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A FRAMEWORK FOR MODELING THE COMPLEX INTERACTION BETWEEN BREAST CANCER AND DIABETES

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ABSTRACT

In 2010, over 200,000 women in the U.S. were diagnosed with invasive breast cancer, and an estimated 17% of those women died from the disease, according to the Centers for Disease Control and Prevention (CDC). Also in 2010, the CDC reported that 12.6 million women had diabetes, the seventh leading cause of death in the U.S. Recent medical literature provides conflicting evidence regarding a link between insulin resistance and breast cancer risk. Although models have characterized these prevalent diseases individually, little research has been conducted regarding the interaction between breast cancer and diabetes. We build a simulation model framework that explores this complex relationship, with an initial goal of assessing the prognosis for women diagnosed with diabetes considering their breast cancer risk. Using data from national survey and surveillance consortium studies, we estimate morbidity and mortality. This framework could be extended to study other diseases that interact with breast cancer.

1 MOTIVATION

The lifetime risk of developing diabetes for a woman born in 2000 is 2 in 5 (Narayan et al. 2003), while 1 in 8 women will develop breast cancer in their lifetime (Howlader 2010). Some women must manage both diseases. Recent evidence suggests that there may be a link between diabetes and the risk of developing breast cancer (Hardelfeldt et al. 2012). However, to the best of our knowledge, no work has been done to understand the impact that diabetes and its care may have on breast cancer incidence at the population level, and no recommendations exist about how to tailor diabetes treatment for women given their future breast cancer risk. We believe that a systematic approach that creates an integrated model for the progression of both diseases and associated comorbidities can be used to inform and ultimately improve treatment.

Almost 26 million adults and children have diabetes in the U.S., and the direct and indirect costs of the disease are estimated at $245 billion/year, according to the American Diabetes Association (ADA 2014). It is estimated that, by the year 2020, diabetes mellitus and pre-diabetes could impact 53% of adult women (up from 43% in 2007-2008) (Huffman et al. 2012). The impact on women's lives is significant, as diabetes is associated with several micro- and macro-vascular complications, including renal disease, cardiovascular disease and stroke.

Breast cancer is one of the leading causes of cancer-related death among U.S. women (USCS 2013). A Surveillance, Epidemiology and End Results (SEER) study estimated that approximately 232,000 U.S. women will be diagnosed with breast cancer in 2013 and over 39,000 will die of the disease (Howlader et al. 2010). Furthermore, breast cancer is associated with the psychological impact and trauma of long-term screening and treatment. Treatment can result in complications and side-effects, such as lymphedema (Shah 2011), and increased risk of other cancers due to metastasis (Van Leeuwen et al. 1994). The projected costs associated with breast cancer in the U.S. for 2012 were $17.35 billion (Liebman 2012).

1.1 Impact of diabetes on breast cancer

Diabetes mellitus and breast cancer both negatively impact quality of life. A meta-analysis by Hardefeldt et al. (2012) on 40 previous studies investigating the link between diabetes and breast cancer found that the odds ratio for breast cancer in women with type 2 diabetes is 1.22. All but one of the studies reached one of two conclusions: either diabetes medication had no association with breast cancer risk, or diabetes medication increased breast cancer risk. Chlebowski et al. (2012) found that women taking metformin had lower breast cancer incidence (HR = 0.75), whereas women on other diabetes medications had a slightly higher incidence of breast cancer (HR = 1.16). Hsieh et al. (2012), Jordan et al. (2009), and Khachatryan et al. (2011) reported that patients with type 2 diabetes, specifically, had significant increases in breast cancer risk with odds ratios of 1.11, 8.4, and 5.53, respectively. However, Cleveland et al. (2012) and 24 (of 40) other studies in the Hardefeldt et al. (2012) meta-analysis reported the relationship between diabetes and breast cancer risk was not statistically significant. The clearly contradictory results of this meta-analysis suggest that further study of the complex interaction between these two diseases and the medications used to treat diabetes is necessary.

