. The LORIS trial was started in 2014 and is set to end in 2020. It is worth updating this analysis after LORIS data becomes available.

6.2 Limitations

Some of challenges and limitations that we had during this research are listed below:

- There is no data available for past active surveillance and as a result no underlying probability distribution for the observation and likelihood functions connecting

observations to state were available. In these cases we fitted the required distributions subjectively.

- As a result of memory limits for the Arena software, the simulation for the African American and white populations could not be run at the same time; and some of the attributes for breast cancer were removed to save memory to be able to run the model.

- It has been shown that hormone replacement therapy (HRT) increases the risk of breast cancer; and as a result, the number of women using HRT has dramatically decreased since 2002. This development might have changed the patterns in breast cancer incidence and recurrence in recent years. However, since the lifetime effect of treating breast cancer was being evaluated, the data before 2002 was also used in the model.

- SEER data does not contain data on systematic treatment, which can have a significant effect on a patient's QALYs after breast cancer treatment.

- The proportion of the African American population in SEER is lower than that of the African American women in the U.S. population. So SEER is not a perfect representation for this population, although, the addition of new registries recently, is changing the proportion to be more representative of the U.S. population.

- The smoothing function for rates of IBC and DCIS increased the rate of breast cancer in African American patients to more than the actual rate; as a result, we might be overestimating breast cancer rates if we run the model for future years.

- The QALYs for breast cancer patients only depend on the breast cancer stage and whether the cancer is an initial breast cancer; however, the type of treatment has no

effect on the QALYs. To the best of our knowledge, there are no QALYs available for different DCIS treatments, and previous work usually assumed numbers similar to local IBC treatment QALYs.

6.3 Future Work

These are some of the future directions to explore following this research:

- We can use the part of the simulation model for calculating the rewards for the POMDP model by starting in the absorbing states in POMDP, i.e., treated DCIS, local IBC, and regional IBC, and calculating the average accumulated QALY at death. After calculating the optimal threshold for individuals in different cohorts, we might be able to find improved policies for the population.

- If in the future QALYs for DCIS treatment become available, we can use them to model the effect of DCIS overtreatment on QALYs more accurately.

- Sensitivity analysis on QALYs for different states and probabilities of change for DCIS types could improve insights on how sensitive the outcomes are to different treatment threshold values.

- Having different thresholds for different DCIS grades and DCIS diagnosis ages might create better policies at the population level because cancer tends to be more aggressive in younger ages.

- Expanding the age range from 35–75 to 30–100 and the number of years patients are in the model (eliminating censoring) might give us better insight as to which policy has better long term effect.

- If the model is written in a programming language with more memory management options, we will be able to run the whole population together (African American and white patients), and we can possibly add tumor growth piece and individual breast cancer risk model.

- Using competing-cause models to predict death and recurrence using the same model would make the simulation results more accurate. More comprehensive data that has the exact time of death is needed for this purpose.

- As more data becomes available such as HER2 status, the recurrence prediction model can be revised. Also if the breast cancer subtype is available, we can increase or decrease the rate of DCIS-P turning to IBC based on the subtype in the simulation as we did in an example in Chapter 3.

- Currently, there is no DCIS growth model; and if in the future such a model is developed and can be added to the simulation, then we can translate the change and no-change observations into actual observations such as increase in size or observing comedo-necrosis in DCIS.

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APPENDICES

APPENDIX

A

DISTRIBUTION FITTING

In all tables, "R" means all P-values were less than or equal to 0.01 for all the goodness of fit tests performed by SAS, in other words, it means all goodness of fit tests run by SAS are rejected at levels greater than or equal to 0.01. In case of at least one of the tests having P-value greater than 0.01, the three numbers represent P-values for Kolmogorov-Smirnov (KS), Cramer-von Mises (CM), and Anderson-Darling (AD) tests, respectively, for Lognormal, Exponential, and Gamma distributions, and the two numbers represent P-values for CM and AD respectively for Weibull distribution. NA means that the goodness of fit test was not available in SAS.

