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Indirect Costs Associated with Human Epidermal Growth Factor Receptor Positive
(HER2+) Metastatic Breast Cancer

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Abstract

Indirect Costs Associated with Human Epidermal Growth Factor Receptor Positive (HER2+) Metastatic Breast Cancer

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Objective

To estimate the indirect costs associated with a diagnosis of human epidermal growth factor receptor positive (HER2+) metastatic breast cancer (mBC) compared to non-cancer controls.

Methods

We performed a matched retrospective cohort analysis using the IBM MarketScan[®] Databases from 2008 – 2018, comparing the differences in hours missed due to absenteeism and days missed due to short-term disability (STD) among adult female patients with HER2+ mBC aged 18-64 compared to non-cancer controls during the first 12 months after mBC diagnosis. We estimated multivariable linear regression models to estimate the indirect costs associated with the diagnosis.

Results

A total of 68 subjects with HER2+ mBC and 198 controls with absenteeism data, and 509 HER2+ mBC subjects and 1522 controls eligible for STD were included in the study. Among employees with absenteeism benefits, patients with HER2+ mBC missed an estimated 372 (95% CI: 240 to 505) more hours during the 12 months after diagnosis compared to controls. This resulted in estimated annual employee absenteeism productivity losses of \$10,424 for patients with HER2+ mBC versus \$3,501 for controls (difference of \$6,923 [95% CI: 779 to 1251]). Among employees with STD eligibility, the estimated the mean missed days among those with HER2+ mBC was 27 (95% CI: 22 to 31) days higher than those without cancer. This resulted in an incremental estimated \$3,942 (95% CI: 3,250 to 4,634) annual productivity loss due to STD for HER2+ mBC patients.

Conclusions

Workplace productivity losses are associated with patients who have HER2+ mBC compared to those without the diagnosis. These indirect costs should be considered when calculating the burden of illness of HER2+ mBC.

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DEDICATION

I dedicate this thesis to my husband, Steve Fassino, my mom, Lucy Wright, and my Aunt Sue. I leaned on all of you more than you will ever know, and I am thankful for your love and support throughout my graduate education.

Chapter 1. INTRODUCTION

1.1 DISEASE AND THERAPEUTIC AREA

An estimated 268,600 new cases of breast cancer were diagnosed in 2019 making it the most common cancer diagnosis among women in the United States.¹ Approximately 6% of all breast cancer cases either progress to distant metastatic disease or are defined as distant metastatic disease upon diagnosis.²

Metastatic breast cancer (mBC) has a 5-year survival of 27.5%, and prognosis depends on the histological subtype of the malignancy.^{2,3} Histological subtypes are defined by hormone receptor (HR, estrogen receptor [ER] and/or progesterone receptor [PR]) and human epidermal growth factor receptor positive (HER2+) status. Those diagnosed with HER2+ breast cancer are usually younger, belong to minority groups, and diagnosed with later stage disease compared to HER2- mBC.² Additionally, differences in disease prognosis have been noted in patients who are diagnosed with metastatic HER2+ disease upon first diagnosis, known as de novo HER2+ mBC, compared to patients who progress to mBC after an initial diagnosis of HER2+ early breast cancer (EBC), known as recurrent HER2+ mBC. Despite being diagnosed with later stage disease, de novo mBC is associated with longer median survival compared to recurrent disease.^{4,5}

National Comprehensive Cancer Network treatment guidelines recommend patients with both de novo or recurrent HER2+ mBC receive HER2+ targeted therapy in combination with chemotherapy because it is associated with prolonged survival and increased quality of life.^{6,7} The treatment landscape for HER2+ targeted therapies continues to rapidly mature. Since 2007, three new trastuzumab biosimilars (Kanjiniti [2019]; Herzuma [2018], Ogiviri [2017]) have been

approved as well as five additional novel HER2+targeted therapies (Herceptin Hylecta [2019], Kadcyła [2019], Tykerb [2007], Nerlynx [2017], and Perjeta [2012]).^{6,8-15}

1.2 COSTS OF HER2+ MBC

The economic burden attributable to breast cancer consists of both direct and indirect costs. Direct costs consist of medical and nonmedical costs associated with treatment, while indirect costs are not attributable explicitly to health care events and include workplace productivity losses incurred due to missed or reduced work productivity. Direct costs of breast cancer are well described and substantial.^{16,17} However, direct costs are only part of the total economic burden of disease, particularly among breast cancer patients who are working age and experience workplace disruption.¹⁸⁻²⁰ Workplace productivity losses attributed to mBC are substantial.¹⁸⁻²¹ Studies examining the rate of return-to-work showed an estimated 40% of patients did not return to work one-year following their mBC diagnosis.¹⁸ Compared with early disease, mBC appears to be more burdensome in terms of productivity losses in the first year after diagnosis, but data are limited and outdated.²² Even less is known about how HER2+ status affects productivity losses.

Causes of productivity losses are multifactorial. One cause is the physical burden of the disease itself. A more aggressive, advanced mBC prognosis can contribute to more workhours missed.¹⁸ Another cause of productivity loss can be attributed to the side effects of cancer treatment. As the treatment landscape matures, productivity losses may decrease if new therapies further improve disease symptoms and/or cause fewer side effects and therefore decrease the physical burden of treatment. It is important to quantify productivity losses among patients with HER2+ mBC to understand the full economic burden of illness. The impact of mBC on work-related productivity losses is not well characterized in the current treatment landscape. To our knowledge, no study to-date has quantified productivity losses among mBC patients with the

HER2+ subtype.^{18,23} The objective of the study was to estimate the impact of a diagnosis of HER2+ mBC on workplace productivity losses, thus adding to the limited data characterizing the burden of illness within this important subpopulation of mBC.

Chapter 2. METHODS

2.1 STUDY DESIGN

We conducted a matched retrospective cohort analysis to estimate the indirect costs associated with HER2+ mBC diagnosis in the United States using the data from a large US national, commercially insured claims database. The study aimed to estimate the extent and cost of a diagnosis of HER2+ mBC on productivity loss. The primary outcome of this study was the difference in hours missed due to absenteeism and days missed due to STD among adult, female patients with HER2+ mBC during the first 12 months after diagnosis compared to non-cancer controls. Secondary objective was to estimate the costs attributed to this worktime missed. As a secondary outcome of interest, primary objectives were stratified into patients with de novo mBC compared to recurrent mBC. An exploratory analysis looked at trends associating productivity losses with the of year of diagnosis.

2.2 DATA SOURCE

Our study population consisted of privately insured US employees in the IBM MarketScan[®] Health and Productivity Management (HPM) and Commercial Claims and Encounters (CCAЕ) databases from January 1, 2008 - December 31, 2018. The HPM database consists of more than 3 million privately insured employees. The database contains data regarding

workplace absence and short-term disability. This information was linked to the medical, pharmacy, and enrollment data in the CCAE database.

2.3 SAMPLE SELECTION

The study population included adult female subjects aged 18 - 64 years with a diagnosis of HER2+ mBC, shown in Figure 1. MBC diagnosis was identified with an International Classification of Disease Clinical Modification (ICD-9-CM or ICD-10-CM) primary diagnosis code for breast cancer preceding an ICD-9-CM or ICD-10-CM for a secondary malignancy between January 2008 to December 2017 (Appendix A). The index date for cases is the date of the first mBC diagnosis. HER2+ targeted therapies have remained a mainstay of treatment for HER2+ mBC throughout the study timeline, therefore, HER2+ status was assumed due to the presence of an inpatient or outpatient claim for a HER2+ targeted therapy between the date of diagnosis for primary breast cancer up to 90 days after the date of diagnosis for secondary malignancy (Appendix A). The median time from diagnosis to treatment is estimated to be 26-49 days, therefore, a window of 90 days allowed for capturing most of the HER2+ population while minimizing selection bias.^{24,25} Study subjects were excluded if they had a diagnosis of cancers other than breast cancer in the 6 months prior to index date. All subjects were required to be eligible for employee benefits of absenteeism and/or short-term disability (STD) and to maintain continuous enrollment for 6 months prior and 12 months after the mBC diagnosis date.