Individually, diabetes mellitus and breast cancer are complicated diseases that have different effects on people of different ages, races, and socio-economic status. Figure 1 describes clinical, socio-demographic, and lifestyle risk factors that have been associated with diabetes and breast cancer incidence. Some risk factors including age, smoking, race, and body mass index (BMI) increase the risk for both diseases, while others are thought to impact only one of the two. Diabetes and other clinical factors can impact the type of medication an individual is prescribed. While insulin may control diabetes and thereby reduce the risk of associated comorbidities and complications, it can also have unintended consequences. For example, insulin has been linked to an increased breast cancer mortality (Currie et al. 2012). There is evidence to suggest that obesity increases insulin resistance, which accelerates the onset and complicates the prognosis of diabetes (Orgel and Mittelman 2013). Obesity, represented in the figure by BMI, will remain a consistent problem in the U.S. population with a projected 86.3% of adults being overweight or obese by 2030 (Wang et al. 2008). Increased insulin resistance results in higher doses of insulin, which in turn increases the risk of developing breast cancer. Clinical decision making will continue to remain a challenge until we can fully capture the potential links between these two diseases and the role of these risk factors.

2 RELEVANT LITERATURE

In the discussion below, we present a brief review of the common disease models for each disease, as well as a summary of the medical evidence related to their interaction.

2.1 Diabetes Models

Natural history models provide a foundation for understanding disease prognosis with the goal of improving treatment decision making. Zhou et al. (2005) used data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy to simulate a semi-Markov model of the natural history of diabetes progression. The Michigan model (based on (Zhou et al. 2005)), has evolved to become an interactive simulation model that follows diabetes progression over time (Barhak et al. 2010, Ye et al. 2012). Palmer et al. (2004) developed the CORE Monte Carlo simulation model, which tracks the outcomes of cohort-based populations with type 1 and type 2 diabetes. The authors use Markov models to simulate an extensive number of diabetes-related complications, including those that are not typically considered in other models, such as ketoacidosis and lactic acidosis. The Cardiff model (McEwan et al. 2010) uses simulation modeling to evaluate the cost utility of newer second-line therapies, such as sulfonylurea, on patients with type 2 diabetes.

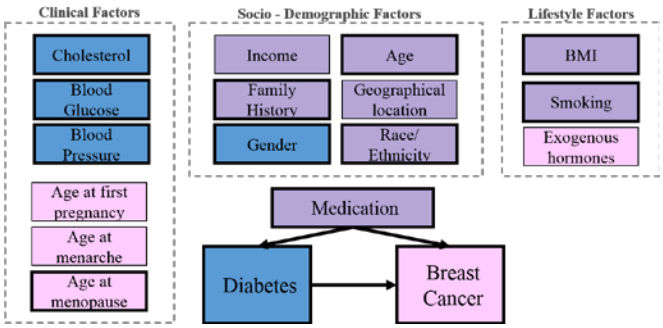

Figure 1: Conceptual Framework: Factors that contribute to increased risk of diabetes and breast cancer. Factors in blue (dark gray) only impact diabetes; factors in pink (light gray) only impact breast cancer; factors in purple (gray) impact both diabetes and breast cancer. Bold outlines indicate those factors that we consider in our model. Family history is a common factor for both diseases, but has been used only in the breast cancer portion of our model.

Some studies have also looked at the optimization of treatment regimens for diabetes patients. Denton et al. (2009) developed a Markov model to determine the optimal start time for statin therapy, while Mason et al. (2014) also used a Markov model to look at managing medication for blood pressure and cholesterol, two factors that can increase the risk for diabetes-related events. Zhang et al. (2014) investigated options for second-line glycemic control therapies, given that a patient is using metformin as a first-line therapy.