Table A.1 Distribution fitting for DCIS grouped by ICD-O-3 coding- Max Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
DCIS 8201	R	R	R	R	0.042, 0.113, 0.008	619
DCIS 8230	R	R	0.018, <0.01	R	0.026, 0.037, 0.013	404
DCIS 8500	R	R	R	R	NA	6280
DCIS 8501	R	R	R	R	>0.5, >0.5, 0.133	1893
DCIS 8503	R	R	>0.25, >0.25	0.082. 0.035, 0.023	>0.25, 0.233,0.143	618
DCIS 8507	R	R	R	R	0.168, 0.056,0.035	194
DCIS 8522	R	R	R	R	0.064, 0.009, <0.001	666

Table A.2 Distribution fitting for DCIS cases grouped by ICD-O-3 coding with no or unknown surgery or radiation - Max Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
DCIS 8201	>0.150, 0.129, 0.080	>0.500, >0.250, >0.250	>0.250, >0.250	>0.500, >0.250, >0.250	>0.500, >0.500, >0.500	13
DCIS 8230	>0.089, 0.048, 0.025	0.034, 0.049, 0.081	>0.250, >0.250	>0.250, >0.250, 0.220	>0.500, >0.500, >0.500	14
DCIS 8500	R	0.025, 0.041, 0.046	0.076, 0.019	0.043, 0.029, 0.011	>0.500, >0.500, >0.500	115
DCIS 8501	R	>0.250, >0.250, >0.500	>0.250, >0.250	>0.250, >0.250, >0.250	>0.250, >0.250, >0.250	32
DCIS 8503	>0.15, >0.5, >0.5	>0.500, >0.500, >0.500	>0.250, >0.250	NA	NA	5
DCIS 8507	>0.15, 0.221, 0.189	0.228, >0.25, >0.25	>0.250, >0.250	NA	NA	5
DCIS 8522	>0.15, >0.500, 0.431	>0.500, >0.500, >0.500	>0.250, >0.250	NA	NA	6

Table A.3 Distribution fitting for DCIS cases grouped by ICD-O-3 coding with surgery or radiation - Max Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
DCIS 8201	R	R	R	R	0.042, 0.127, 0.009	606
DCIS 8230	R	R	0.029, <0.01	R	0.019, 0.037, 0.014	390
DCIS 8500	R	R	R	R	NA	6165
DCIS 8501	R	R	R	R	>0.5, 0.5, 0.147	1861
DCIS 8503	R	R	>0.250, >0.250	0.089, 0.035, 0.022	>0.25, 0.224, 0.142	613
DCIS 8507	R	R	R	R	0.139, 0.07, 0.041	189
DCIS 8522	R	R	R	R	0.057, 0.009, <0.001	660

Table A.4 Distribution fitting for DCIS grouped by grade codes - Max Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
DCIS Grade 1	R	R	R	R	0.015, 0.015, <0.001	920
DCIS Grade 2	R	R	R	R	R	2356
DCIS Grade 3	R	R	R	R	R	1563
DCIS Grade 4	R	R	R	R	R	975
DCIS Grade 9	R	R	R	R	R	5010

Table A.5 Distribution fitting for DCIS grouped by grade codes with no or unknown surgery or radiation - Max Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
DCIS Grade 1	0.079, 0.019, 0.009	>0.500, >0.500, >0.500	>0.250, 0.235	NA	>0.500, >0.500, >0.500	17
DCIS Grade 2	R	0.014, 0.010, 0.019	>0.250, 0.133	0.219, 0.097, 0.041	>0.500, >0.500, >0.500	49
DCIS Grade 3	R	>0.250, 0.246, >0.250	0.128, 0.087	0.154, 0.125, 0.100	>0.250, >0.500, >0.500	31
DCIS Grade 4	0.113, 0.022, 0.019	>0.500, >0.500, >0.500	>0.250, >0.250	NA	>0.500, >0.500, >0.500	33
DCIS Grade 9	0.101, 0.023, 0.007	0.065, 0.029, 0.022	0.230, >0.250	>0.250, >0.250, >0.250	0.101, >0.250, >0.250	64

Table A.6 Distribution fitting for DCIS grouped by grade codes with surgery or radiation - Max Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
DCIS Grade 1	R	R	R	R	0.015, 0.020, <0.001	903
DCIS Grade 2	R	R	R	R	R	2307
DCIS Grade 3	R	R	R	R	R	1532
DCIS Grade 4	R	R	R	R	R	942
DCIS Grade 9	R	R	R	R	R	4946