HER2+ mBC patients were matched 3 to 1 with adult, female non-cancer controls with absenteeism or STD data using greedy matching on 5-year age bins, study enrollment year, geographic region, and CCI score (as measured 6 months prior to index date). Potential controls with missing values for any of the matching covariates were excluded from the match. HER2+

mBC patients and eligible controls were randomly sorted prior to matching, and all matching factors were weighted equally.²⁶

| Criteria | N |
|---|-----------|
| Diagnosis of Breast Cancer from 2007 - 2017 | 1,095,425 |
| Diagnosis of mBC 2008-2017 | 76,420 |
| HER2+ Targeted Therapy | 9,406 |
| Employees with health productivity data and HER2+ mBC diagnosis | 792 |
| Employees with 6 months before and 12 months after index date | 539 |

Figure 1: Flow Chart of Subject Selection

For the secondary analyses, the study HER2+ mBC cohort was stratified into de novo and recurrent HER2+ mBC. De novo HER2+ mBC patients were diagnosed with metastatic disease at first diagnosis, where recurrent HER2+ mBC patients were diagnosed with metastatic disease after an early breast cancer diagnosis. Previous studies have shown treatment patterns and survival outcomes vary between patients with de novo versus recurrent mBC, and that de novo mBC is associated with longer median survival.⁴ A claim for a HER2+ targeted therapy on or after the mBC diagnosis date identified patients with de novo HER2+ mBC. A HER2+ claim between the initial breast cancer diagnosis and mBC diagnosis defined recurrent HER2+ mBC subjects.

For an exploratory analysis, we were interested in the temporal trends associated with date of diagnosis. During the study timeline, eight therapeutic agents were approved. These new therapies have improved the health outcomes of patients with mBC, and therefore could impact productivity losses associated with a diagnosis of HER2+ mBC.²⁴

2.4 MEASUREMENTS

Baseline demographics measured included age, geographic region, index year, employee class (hourly vs salary) at index date, and adapted Charlson Comorbidity Index (CCI) based on the

6 months prior to mBC diagnosis calculated by the presence of 18 conditions. Cancer and metastatic cancer diagnoses were excluded from the CCI calculation.²⁸⁻³⁰

Productivity losses were defined as hours or days missed due to absenteeism or short-term disability (STD) during the first 12 months after index date, respectively. Absenteeism data contained dates of absence, number of hours missed, and reason for absence (sick, disability, leave, vacation, or Family Medical Leave). STD data consisted of dates of leave and number of days missed. We censored STD episodes that extended beyond the last date of study follow up, and the days missed were recalculated using the number of business days between the start date of the leave and the last follow up date. Any duplicate entries were deleted from the analysis. To calculate the indirect cost of missed work, we multiplied the number of hours missed by the median wage rate in the United States for all occupations in 2018, \$18.58 per hour, as determined by the US Department of Labor.³¹ We assumed an 8-hour workday to calculate the indirect costs associated with missed days due to STD.

2.5 STATISTICAL ANALYSIS

We described the demographic and clinical characteristics of the study population during the 6-month pre-index period. Continuous variables were reported using means and standard deviations (SD), and categorical variables were reported using counts and percentages. Standardized mean differences (SMD) were used to compare the HER2+ mBC and non-cancer controls.

For the primary study objective, we compared the mean difference in hours missed due to absenteeism and the mean difference in sick leave days among HER2+ mBC female patients aged 18-64 compared to non-cancer controls during a 12-month period after diagnosis. We estimated multivariable linear regression models, adjusting for region, CCI score, index year, and age at

diagnosis. These models compared the hours missed due to absenteeism and days missed due to STD during the 12-month follow up period.

For the secondary objective, we conducted a subgroup analysis estimating the differences in mean missed work hours for the absenteeism cohort and mean missed work days of the STD cohort comparing subjects with de novo HER2+ mBC compared to recurrent mBC using similar multivariable linear regression models.

We also performed an exploratory trend analyses to evaluate changes in productivity loss over time. We used estimated linear regression models to assess mean missed work hours and mean missed work days across diagnosis years (2008 – 2017), adjusting for de novo cancer status, age at diagnosis, and CCI score among patients with HER2+ mBC using both a heterogeneity test and trend test. In the heterogeneity model, we defined 2008 as the reference year, and we compared each index year to the reference year. To evaluate if there is a temporal relationship between HER2+ mBC and productivity losses, we used linear trend tests to test for the association of missed days or missed hours over time.

For data management, we used SAS, version 9.4, (SAS Institute, Cary, North Carolina). Statistical analyses were performed using R Studio 3.6.1. Alpha levels of < 0.05 were considered statistically significant. The study was exempt from Institutional Review Board (IRB) review by the University of Washington Human Subjects Division IRB as the MarketScan[®] databases was created by a third party analyst, is Health Insurance Portability and Accountability Act of 1996 (HIPAA) compliant (all data are de-identified), and does not meet the US federal definition of “human subjects research”.

Chapter 3. RESULTS

3.1 BASELINE CHARACTERISTICS

The study populations included 68 women with HER2+ mBC and 198 controls with absenteeism data, and 509 HER2+ mBC subjects and 1522 controls eligible for STD (Figure 1). The mean ages were 48 and 49 years for the absenteeism and STD cohorts, respectively. The matching procedure balanced measured covariates between HER2+ mBC patients and controls in both cohorts. Table 5.1 compares the mean values for the HER2+ mBC subjects and controls for each of the absenteeism and STD cohorts.

3.2 INDIRECT COSTS ASSOCIATED WITH HER2+ mBC

3.2.1 *Absenteeism*

More subjects with HER2+ mBC had non-zero absenteeism hours (79.4% vs 69.7%) compared to controls. Patients with HER2+ mBC missed an estimated 561 hours compared to an estimated 188 hours missed among controls for a difference of 373 more hours (95% CI: 240 to 505) over the 12-month follow up period after adjusting for covariates. The mean estimated indirect costs associated with productivity losses due to absenteeism is \$3,501 for the noncancer controls compared to \$10,424 for subjects with HER2+ mBC (cost difference = \$6,923 [95% CI: \$779 to \$1251]) over the 12 months after diagnosis. Results reported in

Table 5.3.

3.2.2 *Short Term Disability*

Patients with HER2+ mBC had more non-zero STD days (54.9% vs 12.5%) compared to controls. After adjusting for covariates, we found a statistically significant difference in mean

missed days during the first 12 months after diagnosis comparing subjects with HER2+ mBC to those without a cancer diagnosis. We estimate the mean missed days among those with HER2+ mBC is 27 (95% CI: 22 to 31) days higher than those without cancer. This results in an indirect cost due to STD of \$5,380 for HER2+ mBC patients compared to \$1,438 for a difference of \$3,942 (95% CI: 3250 to 4634) over the 12-month period. Results are reported in Table 5.5.