The United Kingdom Prospective Diabetes Study (UKPDS) was a randomized controlled trial conducted between 1977 and 1997 that consisted of over 5000 newly-diagnosed patients with type 2 diabetes. The study was designed to determine the impact of different blood glucose-lowering therapies on diabetes complications. It has since resulted in the creation of several models that attempt to capture the progression and management of the disease and its complications. Clarke et al. (2004) developed the UKPDS outcomes model, a simulation model that uses ten risk equations to track the incidence of diabetes complications and related mortality. The equations forecast the following events: ischemic heart disease, myocardial infarction, congestive heart failure, stroke, amputation, blindness, and renal failure. The CDC/RTI model (Herman et al. 2005) used the UKPDS equations in their Markov model to determine the cost-effectiveness of lifestyle modification and metformin interventions. More recently, Hayes et al. (2013) developed the UKPDS Outcomes Model 2 (OM2) to include the 10-year follow up of the 4031 surviving participants in a non-clinical setting. UKPDS OM2 incorporates risks for an additional complication, ulcers; the model equations also estimate the risk of secondary stroke, myocardial infarction and amputation events. Because these equations also use additional clinical and historical

predictors, such as estimated glomerular filtration rate and presence of micro- and macro-albuminuria, they are thought to represent the risks of diabetes-related complications more accurately than the outcomes model developed by Clarke et al. (2004).

2.2 Breast Cancer Models

Natural history models for breast cancer have been developed to aid in the selection of better treatment and screening policies. There have been several analytic models developed for assessing screening policies. Kirch and Klein (1974) used mathematical modeling, Shwartz (1978) used a Markov model, and later, Baker (1998) developed a continuous-time non-Markov model. Maillart et al. (2008) developed a partially observable Markov process model to evaluate various dynamic screening policies.

Although these analytic models provide insights about breast cancer progression and effective screening policies, the simplifying assumptions necessitated by the model structures limit their ability to capture the complex dynamics of the disease behavior. By using simulation, it is possible to more accurately model disease progression and complex interactions between the diseases under various interventions. Simulation can be used to study disease progression for each individual, while allowing for observation of a group as a whole as different system-wide and individual policies are applied.

De Koning et al. (1995) extended the MIcrosimulation Screening Analysis (MISCAN) computer simulation package (first developed for all diseases by Habbema et al. (1985); later developed for breast cancer by Van Oortmarssen et al. (1990)) to evaluate five 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. Michaelson et al. (1999) developed a Monte Carlo-based simulation that uses a Poisson distribution to estimate the number of cell metastasis based on tumor size.

Another important series of models were developed by the Cancer Intervention and Surveillance Modeling Network (CISNET) program to evaluate the impact of screening policies for breast cancer. The CISNET program, comprised of seven models (six of which are simulation models), evaluates the impact of adjuvant therapy and screening policies on the U.S. population from 1975-2000 under different scenarios (Clarke et al. 2006). The Wisconsin model by Fryback et al. (2006) uses discrete event simulation (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. (2006) used the MISCAN-Fadia model to predict and compare 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. Tejada et al. (2013a, 2013b) developed a combined DES and system dynamics (SD) simulation model for breast cancer screening for older women, ages 65 to 80.

3 INTEGRATED SIMULATION MODEL

We chose to use a DES framework for several reasons. First, in the medical setting patients are typically observed at discrete points in time. Furthermore, the integrated simulation model is based on the DES portion of the Tejada et al. (2013a, 2013b) model as explained below. As a result, we annualized the UKPDS OM2 equations to fit within our DES framework.

Breast cancer progression. The breast cancer natural history model developed by Tejada et al.(2013a, 2013b) was used with some modifications as the basis for our combined simulation model. The diabetes model, described next, was then overlaid on the breast cancer progression model. The integrated model uses the cancer incidence, disease progression, and survival and mortality from breast cancer from Tejada et al. Each year, the breast cancer incidence probability is determined for each woman. A woman may either develop invasive breast cancer, in which case a lethal breast cancer age is determined, or she may develop non-invasive Ductal Carcinoma In-situ (DCIS).