Table A.7 Distribution fitting for IBC cases grouped by 6th edition AJCC stage (1988+) coding-Max Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
IBC stage 10	R	R	R	R	R	13535
IBC stage 21	R	R	R	R	R	6162
IBC stage 22	R	R	R	R	R	2808
IBC stage 31	R	R	R	R	0.242, 0.223, 0.134	715
IBC stage 32	R	R	R	NA	R	512
IBC stage 40	R	>0.250, 0.250, 0.158	>0.250, >0.250	NA	0.065, 0.009, 0.003	296
IBC stage 90	R	R	R	R	0.119, 0.034, 0.003	2637

Table A.8 Distribution fitting for IBC cases grouped by 6th edition AJCC stage (1988+) coding with no or unknown surgery or radiation - Max Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
IBC stage 10	>0.150, 0.160, 0.102	R	>0.250, >0.250	>0.500, >0.500, >0.500	>0.500, >0.500, >0.500	29
IBC stage 21	>0.150, 0.462, 0.485	0.047, 0.037, 0.049	>0.250, >0.250	>0.500, >0.500, >0.500	>0.250, >0.250, >0.250	14
IBC stage 22	0.08, 0.051, 0.046	>0.250, 0.226, >0.250	0.016, 0.023	0.112, 0.034, 0.040	0.053, 0.123, 0.161	12
IBC stage 31	>0.150, >0.500, >0.500	>0.500, >0.500, >0.500	>0.250, >0.250	NA	NA	6
IBC stage 32	<0.01, 0.017, 0.011	0.22, >0.500, >0.250	0.207, 0.202	NA	0.189, >0.250, >0.250	17
IBC stage 40	>0.15, 0.127, 0.89	0.195, 0.181, 0.174	>0.250, >0.250	>0.250, >0.250, >0.250	>0.250, >0.250, >0.250	20
IBC stage 90	R	R	>0.021, <0.01	0.056, 0.005, 0.002	>0.500, >0.500, >0.500	122

Table A.9 Distribution fitting for IBC cases grouped by 6th edition AJCC stage (1988+) coding with surgery or radiation - Max Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
IBC stage 10	R	R	R	R	R	13506
IBC stage 21	R	R	R	R	R	6148
IBC stage 22	R	R	R	R	R	2796
IBC stage 31	R	R	R	R	>0.250, 0.244, 0.145	709
IBC stage 32	R	R	R	NA	R	495
IBC stage 40	R	>0.187, 0.142, 0.071	>0.250, >0.250	NA	0.047, 0.004, 0.001	276
IBC stage 90	R	R	R	R	0.082, 0.026, 0.002	2515

Table A.10 Distribution fitting for IBC cases grouped by grade coding- Max Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
IBC Grade 1	R	R	R	R	NA	5772
IBC Grade 2	R	R	R	R	NA	12487
IBC Grade 3	R	R	R	R	R	11071
IBC Grade 4	R	R	R	R	>0.25, >0.25, 0.149	964
IBC Grade 9	R	R	R	R	R	15970

Table A.11 Distribution fitting for IBC cases grouped by grade coding with no or unknown surgery or radiation - Max Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
IBC Grade 1	R	0.111, 0.049, 0.084	0.159, 0.122	0.149, 0.072, 0.070	>0.500, >0.500, >0.500	54
IBC Grade 2	R	>0.500, >0.250, >0.250	>0.250, 0.152	>0.500, >0.250, 0.155	>0.250, >0.250, >0.250	126
IBC Grade 3	R	>0.500, >0.500, >0.500	>0.250, >0.250	0.113, >0.250, >0.250	0.055, 0.127, 0.119	105
IBC Grade 4	>0.150, 0.390, 0.418	0.150, 0.184, 0.236	>0.250, >0.250	NA	NA	9
IBC Grade 9	R	R	>0.250, 0.174	0.168, 0.122, 0.037	0.156, 0.081, 0.055	178

Table A.12 Distribution fitting for IBC cases grouped by grade coding with surgery or radiation - Max Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
IBC Grade 1	R	R	R	R	NA	5718
IBC Grade 2	R	R	R	R	NA	12361
IBC Grade 3	R	R	R	R	R	10966
IBC Grade 4	R	R	R	R	>0.250, >0.250, 0.138	955
IBC Grade 9	R	R	R	R	R	15792