3.3 INDIRECT COSTS ASSOCIATED WITH DE NOVO HER2+ mBC

A total of 68 patients (45 with de novo HER2+ mBC and 23 with recurrent HER2+ mBC) and 509 patients (374 with de novo HER2+ mBC and 135 with recurrent HER2+ mBC) were included in the subgroup analyses evaluating the association between mean missed work time and de novo HER2+mBC. Baseline characteristics between patients with de novo HER2+ mBC and recurrent mBC for absenteeism and STD cohorts are summarized in Table 8.13. No differences between groups were seen at baseline.

We did not see statistically significant evidence that the impact of recurrent HER2+ mBC compared to de novo mBC on absenteeism differed between groups during the 12-month follow up period. The number of patients with non-zero workdays among those with recurrent mBC was 78.3% compared to 77.8% of those with de novo HER2+ mBC. We estimated those with recurrent HER2+ mBC missed an average of 229 hours compared to 422 hours among those with de novo HER2+ mBC for a difference of 193 (95% CI: -120 to 506) hours during the 12 months after diagnosis. Results in Table 5.7.

Mean missed days due to STD was significantly higher in patients with de novo versus recurrent HER2+mBC, however. More patients with de novo HER2+ mBC compared to recurrent had non-zero workdays (42.8% vs 16.3%). We estimated those with recurrent HER2+ mBC missed an estimated 14 days compared to an estimated 45 days missed among those with

de novo HER2+ mBC (difference of 31 days, 95% CI: 23 to 38) over the 12-month follow up period. Results from the STD linear regression models are displayed in Table 5.8.

3.4 TRENDS ASSOCIATED WITH YEAR OF DIAGNOSIS

We estimated linear regression models to describe the association between index year and both absenteeism and STD in order to evaluate chronologic trends. We found modest evidence that more recently diagnosed mBC HER2+ patients had more missed work hours (p-value = 0.02). From 2008 to 2017, patients with HER2+ mBC missed an additional 51.3 (95% CI: 8.22, 94.44) hours for each successive year of diagnosis. We did not find evidence that year of diagnosis is associated with a difference in mean missed STD days (Table 5.10).

Chapter 4. DISCUSSION

This analysis estimated the work hours missed due to absenteeism, workdays missed due to STD, and indirect costs attributable to both absenteeism and STD for patients diagnosed with HER2+ mBC compared to non-cancer controls. We found that there was a substantial and significant difference for all these workplace productivity measures.

When comparing patients with de novo HER2+ mBC compared to recurrent HER2+ mBC, patients with de novo mBC experienced an incremental mean difference of 31 additional missed days compared to those with recurrent mBC. Although patients with de novo mBC have a longer median survival compared to recurrent mBC, they are often diagnosed with more advanced-stage disease and higher tumor burdens compared to those with recurrent mBC.^{4,5} This higher disease burden could contribute to the increased number of missed days during the first 12 months after diagnosis. Interestingly, despite significant therapeutic development in the treatment of HER2+ mBC during the study timeline, we found a trend of more missed hours due

to absenteeism over time. Trends in survival among patients with de novo mBC and recurrent mBC have been demonstrated from 1990 to 2010, therefore, it is possible that the novel treatments are allowing people to live longer with more progressed disease, and patients with more progressed disease are missing more work.³² Our small sample size limits the interpretability of these results. No association was seen between year of diagnosis and STD days missed.

Our findings are consistent with previous literature describing the association between mBC and productivity losses. Wan et al. estimated the incremental indirect costs of mBC compared to non-cancer controls and found patients with mBC experienced STD costs of \$1,010 (2009 USD) more compared to controls \$2,383 compared to \$1,282 (2009 USD) during the first 12 months after diagnosis.¹⁹ Similarly, Fu and all estimated the incremental indirect costs to be \$1,911 and \$6,157 (2009 USD) for absenteeism and STD respectively comparing mBC patient to non-cancer controls during the first 12 months after diagnosis.¹⁸ Neither study stratified the results by HER2 status.

Our study is the only retrospective cohort study focusing on productivity losses among mBC patients with HER2+ status. Our findings are larger in magnitude compared to the previous similarly designed studies evaluating productivity losses among patient with mBC regardless of HER2 status, thus demonstrating a potential difference between HER2+ compared to HER2- patient populations.^{18,19}

This study has several limitations. First, the continuous enrollment criteria select for patients who survived the 12 months after diagnosis. This may bias our population toward healthier subjects, thus limiting the generalizability of the results. We also lack specificity in the diagnosis codes for identifying HER2+ status. We allowed HER2+ treatment from the time of

the primary breast cancer diagnosis up to 90 days after the metastatic diagnosis. Previous studies identified the median time for HER2+ mBC patients to be treated with a HER2+ therapy is 26 - 49 days, therefore the 90-day window captured most of the population with HER2+ mBC while minimizing selection bias, but may have misclassified patients with HER2+ mBC who were treated after the 90-day window. We performed an analysis to evaluate the attrition rate after implementing the 90-day criteria and 2,096 subjects out of 11,502 (18.2%) subjects with HER2+ mBC were treated after the 90-day window. Additionally, although treatment with a HER2+ directed therapy has remained the standard of care throughout study timeline, the inclusion criteria relies on the assumption that all HER+ patients received HER2+ treatment at first line treatment or soon after mBC diagnosis. Third, we used a linear regression model to estimate between group differences, which may be biased due to the skewed outcome data and large number of enrollees with zero missed work hours and zero missed workdays. The generalized linear model may be more appropriate particularly in estimating indirect cost due to absenteeism considering the small sample size. Finally, the HPM data source consists of privately insured patients, therefore, the sample does not represent patients who have public insurances or who are uninsured. It also only quantifies indirect costs attributed to absenteeism or STD and does not quantify indirect costs associated with premature mortality.

To our knowledge, this is the first study evaluating the indirect costs associated with HER2+ mBC. This study provides evidence that both the work hours missed and STD days missed during the first 12 months after diagnosis of HER2+ mBC may be significantly higher among employees with a diagnosis with HER2+ mBC. Additionally, de novo HER2+ mBC patients could have higher indirect costs due to STD compared to recurrent HER2+ mBC patients. This study demonstrates the substantial workplace productivity losses associated with a

common subtype of mBC. These results can be used to inform economic models from the societal perspective and can have important implications on the value proposition of novel therapies that result in less workplace disruption.