Individual attributes. We modified the DES part of the Tejada et al. (2013a, 2013b) model to accommodate women of all ages between 35 and 84. Data from the Breast Cancer Surveillance

Consortium (Barlow et al. 2006) was used to simulate individual women of ages 35 to 84 with different attributes. Premenopausal and postmenopausal regression risk models from Barlow et al. (2006) were used to estimate probability of breast cancer diagnosis for each woman, every year. Statistically significant risk factors for breast cancer diagnosis among premenopausal women include age, breast density, family history of breast cancer, and history of a prior breast procedure. For postmenopausal women, the statistically significant factors include age, breast density, race, ethnicity, family history of breast cancer, history of a prior breast procedure, BMI, menopause, hormone therapy, and a prior false-positive mammogram. Since the Tejada et al. model only included postmenopausal women over age 65, we updated the model to reflect variations in age at menopause by race. The subset of women from the BCSC data set who were premenopausal were assigned a menopausal age according to an empirical distribution, based on Henderson et al. (2008), as shown in Table 1, assuming that all women will reach menopause naturally. After assigning each woman to one of the four age groups for menopausal age, the exact age at menopause within the selected age group was assigned uniformly.

Table 1: Percentage of menopause for each age group based on race, based on Henderson et al. (2008).

RACE	**AGE AT NATURAL MENOPAUSE**			
	40-44	**45-49**	**50-54**	**>=55**
White, Non-Latina	15.03 %	34.68 %	40.46 %	9.83 %
African-American	20.58 %	31.86 %	36.06 %	11.50 %

Diabetes-related events. The UKPDS OM2 served as the basis for the development of our diabetes sub-models. We incorporated all first-instance diabetes-related events modeled by Hayes et al. (2013) into our framework, including myocardial infarction (MI), stroke (ST), renal failure (RF), blindness (BL), ulcer (UL), amputation (AMP), congestive heart failure (CHF), and ischemic heart disease (IHD). Only a few diabetes-related demographic and clinical attributes (current age, race, and BMI) could be obtained from the available BCSC clinical data. The distributions for the remaining clinical attributes were obtained from the National Health and Nutrition Examination Survey (NHANES) data sets, continuous cycles 2009-2010 and 2011-2012 (Huffman et al. 2012), as well as from the diabetes literature. We determined race-based prevalence estimates on a subset of 202 women between the ages of 35 and 80 who were diagnosed with diabetes as adults in NHANES. The complete list of attributes in the combined model are listed in Figure 2. In this model, we assume all entities are women who have been diagnosed with diabetes.

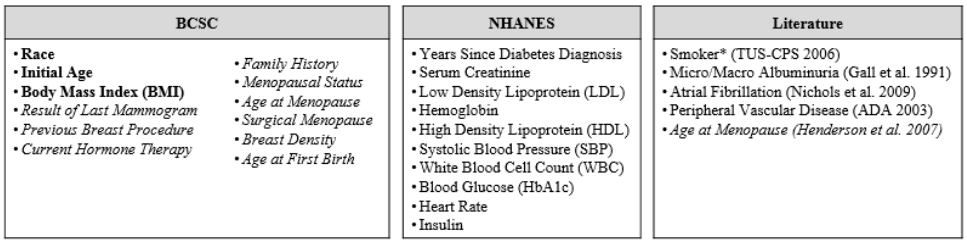

Figure 2: Data Sources for person-level attributes. Inputs used in both sub-models are bolded. Inputs used only in the breast cancer sub-model are italicized. Inputs used only in the diabetes sub-model are in regular text. Regression was applied to inputs with (*).

As a woman moves through the model, her risks for each of the diabetes-related complications and for breast cancer are calculated and tracked. These risks, calculated annually, are then used to determine which complication(s), if any, an individual will experience during the upcoming year. Event history is

also updated and tracked for each woman as events occur. Tables showing the distributions used to calculate risk for each diabetes-related event can be found in Hayes et al. (2013).