Table A.13 Distribution fitting for DCIS grouped by ICD-O-3 coding- Min Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
DCIS 8201	R	R	R	R	KS:0.063, 0.108,0.006	638
DCIS 8230	R	R	0.022, <0.01	R	KS:0.047, 0.052,0.021	413
DCIS 8500	R	R	R	R	NA	6491
DCIS 8501	R	R	R	R	KS:>0.5, >0.5,0.142	1958
DCIS 8503	R	R	>0.25, >0.25	0.060.0.022,0.015	KS:>0.25, >0.250,0.206	648
DCIS 8507	R	R	R	R	KS:0.168, 0.056,0.035	194
DCIS 8522	R	R	R	R	KS:0.064, 0.009,<0.001	666

Table A.14 Distribution fitting for DCIS cases grouped by ICD-O-3 coding with no or unknown surgery or radiation - Min Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
DCIS 8201	>0.150, 0.129, 0.080	>0.500, >0.250, >0.250	>0.250, >0.250	>0.500, >0.250, >0.250	>0.500, >0.500, >0.500	13
DCIS 8230	>0.15, 0.145, 0.064	0.01, 0.018, 0.031	>0.250, >0.250	>0.50, >0.50, >0.250	>0.500, >0.500, >0.500	13
DCIS 8500	R	0.054, 0.038, 0.037	0.079, 0.017	0.052, 0.037, 0.010	>0.250, >0.250, >0.500	121
DCIS 8501	0.027, <0.005, <0.005	>0.500, >0.250, >0.250	>0.250, >0.250	>0.500, >0.250, >0.250	>0.250, >0.500, >0.250	34
DCIS 8503	>0.15, >0.5, >0.5	>0.500, >0.500, >0.500	>0.250, >0.250	NA	NA	5
DCIS NonComedo	R	R	0.039, <0.010	0.021, 0.009, 0.002	>0.250, >0.250, >0.500	152

Table A.15 Distribution fitting for DCIS cases grouped by ICD-O-3 coding with surgery or radiation - Min Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
DCIS 8201	R	R	R	R	0.063, 0.119, 0.007	625
DCIS 8230	R	R	0.039, <0.01	0.015, 0.004, <0.001	0.035, 0.056, 0.023	400
DCIS 8500	R	R	R	R	NA	6370
DCIS 8501	R	R	R	R	>0.5, >0.5, 0.156	1924
DCIS 8503	R	R	>0.250, >0.250	0.057, 0.021, 0.014	>0.25, >0.250, 0.201	643
DCIS 8507	R	R	R	R	0.139, 0.07, 0.041	189
DCIS 8522	R	R	R	R	0.057, 0.009, <0.001	660

Table A.16 Distribution fitting for DCIS grouped by grade codes - Min Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
DCIS Grade 1	R	R	R	R	0.015, 0.009, <0.001	939
DCIS Grade 2	R	R	R	R	R	2391
DCIS Grade 3	R	R	R	R	R	1589
DCIS Grade 4	R	R	R	R	R	990
DCIS Grade 9	R	R	R	R	R	5136

Table A.17 Distribution fitting for DCIS grouped by grade codes with no or unknown surgery or radiation - Min Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
DCIS Grade 1	0.069, 0.008, <0.005	>0.500, >0.500, >0.500	>0.250, 0.111	NA	>0.500, >0.500, >0.500	19
DCIS Grade 2	R	R	>0.250, 0.134	0.181, 0.115, 0.037	>0.250, >0.250, >0.250	49
DCIS Grade 3	R	0.232, 0.183, 0.208	0.077, 0.045	0.090, 0.082, 0.058	>0.250, >0.250, >0.500	32
DCIS Grade 4	0.136, 0.026, 0.019	>0.500, >0.500, >0.500	>0.250, >0.250	NA	>0.500, >0.500, >0.250	33
DCIS Grade 9	0.101, 0.023, 0.007	0.065, 0.029, 0.022	0.230, >0.250	>0.250, >0.250, >0.250	0.101, >0.250, >0.250	64

Table A.18 Distribution fitting for DCIS grouped by grade codes with surgery or radiation - Min Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**N**
DCIS Grade 1	R	R	R	R	0.013, 0.015, <0.001	920
DCIS Grade 2	R	R	R	R	R	2342
DCIS Grade 3	R	R	R	R	R	1557
DCIS Grade 4	R	R	R	R	R	957
DCIS Grade 9	R	R	R	R	R	5072