Chapter 5. TABLES

Table 5.1. Baseline Demographics

| | Short Term Disability Population* | | | Absenteeism Population* | | |
|--------------------------------|-----------------------------------|--------------|-------|-------------------------|--------------|-------|
| | Controls | HER2+ mBC | | Controls | HER2+ mBC | |
| n | 1522 | 509 | SMD | 198 | 68 | SMD |
| Age, mean (sd) | 49.5 (8.2) | 49.5 (8.19) | 0.002 | 48.7 (8.7) | 48.8 (8.7) | 0.012 |
| Diagnosis index year, n (%) | | | 0.007 | | | 0.058 |
| 2008 | 45 (3.0) | 15 (2.9) | | 12 (6.1) | 4 (5.9) | |
| 2009 | 51 (3.4) | 17 (3.3) | | 12 (6.1) | 4 (5.9) | |
| 2010 | 66 (4.3) | 22 (4.3) | | 18 (9.1) | 6 (8.8) | |
| 2011 | 114 (7.5) | 38 (7.5) | | 21 (0.6) | 7 (10.3) | |
| 2012 | 117 (7.7) | 40 (7.9) | | 12 (6.1) | 5 (7.4) | |
| 2013 | 134 (8.8) | 45 (8.8) | | 8 (4.0) | 3 (4.4) | |
| 2014 | 209 (13.7) | 70 (13.8) | | 26 (13.1) | 9 (13.2) | |
| 2015 | 222 (14.6) | 74 (14.5) | | 18 (9.1) | 6 (8.8) | |
| 2016 | 273 (17.9) | 91 (17.9) | | 35 (17.7) | 12 (17.6) | |
| 2017 | 291 (19.1) | 97 (19.1) | | 36 (18.2) | 12 (17.6) | |
| Region, n (%) | | | 0.006 | | | 0.085 |
| Northeast | 251 (16.5) | 85 (16.7) | | 8 (4.0) | 4 (5.9) | |
| North Central | 333 (21.9) | 111 (21.8) | | 50 (25.3) | 17 (25.0) | |
| South | 629 (41.3) | 210 (41.3) | | 113 (57.1) | 38 (55.9) | |
| West | 309 (0.3) | 103 (20.2) | | 27 (13.6) | 9 (13.2) | |
| Age Categories, n (%) | | | 0.004 | | | 0.029 |
| 18-34 | 78 (5.1) | 26 (5.1) | | 24 (12.1) | 8 (11.8) | |
| 35-44 | 324 (21.3) | 108 (21.2) | | 17 (8.6) | 6 (8.8) | |
| 45-54 | 647 (42.5) | 216 (42.4) | | 101 (51.0) | 34 (50.0) | |
| 55-65 | 473 (31.1) | 159 (31.2) | | 56 (28.3) | 20 (29.4) | |
| Comorbidity Index, n (%) | | | 0.011 | | | 0.105 |
| 0 | 1002 (65.8) | 334 (65.6) | | 135 (68.2) | 45 (66.2) | |
| 1 | 387 (25.4) | 129 (25.3) | | 51 (25.8) | 17 (25.0) | |
| 2 | 83 (5.5) | 29 (5.7) | | 8 (4.0) | 4 (5.9) | |
| 3+ | 50 (3.3) | 17 (3.3) | | 4 (2.0) | 2 (2.9) | |
| Class, n (%) | | | 0.181 | | | 0.19 |
| Salary | 594 (39.0) | 223 (43.8) | | 103 (52.0) | 39 (57.4) | |
| Hourly | 600 (39.4) | 157 (30.8) | | 78 (39.4) | 21 (30.9) | |
| Other | 328 (21.6) | 129 (25.3) | | 17 (8.6) | 8 (11.8) | |

| | | | | | | |
|--|--|------------|--|--|-----------|--|
| De Novo mBC, n (%) | | 374 (73.5) | | | 45 (66.2) | |
| Key: STD = short term disability; sd = standard deviation; n = number; HER2+ = Human Epidermal Growth Factor Receptor Positive; mBC = metastatic breast cancer; SMD = standardized mean difference, CI = confidence interval * Short-term disability and absenteeism populations are not mutually exclusive | | | | | | |

Table 5.2. Unadjusted Productive Time Missed and Indirect Cost of Study Population

| | Short Term Disability Population* | | Absenteeism Population* | |
|--|-----------------------------------|-------------|-------------------------|----------------|
| | Controls | HER2+ mBC | Controls | HER2+ mBC |
| n | 1522 | 509 | 198 | 68 |
| Patients w/ non-zero sick leave n (%) | | | | |
| Days | 80 (5.3) | 182 (35.8) | | |
| Hours | | | 136 (68.7) | 53 (77.9) |
| Average time missed | | | | |
| Days | 2.24 (12.5) | 28.8 (53.3) | | |
| Hours | | | 134 (126) | 502 (527) |
| Average indirect cost (USD) of time missed (sd) | 333 (1857) | 4276 (7919) | 2,491 (2,349) | 9,327 (10,633) |
| Key: STD = short term disability; sd = standard deviation; n = number; HER2+ = Human Epidermal Growth Factor Receptor Positive; mBC = metastatic breast cancer; SMD = standardized mean difference, CI = confidence interval * Short-term disability and absenteeism populations are not mutually exclusive | | | | |

Table 5.3. Regression Model of Productive Hours Lost Due to Absenteeism Associated with HER2+ mBC

| | Coefficient | 95% CI | p-value |
|----------------------|--------------------|-------------------|------------------|
| Intercept | 188.44 | (-117.93, 494.8) | 0.23 |
| HER2+ mBC | 372.62 | (239.98, 505.26) | <0.001 |
| Age | -2.59 | (-7.22, 2.04) | 0.27 |
| Diagnosis index year | | | |
| 2008 | ref | | |
| 2009 | -96.33 | (-237.14, 44.48) | 0.18 |
| 2010 | -87.82 | (-234.11, 58.47) | 0.24 |
| 2011 | 38.55 | (-105.88, 182.98) | 0.60 |
| 2012 | -156.96 | (-322.5, 8.59) | 0.06 |
| 2013 | -100.56 | (-253.89, 52.77) | 0.20 |

| | | | |
|--|---------|-------------------|--------|
| 2014 | -39.36 | (-178.47, 99.74) | 0.58 |
| 2015 | -139.82 | (-264.56, -15.08) | 0.03 |
| 2016 | 11.76 | (-128.52, 152.05) | 0.87 |
| 2017 | 67.75 | (-85.92, 221.43) | 0.39 |
| Region | | | |
| Northeast | ref | | |
| North Central | 100.54 | (-73.65, 274.73) | 0.26 |
| South | 104.07 | (-56.91, 265.05) | 0.20 |
| West | 230.14 | (44.17, 416.11) | 0.02 |
| Charlson Comorbidity index | | | |
| 0 | ref | | |
| 1 | -65.18 | (-154.39, 24.03) | 0.15 |
| 2 | -185.20 | (-312.46, -57.94) | <0.001 |
| 3+ | 329.08 | (-36.62, 694.78) | 0.08 |
| Key: STD = short term disability; sd = standard deviation; n = number; HER2+ = Human Epidermal Growth Factor Receptor Positive; mBC = metastatic breast cancer; SMD = standardized mean difference, CI = confidence interval | | | |

Table 5.4. Regression Model of Indirect Cost Due to Absenteeism Associated with HER2+ mBC

| | Coefficient | 95% CI | p-value |
|-----------------------------|--------------------|---------------------|----------------|
| Intercept | 3501.161 | (-2191.13, 9193.45) | 0.226884 |
| HER2+ mBC | 6923.336 | (4458.91, 9387.76) | < 0.001 |
| Age | -48.1069 | (-134.2, 37.99) | 0.272185 |
| Diagnosis index year | | | |
| 2008 | ref | | |
| 2009 | -1789.81 | (-4406.1, 826.49) | 0.179086 |
| 2010 | -1631.64 | (-4349.73, 1086.44) | 0.238212 |
| 2011 | 716.2658 | (-1967.32, 3399.86) | 0.599572 |
| 2012 | -2916.24 | (-5992.09, 159.61) | 0.063029 |
| 2013 | -1868.41 | (-4717.24, 980.43) | 0.197648 |
| 2014 | -731.399 | (-3315.89, 1853.1) | 0.577771 |
| 2015 | -2597.78 | (-4915.44, -280.11) | 0.028187 |
| 2016 | 218.5927 | (-2387.98, 2825.17) | 0.868943 |
| 2017 | 1258.835 | (-1596.45, 4114.12) | 0.386046 |
| Region | | | |
| Northeast | ref | | |
| North Central | 1868.032 | (-1368.33, 5104.4) | 0.256703 |
| South | 1933.643 | (-1057.38, 4924.66) | 0.204105 |
| West | 4275.998 | (820.72, 7731.28) | 0.015497 |

| | | | |
|--|----------|----------------------|----------|
| Charlson Comorbidity index | | | |
| 0 | ref | | |
| 1 | -1211.06 | (-2868.58, 446.47) | 0.151397 |
| 2 | -3441 | (-5805.55, -1076.45) | 0.004511 |
| 3+ | 6114.324 | (-680.33, 12908.98) | 0.077561 |
| Key: STD = short term disability; sd = standard deviation; n = number; HER2+ = Human Epidermal Growth Factor Receptor Positive; mBC = metastatic breast cancer; SMD = standardized mean difference, CI = confidence interval | | | |