Mortality. A woman's death will be attributed to one of three causes: diabetes-related complications, breast cancer, or other-cause. Death from breast cancer is determined by the tumor reaching lethal size as mentioned above. Diabetes-related deaths depend on her diabetes-related event history, and are based on death equations from Hayes et al. (2013). These equations calculate the risk of death in the current year for women with the following (mutually exclusive) characteristics: event this year but no previous event history, no event this year but previous event history, or both - an event this year and previous event history. Lastly, if a woman does not die from diabetes-related complications then she may die of other causes. In this model, to determine other-cause mortality, we use one of the UKPDS equations (D1) (Hayes et al. (2013)) to calculate the annual probability of death for a diabetes patient with no diabetes-related event history. If a woman dies in a given year, then she moves into a sub-model where cause of death is evaluated, statistics are recorded and then leaves the system. If a woman does not die in a given year, her age is incremented by one year, her HbA1c level is updated as described next, and then she moves back to the risk assignment sub-model to begin her next cycle through the model.

Diabetes progression and medication. Each woman's HbA1c level is evaluated on an annual basis, and a decision is made about the diabetes medications she should be prescribed. At the end of each annual cycle, the HbA1c attribute is increased by 0.2% as used in other models (CDC 2002). Two different interventions are modeled, each following a different American Association of Clinical Endocrinologists (AACE) guideline-based medication policy, driven by the HbA1c (Garber et al. 2013). In the first intervention, women with an HbA1c > 9% are started on insulin which we assume immediately decreases their HbA1c to 6.5%, and they remain on insulin for the remainder of their time in the simulation. In the second intervention, metformin is prescribed once an individual's HbA1c level exceeds 6.5%, and treatment commencement drops the HbA1c level by a percentage according to a triangular distribution as shown in Table 2 (Hirst et al. 2012). If the HbA1c level exceeds 7.5% at entry, a second-line therapy is initiated, and the woman is dually treated with both metformin and insulin, resulting in a drop of her HbA1c level to 6.5%. Once a woman is on insulin, it is assumed that HbA1c remains constant at 6.5%, otherwise HbA1c increases annually by 0.2%. The two interventions are summarized in Table 2 below. Figure 3 presents a high-level overview of entity flow through the model.

Table 2: Intervention by medication and HbA1c level per the AACE guidelines (Garber et al. 2013).

INTERVENTION – INSULIN ONLY		
HbA1c level	**Intervention**	**Impact of intervention on HbA1c level**
> 9%	Insulin	Drops to 6.5%
≤ 9%	None	Increases by 0.2%
INTERVENTION – METFORMIN AND INSULIN		
HbA1c level	**Intervention**	**Impact of intervention on HbA1c level**
≥ 7.5%	Metformin + Insulin	Drops to 6.5%
> 6.5% and < 7.5%	Metformin	Drops by Tri(0.92%, 1.12%, 1.32%)
≤ 6.5%	None	Increases by 0.2%

Diabetes and breast cancer. The interaction between breast cancer and diabetes is incorporated into our model primarily through changes in breast cancer annual incidence risk due to treatment regimens. We assume metformin has a protective effect, resulting in an annual 25% decrease in risk of developing localized breast cancer (Chlebowski et al. 2012). Insulin increases the annual incidence risk by 13%, while dual treatment (both metformin and insulin) results in an overall annual relative increase in incidence risk by 7.8% (Currie et al. 2012).

Arena is run with a population of 20,582 women (ages 35 to 84), as suggested in Tejada et al. (2013a). The model is run for 10 replications of 20 years each, per scenario. We design the sampling to be racially representative of our target population, women with diabetes. Carter et al. (1996) found that

diabetes is 1.4-2.2 times more prevalent in African-American men and women than in white men and women. For our study, we consider a population consisting of 66.67% African-American women and 33.33% white women. We investigate the following scenarios in our model, using the two different interventions (Table 2) and the two different effects, resulting in four combinations.