Table A.19 Distribution fitting for IBC cases grouped by 6th edition AJCC stage (1988+) coding-Min Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
IBC stage 10	R	R	R	R	R	17336
IBC stage 32	R	R	R	R	R	7317
IBC stage 33	R	R	R	R	0.014, 0.004, <0.001	2743
IBC stage 51	R	R	0.053, 0.060	NA	0.044, 0.024, 0.022	174
IBC stage 52	R	R	R	R	>0.250, >0.250, 0.130	1826
IBC stage 53	R	0.017, 0.042, 0.045	0.040, 0.028	NA	R	469
IBC stage 54	R	0.024, 0.018, 0.007	0.073, 0.018	NA	R	934
IBC stage 70	R	0.021, 0.023, 0.013	>0.250, 0.238	NA	R	412
IBC stage 88	>0.150, 0.229, 0.117	>0.500, >0.500, >0.500	>0.250, >0.250	>0.500, >0.500, >0.500	0.113, 0.210, >0.250	37
IBC stage 99	R	R	R	R	0.008, 0.236, 0.018	3035

Table A.20 Distribution fitting for IBC cases grouped by 6th edition AJCC stage (1988+) coding with no or unknown surgery or radiation - Min Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
IBC stage 10	R	R	0.036, 0.019	R	0.108, 0.147, 0.169	50
IBC stage 32 ‘	R	R	0.179, 0.141	0.085, 0.034, 0.025	0.181, 0.024, 0.016	36
IBC stage 33	R	0.085, 0.171, 0.206	0.074, 0.048	0.078, 0.079, 0.061	>0.500, >0.500, >0.500	28
IBC stage 51	R	0.132, 0.141, 0.187	0.042, 0.024	NA	NA	9
IBC stage 52	>0.150, >0.500, >0.500	>0.250, >0.500, >0.500	>0.250, >0.250	>0.500, >0.500, >0.500	0.131, 0.065, 0.077	11
IBC stage 53	0.106, 0.012, <0.005	>0.500, >0.500, >0.500	>0.250, >0.250	>0.500, >0.500, >0.250	>0.250, 0.222, 0.194	26
IBC stage 54	>0.150, 0.267, 0.203	>0.250, >0.500, >0.500	0.247, 0.239	NA	NA	6
IBC stage 70	0.101, 0.018, <0.005	>0.250, >0.500, >0.500	>0.250, >0.250	0.125, >0.250, >0.250	0.038, 0.061, 0.040	73
IBC stage 88	R	R	R	R	R	1
IBC stage 99	R	0.018, 0.003, 0.002	0.090, 0.025	0.092, 0.081, 0.018	0.165, 0.105, 0.145	226

Table A.21 Distribution fitting for IBC cases grouped by 6th edition AJCC stage (1988+) coding with surgery or radiation - Min Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
IBC stage 10	R	R	R	R	R	17286
IBC stage 32	R	R	R	R	R	7281
IBC stage 33	R	R	R	R	R	2715
IBC stage 51	R	R	0.017, 0.021	NA	0.042, 0.040, 0.033	165
IBC stage 52	R	R	R	R	>0.250, >0.500, 0.149	1815
IBC stage 53	R	0.007, 0.027, 0.033	0.020, 0.017	NA	R	443
IBC stage 54	R	0.024, 0.016, 0.006	0.063, 0.015	NA	R	928
IBC stage 70	R	0.033, 0.019, 0.008	>0.250, >0.250	NA	R	339
IBC stage 88	>0.150, 0.151, 0.075	>0.500, >0.500, >0.500	>0.250, >0.250	>0.500, >0.500, >0.500	0.125, 0.247, >0.250	36
IBC stage 99	R	R	R	R	0.023, 0.197, 0.010	2809

Table A.22 Distribution fitting for IBC cases grouped by grade coding- Min Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
IBC Grade 1	R	R	R	R	NA	5818
IBC Grade 2	R	R	R	R	NA	12599
IBC Grade 3	R	R	R	R	R	11131
IBC Grade 4	R	R	R	R	>0.25, >0.25, 0.128	968
IBC Grade 9	R	R	R	R	R	16012