Table 5.5. Regression Model of Productive Days Missed Associated with HER2+ mBC

| Variable | Coefficient | 95% CI | p-value |
|----------------------------|-------------|----------------|---------|
| Intercept | 9.68 | (-0.39, 19.74) | 0.06 |
| HER2+ mBC | 26.53 | (21.87, 31.18) | <0.001 |
| Age | -0.13 | (-0.3, 0.04) | 0.14 |
| Diagnosis index year | | | |
| 2008 | ref | | |
| 2009 | -6.36 | (-14.04, 1.32) | 0.10 |
| 2010 | 3.69 | (-6.43, 13.81) | 0.47 |
| 2011 | -3.13 | (-10.65, 4.39) | 0.41 |
| 2012 | -3.58 | (-10.83, 3.68) | 0.33 |
| 2013 | -5.90 | (-12.77, 0.96) | 0.09 |
| 2014 | -3.67 | (-10.68, 3.35) | 0.31 |
| 2015 | -2.85 | (-9.74, 4.03) | 0.42 |
| 2016 | -2.21 | (-9.17, 4.74) | 0.53 |
| 2017 | 0.19 | (-6.68, 7.06) | 0.96 |
| Region | | | |
| Northeast | ref | | |
| North Central | 1.36 | (-2.75, 5.48) | 0.52 |
| South | 0.31 | (-3.16, 3.77) | 0.86 |
| West | -0.08 | (-4.48, 4.32) | 0.97 |
| Charlson Comorbidity index | | | |
| 0 | ref | | |
| 1 | 1.68 | (-1.23, 4.58) | 0.26 |
| 2 | 1.79 | (-4.01, 7.58) | 0.55 |
| 3+ | 8.36 | (0.04, 16.69) | 0.05 |

Key: STD = short term disability; sd = standard deviation; n = number; HER2+ = Human Epidermal Growth Factor Receptor Positive; mBC = metastatic breast cancer; SMD = standardized mean difference, CI = confidence interval

Table 5.6. Regression Model of Indirect Cost Due to STD Associated with HER2+ mBC

| Variable | Coefficient | 95% CI | p-value |
|----------------------------|-------------|--------------------|---------|
| Intercept | 1438 | (-58.46, 2934.89) | 0.06 |
| HER2+ mBC | 3943 | (3250.88, 4634.92) | <0.001 |
| Age | -19 | (-44.14, 6.46) | 0.144 |
| Diagnosis index year | | | |
| 2008 | ref | | |
| 2009 | -946 | (-2087.2, 195.7) | 0.104 |
| 2010 | 548 | (-955.75, 2052.75) | 0.475 |
| 2011 | -465 | (-1583.52, 652.92) | 0.415 |
| 2012 | -532 | (-1610.08, 546.68) | 0.334 |
| 2013 | -877 | (-1898.01, 143.14) | 0.092 |
| 2014 | -545 | (-1588.09, 497.82) | 0.305 |
| 2015 | -424 | (-1447.24, 598.86) | 0.416 |
| 2016 | -329 | (-1362.81, 704.56) | 0.532 |
| 2017 | 28 | (-993.01, 1049.13) | 0.957 |
| Region | | | |
| Northeast | ref | | |
| North Central | 203 | (-408.88, 814.54) | 0.516 |
| South | 45 | (-469.35, 560.06) | 0.863 |
| West | -12 | (-666.11, 641.85) | 0.971 |
| Charlson Comorbidity index | | | |
| 0 | ref | | |
| 1 | 250 | (-182.32, 681.5) | 0.257 |
| 2 | 266 | (-595.44, 1126.55) | 0.545 |
| 3+ | 1243 | (5.36, 2481.38) | 0.049 |

Table 5.7. Regression Model of Productive Hours Lost Associated with De Novo compared to recurrent HER2+ mBC

| Variable | Coefficient | 95% CI | p-value |
|-------------|-------------|--------------------|---------|
| Intercept | 229.29 | (-772.55, 1231.14) | 0.65 |
| De novo mBC | 193.33 | (-120.11, 506.76) | 0.22 |
| Age | -5.06 | (-21.49, 11.37) | 0.54 |

| | | | |
|--|---------|-------------------|------|
| Diagnosis index year | | | |
| 2008 | ref | | |
| 2009 | -195.38 | (-457.51, 66.76) | 0.14 |
| 2010 | 113.19 | (-410.49, 636.87) | 0.67 |
| 2011 | 230.92 | (-331.84, 793.67) | 0.41 |
| 2012 | 1.36 | (-615.51, 618.23) | 1.00 |
| 2013 | -8.19 | (-398.49, 382.1) | 0.97 |
| 2014 | 273.90 | (-258.06, 805.87) | 0.31 |
| 2015 | -149.69 | (-433.36, 133.98) | 0.29 |
| 2016 | 382.36 | (-34.54, 799.27) | 0.07 |
| 2017 | 554.10 | (25.93, 1082.28) | 0.04 |
| Region | | | |
| Northeast | ref | | |
| North Central | 115.81 | (-291.42, 523.05) | 0.57 |
| South | 212.32 | (-172.56, 597.2) | 0.27 |
| West | 478.31 | (18.27, 938.35) | 0.04 |
| Charlson Comorbidity index | | | |
| 0 | ref | | |
| 1 | -83.16 | (-407.3, 240.99) | 0.61 |
| 2 | -462.02 | (-900.67, -23.38) | 0.04 |
| 3+ | 627.41 | (10.73, 1244.09) | 0.05 |
| Key: STD = short term disability; sd = standard deviation; n = number; HER2+ = Human Epidermal Growth Factor Receptor Positive; mBC = metastatic breast cancer; SMD = standardized mean difference, CI = confidence interval | | | |

Table 5.8. Regression Model of Productive Days Lost Associated with De Novo HER2+ mBC

| Variable | Coefficient | 95% CI | p-value |
|----------------------|-------------|-----------------|---------|
| Intercept | 13.69 | (-22.94, 50.33) | 0.46 |
| De novo mBC | 30.65 | (23.23, 38.08) | <0.001 |
| Age | -0.18 | (-0.82, 0.46) | 0.58 |
| Diagnosis index year | | | |
| 2008 | ref | | |
| 2009 | -20.77 | (-43.26, 1.72) | 0.07 |
| 2010 | 17.28 | (-18.16, 52.73) | 0.34 |
| 2011 | -3.31 | (-29.72, 23.1) | 0.81 |
| 2012 | -13.35 | (-36.91, 10.22) | 0.27 |

| | | | |
|--|--------|-----------------|------|
| 2013 | -14.42 | (-37.26, 8.42) | 0.22 |
| 2014 | -2.73 | (-26.8, 21.34) | 0.82 |
| 2015 | 0.96 | (-22.89, 24.81) | 0.94 |
| 2016 | 2.32 | (-21.51, 26.15) | 0.85 |
| 2017 | 8.91 | (-14.59, 32.4) | 0.46 |
| Region | | | |
| Northeast | ref | | |
| North Central | 2.70 | (-11.77, 17.18) | 0.71 |
| South | 1.14 | (-11.06, 13.34) | 0.85 |
| West | 1.12 | (-14.37, 16.61) | 0.89 |
| Charlson Comorbidity index | | | |
| 0 | ref | | |
| 1 | -0.03 | (-10.4, 10.34) | 1.00 |
| 2 | -1.62 | (-17.36, 14.11) | 0.84 |
| 3+ | 24.50 | (0.02, 48.97) | 0.05 |
| Key: STD = short term disability; sd = standard deviation; n = number; HER2+ = Human Epidermal Growth Factor Receptor Positive; mBC = metastatic breast cancer; SMD = standardized mean difference, CI = confidence interval | | | |