S1. Diabetes and medications have no effect on breast cancer, intervention "Insulin Only"
S2. Diabetes and medications have no effect on breast cancer, intervention "Metformin and Insulin"
S3. Only diabetes medication has an effect on breast cancer, intervention "Insulin Only"
S4. Only diabetes medication has an effect on breast cancer, intervention "Metformin and Insulin"

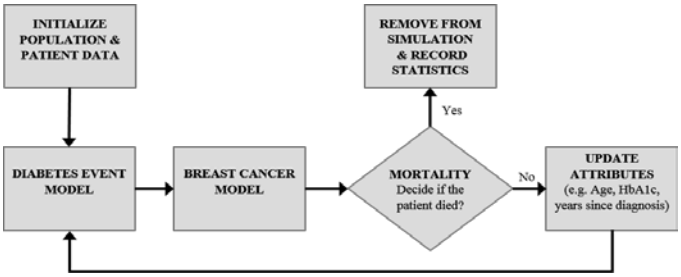

Figure 3: High-level outline of model flow.

4 RESULTS

The mortality-related results are shown in Table 3. For scenarios S1-S4, we track the number of cancer-related, diabetes-related and other-cause deaths, as well as the number of diabetes events. General trends indicate that diabetes poses the greatest risk for mortality among the three causes of death, with diabetes-related deaths occurring in almost ten times the number of women as breast cancer. Interestingly, the lifespans associated with the two diseases are similar. For example, in S4, the average lifespan of women dying from breast cancer is 65.64 (CI ±0.28) years, compared with diabetes-related deaths, where the average lifespan is 65.13 (CI ±0.09) years. On average, women tend to die from other-cause death later than from either disease, at 75.49 (CI ±0.16) years. In terms of the frequency of diabetes events, RF and MI contribute most heavily to diabetes-related deaths with 51.7% and 19.0% of the total events, respectively. These trends are similar across all scenarios. In S4, 3.17% of survivors have cancer at the end of the simulation. As expected, scenario S3 resulted in the maximum number of cancers present at the time of a diabetes-related death. Race also contributes to differences in the frequency of diabetes-related events, as shown in Table 4.

4.1 Impact of race

Under S4, 3.3% of all African-American women versus 3.5% of all white women die from breast cancer death. Rather counterintuitively, 30.1% of all African-American women, as compared with 35.8% of all white women, die from a diabetes-related event. This can perhaps be explained by the fact that white women experience, on average, a higher number of events per person (0.58) than African-American women do (0.52) (Table 4). MI contributes to over 35.7% of the total number of events experienced by white women, compared to MI accounting for 9.6% of the total events experienced by African American women. Once again, these trends are consistent across scenarios.

4.2 Impact of increased breast cancer risk

When observing the impact of increased risk in the insulin-only intervention, it appears that diabetes and breast cancer are competing mortality risks. Breast cancer deaths across both races in the risk (S3) and no risk (S1) scenarios are as expected (812 versus 749, respectively; see Table 3). Diabetes-related events result in slightly fewer deaths (6,646) when breast cancer risk is considered, compared to diabetes-related

deaths (6,664) when breast cancer risk is not considered. Studying the numbers of total deaths, other-cause deaths, and survivors from the two diseases, we see that they are comparable under both types of risk assumptions. Therefore, in the insulin-only intervention, when the number of deaths from one disease decreases, the number of deaths in the other increases, indicating competing risks.

Under S4, the reduction in risk associated with metformin has a larger impact than dual therapy does, resulting in a fewer cancer deaths. This is consistent with the fact that metformin is the preferred first-line therapy as compared with insulin, which is only used at entry when HbA1c levels cannot be controlled by metformin alone.