Table A.23 Distribution fitting for IBC cases grouped by grade coding with no or unknown surgery or radiation - Min Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
IBC Grade 1	R	0.082, 0.038, 0.066	0.128, 0.088	0.124, 0.048, 0.046	>0.500, >0.500, >0.500	53
IBC Grade 2	R	>0.250, >0.250, >0.250	>0.250, 0.101	>0.500, 0.249, 0.115	>0.500, >0.500, >0.500	126
IBC Grade 3	R	>0.500, >0.500, >0.500	>0.250, >0.250	0.113, >0.250, >0.250	0.055, 0.127, 0.119	105
IBC Grade 4	>0.150, 0.390, 0.418	0.150, 0.184, 0.236	>0.250, >0.250	NA	NA	9
IBC Grade 9	R	R	>0.250, 0.188	0.153, 0.125, 0.040	0.153, 0.080, 0.054	176

Table A.24 Distribution fitting for IBC cases grouped by grade coding with surgery or radiation - Min Max approach

Subgroup	**Lognormal** (KS, CM, AD)	**Exponential** (KS, CM, AD)	**Weibull** (CM, AD)	**Gamma** (KS, CM, AD)	**Beta** (KS, CM, AD)	**Size**
IBC Grade 1	R	R	R	R	NA	5765
IBC Grade 2	R	R	R	R	NA	12473
IBC Grade 3	R	R	R	R	R	11026
IBC Grade 4	R	R	R	R	>0.250, 0.231, 0.115	959
IBC Grade 9	R	R	R	R	R	15836

APPENDIX

B

SEER DATA DICTIONARY

ICD-O-3 Histology Codes for DCIS

The codes corresponding to each of the histology type and their descriptions are as below (acquired from International Agency for Research on Cancer website [129]):

8201: cribriform carcinoma in situ.

8230: solid type, ductal carcinoma in situ.

8500: not otherwise specified (NOS), ductal carcinoma in situ, a neoplastic proliferation of epithelial cells confined to the mammary ductal-lobular system and characterized by subtle to marked cytological atypia and an inherent but not necessarily obligate tendency for progression to invasive breast cancer.

8501: comedocarcinoma, noninfiltrating, a ductal carcinoma in situ characterized by the presence of neoplastic cells with severe dysplasia and the formation of micropapillary, cribriform, or solid patterns. The nuclei show marked pleomorphism and have prominent nucleoli. Mitotic activity is usually present. There is comedo-type of necrosis present in the ducts. The necrotic debris is surrounded by pleomorphic malignant cells.

8503: noninfiltrating intraductal papillary adenocarcinoma, intraductal papillary carcinoma is a malignant non-invasive neoplastic epithelial proliferation with papillary architectural features occurring in the lumen of the ductal-lobular system.

8507: intraductal micropapillary carcinoma, an intraductal papillary carcinoma in which the neoplastic epithelial cells are arranged in micropapillary patterns.

8522: intraductal carcinoma and lobular carcinoma in situ, the co-existence of ductal and lobular carcinoma in situ in the breast, without evidence of stromal invasion.

Adjusted AJCC 6th Stage (1988+) Codes[82]

10: I

21: IEB

22: IE

32: IIA

33: IIB

40: IIS

51: III NOS

52: IIIA

53: IIIB

54: IIIC

70: IV

88: not applicable (N/A), not an AJCC category but designates the histologies that AJCC does not stage e.g. sarcomas are excluded.

99: Unknown Stage, cases that do not have enough information to be staged.

Grade Codes [130]

In our data analysis, we called grade 1 and grade 2 low grade and intermediate grade and we grouped grade 3 and grade 4 as high grade: **1:** Grade I, grade i, grade 1, well differentiated, differentiated NOS.

2: Grade II, grade ii, grade 2, moderately differentiated, moderately differentiated, intermediate differentiation.

3: Grade III, grade iii, grade 3, poorly differentiated, differentiated.

4: Grade IV, grade iv, grade 4, undifferentiated, anaplastic.

9: Cell type not determined, not stated or not applicable.

Behavior Codes ICD-O-3 (1973+)[131]

2: Carcinoma in situ, intra-epithelial, non-infiltrating, noninvasive.

3: Malignant, primary site (invasive), infiltrating.

Estrogen/Progesterone Status Codes [130]

1: Positive

2: Negative

3: Borderline

4: Unknown

9: Not 1990+ breast cancer.