Table 5.9. Regression Model of Absenteeism Hours and Index Year

| Variable | Coefficient | 95% CI | p-value |
|-----------------------------|-------------|-------------------|--------------|
| Intercept | 229.3 | (-772.5, 1231.1) | 0.6 |
| Diagnosis index year | | | |
| 2008 | ref | | |
| 2009 | 229.3 | (-457.5, 66.8) | 0.648 |
| 2010 | -195.4 | (-410.49, 636.87) | 0.141 |
| 2011 | 113.2 | (-331.84, 793.67) | 0.666 |
| 2012 | 230.9 | (-615.51, 618.23) | 0.414 |
| 2013 | 1.4 | (-398.49, 382.1) | 0.996 |
| 2014 | -8.2 | (-258.06, 805.87) | 0.967 |
| 2015 | 273.9 | (-433.36, 133.98) | 0.306 |
| 2016 | -149.7 | (-34.54, 799.27) | 0.294 |
| 2017 | 382.4 | (25.93, 1082.28) | 0.071 |
| Trend | 51.3 | (8.22, 94.44) | 0.020 |

Table 5.10. Regression Model of Productive Days Lost Associated with Index Year

| Variable | | | |
|----------|--|--|--|
| | | | |

| | Coefficient | 95% CI | p-value |
|-------------------------|--------------------|---------------|----------------|
| Intercept | 15.0 | (-22, 52) | 0.427 |
| Diagnosis index year | | | |
| 2008 | ref | | |
| 2009 | -20.5 | (-43.0, 1.9) | 0.073 |
| 2010 | 17.5 | (-18.0, 52.9) | 0.333 |
| 2011 | -3.1 | (-29.5, 23.2) | 0.816 |
| 2012 | -13.3 | (-36.8, 10.1) | 0.264 |
| 2013 | -14.1 | (-36.9, 8.6) | 0.223 |
| 2014 | -2.5 | (-26.5, 21.4) | 0.835 |
| 2015 | 1.2 | (-22.6, 24.9) | 0.922 |
| 2016 | 3.9 | (-20.8, 28.5) | 0.757 |
| 2017 | 9.1 | (-14.3, 32.4) | 0.447 |
| Trend | 1.8 | (-0.1, 3.6) | 0.058 |

Chapter 6. BIBLIOGRAPHY

- [1] Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019.
- [2] Howlader N, Cronin KA, Kurian AW, Andridge R. *Cancer Epidemiol Biomarkers Prev.* 2018 Jun;27(6):619-626. doi: 10.1158/1055-9965.EPI-17-0627. Epub 2018 Mar 28.
- [3] Siotos C, McColl M, Psoter K, et al. Tumor Site and Breast Cancer Prognosis. *Clin Breast Cancer.* 2018;18(5):e1045–e1052. doi:10.1016/j.clbc.2018.05.007
- [4] Tripathy D, Brufsky A, Cobleigh M, et al. De Novo Versus Recurrent HER2-Positive Metastatic Breast Cancer: Patient Characteristics, Treatment, and Survival from the SystHERs Registry. *Oncologist.* 2020;25(2):e214–e222. doi:10.1634/theoncologist.2019-0446
- [5] Yardley DA, Kaufman PA, Brufsky A, et al. Treatment patterns and clinical outcomes for patients with de novo versus recurrent HER2-positive metastatic breast cancer. *Breast Cancer Res Treat.* 2014;145(3):725-734. doi:10.1007/s10549-014-2916-8
- [6] Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2+for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* 2001;344(11):783–792. doi:10.1056/NEJM200103153441101
- [7] National Comprehensive Cancer Network. Breast Cancer (Version 2.2020). https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf (Accessed February 22, 2020)
- [8] KanjintiTM (trastuzumab-anns). [Package Insert], Thousand Oaks, CA: Amgen, Allergan; 2019.
- [9] Herzuma[®] (trastuzumab-pkrb). [Package Insert], North Wales, PA: Teva Pharmaceuticals; 2019. Ogiviri (trastuzumab-dkst). [Package Insert], Zurich, Switzerland: Mylan; 2017.
- [10] Ogiviri (trastuzumab-dkst). [Package Insert], Zurich, Switzerland: Mylan; 2017.
- [11] Herceptin HylectaTM (trastuzumab and hyaluronidase-oysk). South San Francisco, CA: Genentech, Inc; 2019
- [12] KadcylaTM (ado-trastuzumab emtansine). [Package Insert], South San Francisco, CA: Genentech, Inc; 2019
- [13] Tykerb (lapatinib).[Package Insert], Research Triangle Park, NC: GlaxoSmithKline; 2007

- [14] Nerlynx (neratinib). [Package Insert], Los Angeles, CA: Puma Biotechnology Inc, 2017
- [15] Perjeta (pertuzumab). [Package Insert], South San Francisco, CA: Genentech, Inc, 2013
- [16] Park J, Look KA. Health Care Expenditure Burden of Cancer Care in the United States. *Inquiry*. 2019;56:46958019880696. doi:10.1177/0046958019880696
- [17] Sussell JA, Sheinson D, Wu N, Shah-Manek B, Seetasith A. HER2-Positive Metastatic Breast Cancer: A Retrospective Cohort Study of Healthcare Costs in the Targeted-Therapy Age [published online ahead of print, 2020 Mar 14]. *Adv Ther*. 2020;10.1007/s12325-020-01283-4. doi:10.1007/s12325-020-01283-4
- [18] Fu AZ, Chen L, Sullivan SD, Chirstainsen NP. Absenteeism and short-term disability associated with breast cancer. *Breast Cancer Res Treat*. 2011 Nov;130(1):235-42. doi: 10.1007/s10549-011-1541-z. Epub 2011 May 13.
- [19] Wan Y, Gao X, Mehta S, Wang Z, Faria C, Schwartzberg L. Indirect costs associated with metastatic breast cancer. *J Med Econ*. 2013;16(10):1169–1178. doi:10.3111/13696998.2013.826228
- [20] Sun Y, Shigaki CL, Armer JM. Return to work among breast cancer survivors: A literature review. *Support Care Cancer*. 2017;25(3):709–718. doi:10.1007/s00520-016-3446-1
- [21] Kamal KM, Covvey JR, Dashputre A, et al. A Systematic Review of the Effect of Cancer Treatment on Work Productivity of Patients and Caregivers. *J Manag Care Spec Pharm*. 2017;23(2):136 - 162. doi:10.18553/jmcp.2017.23.2.136
- [22] Yin W, Horblyuk R, Perkins JJ, et al. Association Between Breast Cancer Disease Progression and Workplace Productivity in the United States. *J Occup Environ Med*. 2017;59(2):198–204. doi:10.1097/JOM.0000000000000936
- [23] Miller EM, Schwartzberg LS. Biosimilars for breast cancer: a review of HER2-targeted antibodies in the United States. *Ther Adv Med Oncol*. 2019;11:1758835919887044. Published 2019 Nov 14. doi:10.1177/1758835919887044
- [24] Yoo TK, Han W, Moon HG, et al. Delay of Treatment Initiation Does Not Adversely Affect Survival Outcome in Breast Cancer. *Cancer Res Treat*. 2016;48(3):962-969. doi:10.4143/crt.2015.173
- [25] Wharam JF, Zhang F, Lu CY, et al. Breast Cancer Diagnosis and Treatment After High-Deductible Insurance Enrollment. *J Clin Oncol*. 2018;36(11):1121-1127. doi:10.1200/JCO.2017.75.2501
- [26] Kosanke J, Bergstralh, E. gmatch. April 7, 2004.. Version 2. Mayo Clinic College of Medicine. <http://bioinformaticstools.mayo.edu/downloads/sas/gmatch.sas>