Table 3: Distribution of Outcomes by Scenario

Scenario	Breast Cancer Death	Half-width	Diabetes Death	Half-width	Other-cause Death	Half-width	Survivors	Half-width	Total
S1 Insulin only, No risk									
White	242	11.3	2473	27.0	1185	23.9	2937	14.2	6837
AA	507	14.2	4191	31.5	2370	44.4	6677	34.2	13745
Total	749	19.6	6664	38.4	3555	39.1	9614	39.7	**20582**
S2 Insulin + metformin, No risk									
White	238	11.1	2441	26.2	1192	15.6	2994	32.1	6865
AA	508	23.2	4128	52.8	2369	30.9	6712	50.6	13717
Total	746	27.0	6569	56.8	3561	35.0	9706	44.5	**20582**
S3 Insulin only, Risk									
White	260	11.8	2468	20.7	1187	18.8	2933	26.5	6848
AA	552	13.7	4178	29.8	2365	24.9	6639	46.0	13734
Total	812	16.9	6646	40.0	3552	32.4	9572	51.2	**20582**
S4 Insulin + metformin, Risk									
White	237	6.1	2451	38.1	1193	23.7	2970	31.4	6851
AA	458	18.4	4134	33.0	2394	35.8	6745	47.2	13731
Total	695	18.8	6585	49.3	3587	43.7	9715	36.5	**20582**

Table 4**:** Number of Diabetes Events in S4

Category	Myocardial Infarction	Ischemic Heart Disease	Coronary Heart Failure	Stroke	Renal Failure	Blindness	Ulcer	Amputation	Total
White	1424	355	295	180	1485	52	22	178	**3991**
Half-width	35.9	10.8	10.4	9.7	31.3	5.5	2.9	8.1	--
AA	678	583	719	407	4236	94	46	316	**7079**
Half-width	19.8	22.0	10.7	17.0	32.2	7.4	4.5	13.7	--
Total	2102	938	1014	587	5721	146	68	494	**11070**
Half-width	33.0	28.1	14.2	22.8	40.9	7.9	4.6	19.6	--

4.3 Impact of intervention type

As expected, the number of diabetes-related events decreases with the metformin and insulin interventions, resulting in an increase in the number of survivors. While the medication does not have an impact on the breast cancer risk by design in scenario S1, the medication regimen S2, including both metformin and insulin, initiates treatment earlier and leads to fewer diabetes-related deaths (Table 3). Comparing scenarios with an increased risk of breast cancer, S3 and S4, we notice that the protective impact of metformin comes into play and both diabetes and breast cancer deaths reduce in S4.

5 DISCUSSION & CONCLUSION

Our model represents the first effort to create an integrated model for breast cancer and diabetes, which will ultimately serve as a test-bed for studying the complex interactions in comorbid diseases. Currently

diabetes treatment guidelines are the same for all women, regardless of their breast cancer risk. This may not be optimal. Our model has the potential to improve care decision-making for women with diabetes.

As an initial effort, we realize this model has limitations, some of which are discussed here. Due to data limitations, we had to create empirical distributions according to NHANES data and overlay it on BCSC to fill in the missing values for diabetes status and other attributes needed for the diabetes model that are not included in the BCSC dataset. Patient attributes like BMI and HDL change for each woman throughout her lifetime. In this paper we assume that values for all attributes (except for HbA1c) are static, as assigned in the beginning of the model. The increased or decreased risk of breast cancer based on these drugs is derived from multiple papers. In our scenarios, we assumed diabetes patients are either using insulin or insulin and metformin. We did not run the model with other glycemic control regimes or in the absence of any of these drugs. Further study should be done in order to see how patient's status changes when other treatment plans are used or she is not using any drugs to control her diabetes, and the risk associated with diabetes and medications should be examined in more detail. More research needs to be done to explore ways of attributing mortality to cause of death because the available sources are not ideal for comparing more than one disease. In the future, we would like to explore alternative models for diabetes (particularly those that are based on samples from the US population) and compare the results with the current model.

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