HER2 Status Codes [131]

1: Positive

2: Negative

3: Borderline

4: Unknown

9: Not 2010+ breast cancer

Surgery Codes[132][133]

We used the SEER surgery codes (RX Summ–Surg Prim Site) for years 1998 onwards (some of the categories were aggregated in one group) and SEER surgery codes (RX SummâĂŤ-Surgery Type) for years 1973-1997. The codes are included in parentheses if a specific code

is representing more than one category in original SEER data dictionary:

00: None, no surgery of primary site, autopsy only.

19: Local tumor destruction NOS.

20 (20,21,23,24): Partial mastectomy, less than total mastectomy.

22: Lumpectomy or excisional biopsy.

30: Subcutaneous mastectomy/Nipple-sparing mastectomy.

40 (40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 75): Total (simple) mastectomy.

50 (50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 63): Modified radical mastectomy.

60 (60, 61, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74): Radical mastectomy.

76: Bilateral mastectomy for a single tumor involving both breasts, as for bilateral inflammatory carcinoma.

80: Mastectomy NOS.

90: Surgery NOS.

99: Unknown if surgery performed, death certificate only.

Radiation Codes [131]

0: None, diagnosed at autopsy.

1: Beam radiation.

2: Radioactive implants.

3: Radioisotopes.

4: Combination of 1 with 2 or 3.

5: Radiation, NOS - method or source not specified.

6: Other radiation (1973-1987 cases only).

7: Patient or patient

s guardian refused radiation therapy

8: Radiation recommended, unknown if administered.

9: Unknown if radiation administered.

Tumor Size[132][134]

There are two sets of codes for tumor size in SEER data base: extent of disease (EOD) TUMOR SIZE (available for cases diagnose in 1988-2003) and Collaborative Stage (CS) TUMOR SIZE (available for cases diagnosed in 2004 onwards). We used CS coding and combined the tumor size for EOD and CS to have tumor size for cases diagnosed in 1988 onwards. The codes in parentheses indicates the EOD and CS code that the code category includes in case there is a difference in coding between the two.

000: Indicates no mass or no tumor found.

888: Not applicable.

001-988: Exact size in millimeters.

989: 989 millimeters or larger.

990 (EOD size=001 or CS size=990): Microscopic focus or foci only, no size of focus is given.

991 (EOD size= 009 or CS size=991): Described as less than 1 cm.

992 (EOD size= 019 or CS size=992): Described as less than 2 cm.

993: Described as less than 3 cm.

994: Described as less than 4 cm.

995: Described as less than 5 cm.

996 (EOD size= 002 or CS size=996): Mammographic/xerographic diagnosis only, no size

given, clinically not palpable.

997: Paget's Disease of nipple with no demonstrable tumor.

998: Diffused tumor.

999: Unknown, size not stated, not stated in patient record.

1000: Missing (" in the original database).

Ethnicity Code [131]

0: Non-Spanish-Hispanic-Latino.

1: Spanish-Hispanic-Latino.

APPENDIX

C

SIMULATION INPUTS

Table C.1 QALY multiplier for breast cancer states and their source

State	Multiplier	Lidgren et al. 2007[123] Values
In Situ 1st Year	0.9	First year after primary breast cancer (Receiving adjuvant hormone therapy)
In Situ Later Years	1	Second and following years after primary breast cancer/recurrence (Receiving adjuvant hormone therapy)
In Situ Recurrence	0.99	First year after recurrence (Receiving adjuvant hormone therapy)
Local 1st Year	0.85	First year after primary breast cancer (Mean for all)
Local Later Years	0.98	Second and following years after primary breast cancer/recurrence (Mean for all)
Local Recurrence	0.95	First year after recurrence (Mean for all)
Regional/Unknown 1st Year	0.75	First year after primary breast cancer (Receiving adjuvant chemotherapy)
Regional/Unknown Later Years	0.95	Second and following years after primary breast cancer/recurrence (Mean for all)
Regional/Unknown Recurrence	0.93	First year after recurrence (Receiving adjuvant chemotherapy)
Distant 1st Year	0.75	First year after primary breast cancer (Receiving adjuvant chemotherapy)
Distant Later Years	0.83	Distant breast cancer (Mean for all)
Distant Recurrence	0.75	First year after primary breast cancer (Receiving adjuvant chemotherapy)