- [27] Zhiyuan Zheng, Ahmedin Jemal, Matthew P. Banegas, Xuesong Han, and K. Robin Yabroff. High-Deductible Health Plans and Cancer Survivorship: What Is the Association With Access to Care and Hospital Emergency Department Use. *Journal of Oncology Practice* 2019 15:11, e957-e968
- [28] Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol.* 1994;47(11):1245-1251. doi:10.1016/0895-4356(94)90129-5
- [29] Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005;43(11):1130-1139.
- [30] Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol.* 2011;173(6):676-682. doi:10.1093/aje/kwq433
- [31] US Department of Labor. May 2018 National Occupational Employment and Wage Estimates United States: All Occupations. Bureau of Labor Statistics. Available at: https://www.bls.gov/oes/current/oes_nat.htm#00-0000 Accessed 3 March 2020. B. Kennedy, *Power Quality Primer*, McGraw-Hill, 2000
- [32] Caswell-Jin JL, Plevritis SK, Tian L, et al. Change in Survival in Metastatic Breast Cancer with Treatment Advances: Meta-Analysis and Systematic Review. *JNCI Cancer Spectr.* 2018;2(4):pky062. doi:10.1093/jncics/pky062

Chapter 7. APPENDIX A

Table 7.11 Identification Codes for Metastatic Breast Cancer and Sites of Metastases

| | ICD-9-CM | ICD-10-CM | HCPCS |
|---------------------------------------|--|---|---|
| Breast Cancer | 174.XX, 175.XX | C50.X, D05.X, Z90.1X, Z17.0, Z17.1, Z85.3 | |
| Secondary Malignant Neoplasm | Stage 3: 196.0, 196.3, 198.2 Stage 4: 197%, 196.1, 196.2, 196.5, 196.6, 196.8, 196.9, 198.0, 198.1, 198.4, 198.5, 198.6, 198.8, 198.82, 198.89, 199.0, 199.1 | Stage 3: C77.0, C77.3, C792 Stage 4: C78.X, C79.0X, C79.1X, C79.4X, C79.5X, C77.71, C77.72, C77.75, C77.8, C77.9, C79.82, C79.89, C79.9, C80.0, C80.1 | |
| Brain | 198.3 92.23–92.24, 92.30– 92.33, 92.39, 92.30– 92.33, 92.39, 01.21– 01.25, 01.31, 01.51, 1.59 | C79.3X | 61793, 61796– 61800, 77371– 77372, 77432, G0173, G0242, G0243, G0251, G0338, G0339, G0340 |
| Other Cancers (exclusion criteria) | 140.xx–173.xx, 176.xx–195.xx, 200.xx–208.xx | C16.X, C17.X, C18.X, C21.X, C25.X, D12.X, C56.X, C57.X, C48.X, C54.X, C55.X, C25.X, C61.X, C64.X, C65.X, C66.X, C67.X, C68.X, C43.X, C73.X, C74.X, C75.X, D35.X, E20.X, E21.X, C69.X, C70.X, C71.X | |

Table 7.12 Identification Codes HER2+ Targeted Therapy

| HER2+ Directed Therapy | HCPCS | NDC |
|---|--------------|--|
| Herceptin® (trastuzumab) | J9355, J3590 | 50242-132-01; 50242-0132-01 |
| Kanjinti™ (trastuzumab-anns) | C9399 | 55513-132-01 |
| Herceptin Hylecta™ (trastuzumab and hyaluronidase-oysk) | J9356 | 50242-077-01, 50242-0077-01 |
| Ogiviri™ (trastuzumab-dkst) | Q5114 | 67457-845-50, 67457-846-20, 67457-847-44, 67457-991-15 |
| Perjeta® (pertuzumab) | J9306 | 50242-145-01, 50242-0145-01 |
| Kadcyla® (ado-trastuzumab emtansine) | J9354 | 50242-088-01, 50242-0088-01, 50242-087-01, 50242-0087-01 |
| Tykerb® (lapatinib) | NA | 0078-0671-19 |
| Nerlynx® (neratinib) | NA | 70437-240-18 |

Chapter 8. APPENDIX B

Table 8.13 Baseline Characteristics for Patients with De Novo and Recurrent mBC

| | Short Term Disability Population* | | | Absenteeism Population* | | |
|-----------------------------|-----------------------------------|-------------------|-------|-------------------------|-------------------|-------|
| | Recurrent HER2+ mBC | De Novo HER2+ mBC | | Recurrent HER2+ mBC | De Novo HER2+ mBC | |
| n | 135 | 374 | SMD | 23 | 45 | SMD |
| Age, mean (SD) | | | | | | |
| Diagnosis index year, n (%) | | | 0.554 | | | 0.387 |
| 2008 | 2 (8.7) | 2 (4.4) | | 4 (3.0) | 11 (2.9) | |
| 2009 | 2 (8.7) | 2 (4.4) | | 4 (3.0) | 13 (3.5) | |
| 2010 | 1 (4.3) | 5 (11.1) | | 3 (2.2) | 19 (5.1) | |
| 2011 | 2 (8.7) | 5 (11.1) | | 8 (5.9) | 30 (8.0) | |
| 2012 | 1 (4.3) | 4 (8.9) | | 6 (4.4) | 34 (9.1) | |
| 2013 | 2 (8.7) | 1 (2.2) | | 11 (8.1) | 34 (9.1) | |
| 2014 | 4 (17.4) | 5 (11.1) | | 26 (19.3) | 44 (11.8) | |
| 2015 | 2 (8.7) | 4 (8.9) | | 25 (18.5) | 49 (13.1) | |
| 2016 | 3 (13.0) | 9 (20.0) | | 28 (20.7) | 63 (16.8) | |
| 2017 | 4 (17.4) | 8 (17.8) | | 20 (14.8) | 77 (20.6) | |
| Region, n (%) | | | 0.269 | | | 0.074 |
| Northeast | 2 (8.7) | 2 (4.4) | | 25 (18.5) | 60 (6.0) | |
| North Central | 5 (21.7) | 12 (26.7) | | 28 (20.7) | 83 (22.2) | |

| | | | | | | |
|--------------------------|-----------|-----------|-------|-----------|------------|-------|
| South | 12 (52.2) | 26 (57.8) | | 54 (40.0) | 156 (41.7) | |
| West | 4 (17.4) | 5 (11.1) | | 28 (20.7) | 75 (20.1) | |
| Age Categories, n (%) | | | 0.608 | | | 0.232 |
| 18-34 | 2 (8.7) | 6 (13.3) | | 3 (2.2) | 23 (6.1) | |
| 35-44 | 0 (0.0) | 6 (13.3) | | 27 (20.0) | 81 (21.7) | |
| 45-54 | 14 (60.9) | 20 (44.4) | | 56 (41.5) | 160 (42.8) | |
| 55-65 | 7 (30.4) | 13 (28.9) | | 49 (36.3) | 110 (29.4) | |
| Comorbidity Index, n (%) | | | 0.48 | | | 0.171 |
| 0 | 15 (65.2) | 30 (66.7) | | 93 (68.9) | 241 (64.4) | |
| 1 | 7 (30.4) | 10 (22.2) | | 28 (20.7) | 101 (27.0) | |
| 2 | 0 (0.0) | 4 (8.9) | | 10 (7.4) | 19 (5.1) | |
| 3+ | 1 (4.3) | 1 (2.2) | | 4 (3.0) | 13 (3.5) | |

Table 8.14. Unadjusted Productive Time Missed and Indirect Cost of HER2+ mBC

Population

| | Short Term Disability Population* | | Absenteeism Population* | |
|---|-----------------------------------|-------------|-------------------------|---------------|
| | Controls | HER2+ mBC | Controls | HER2+ mBC |
| n | 135 | 374 | 23 | 45 |
| Patients w/ non-zero sick leave n (%) | | | | |
| Days | 22 (16.3) | 160 (42.8) | | |
| Hours | | | 18 (78.3) | 35 (77.8) |
| Average time missed | | | | |
| Days | 1 (4.8) | 23.9 (48.8) | | |
| Hours | | | 379 (452) | 565 (620) |
| Average indirect cost (USD) of time missed (sd) | 149 (3554) | 713 (7255) | 7051 (8392) | 10490 (11527) |
| <p>Key: STD = short term disability; sd = standard deviation; n = number; HER2+ = Human Epidermal Growth Factor Receptor Positive; mBC = metastatic breast cancer; SMD = standardized mean difference, CI = confidence interval</p> <p>* Short-term disability and absenteeism populations are not mutually exclusive</p> | | | | |

Chapter 9. APPENDIX C

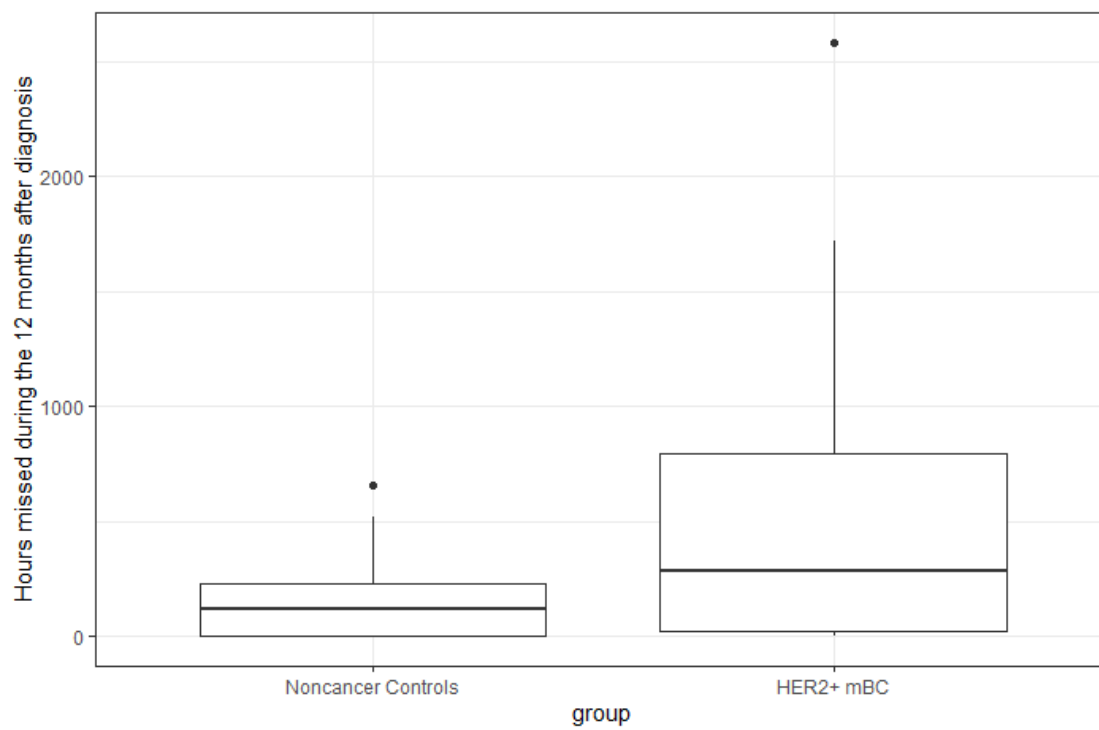


Figure 2: Boxplot of Hours Lost Due to Absenteeism

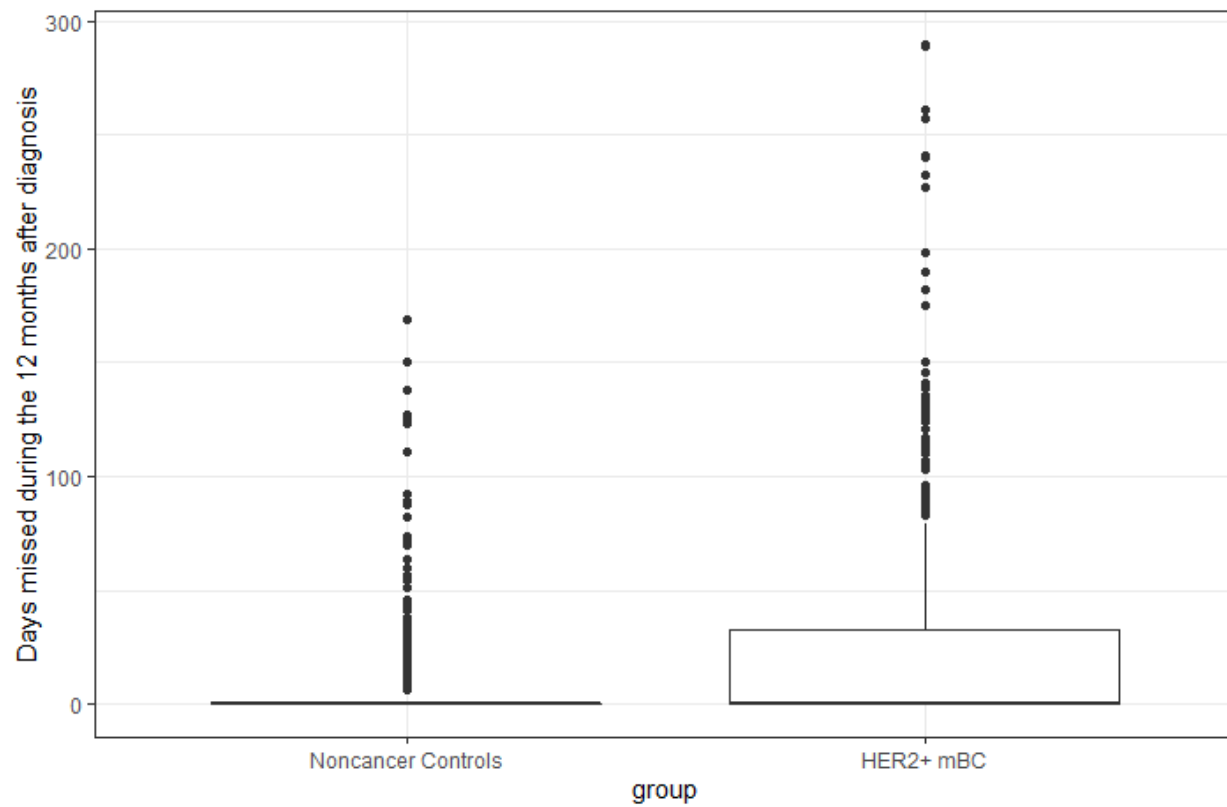


Figure 3: Boxplot of Days Lost Due to STD