

**Heart failure Among Younger Versus Older Breast Cancer Survivors:
A Longitudinal Cohort Analysis**

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Abstract

Background

Breast cancer is the leading cancer-related cause of death for women worldwide (American Cancer Society, *Cancer Facts & Figures*, 2020). In the United States, about 1 in 8 women (approximately 18%) will develop invasive breast cancer over the course of her lifetime (American Cancer Society, *Cancer Facts & Figures*, 2020). Recent studies have shown that patients treated for breast cancer are more than three times more likely to develop congestive heart failure when compared to patients without cancer (Mayo Clinic & Klein, 2018). In this cohort analysis, we assessed the risk of heart failure stratified by age. When stratified by age, we predict that the risk of heart failure for breast cancer survivors will be higher among older versus younger patients.

Methods

A population-based, retrospective cohort study of 22,299 female breast cancer survivors were selected. SAS version 9.4 was used for survival analysis on breast cancer survivors with heart failure as the outcome, then stratified by two age groups (18-64, 65+). Kaplan Meier curves were analyzed as well as the Cox Proportional Hazards model. ArcMap version 10.1 was used to geocode a further subsection of this cohort, 7,193 breast cancer survivors living in Chicago with a match rate of 68%. Geographic Information Systems (GIS) maps were created to display the spatial distribution of breast cancer survivors per community area, breast cancer cases stratified by age, heart failure cases per community areas, heart failure cases stratified by age, a hotspot analysis of breast cancer cases stratified by age, and a hotspot analysis of heart failure cases stratified by age.

Results

The age group of 65+ breast cancer survivors had a 1.291 times higher risk of heart failure in comparison to younger breast cancer survivors (18-64). Metastasized cancer, hypertension medication at baseline, hypertension medication most recent, diabetes medication most recent, diabetes medication at baseline, smoking status, race, ethnicity, hypertension, myocardial infarction, diabetes mellitus, coronary artery disease, atrial fibrillation, SBP baseline, and BMI baseline were adjusted for in this analysis. In ArcMap, geocoded patient data showed breast cancer survivors and heart failure cases clustered in the North side of Chicago (Lincoln Park, Lakeview, Edgewater) as well as downtown Chicago (Near North Side). The highest rates of heart failure among breast cancer survivors were between 19-33% in Fuller Park, Roseland, and South Lawndale communities. Hot spot analysis showed the highest rate of heart failure among breast cancer survivors

Discussion

Age was found to increase the risk of heart failure in older versus younger breast cancer survivors. Sample size limited this analysis of the influence of only two age categories on heart failure in breast cancer survivors. This study was limited to cancer patients within the Northwestern Medicine network, which biases the population to a higher concentration of cases nearer to Northwestern Medicine. To combat this, future studies could partner with other hospital networks like the Advocate Health Care system with more locations on the South and West sides of Chicago.

Introduction

In 2020, an estimated 276,480 cases of invasive breast cancer and 48,530 cases of non-invasive breast cancer are predicted to be diagnosed among women living in the United States (American Cancer Society, *Cancer Facts & Figures*, 2020; Barnard, Boeke, & Tamimi, 2015). Besides skin cancer, breast cancer is the most common cancer diagnosis and the leading cause of cancer death for women living in the United States (American Cancer Society, *Cancer Facts & Figures*, 2020; American Cancer Society, *How Common Is Breast Cancer*, 2020). In women under 45, breast cancer is more common in black women than white women, and black women are more likely to die of breast cancer (American Cancer Society, *How Common Is Breast Cancer*, 2020). There are many established risk factors for breast cancer, including age, race, genetic predisposition, diet, body mass index, occupational exposure (American Cancer Society, *Breast Cancer Risk Factors You Cannot Change*, 2019; National Cancer Institute, 2018; Barnard, Boeke, & Tamimi, 2015).

As of January 2020, the American Cancer Society found there are more than 3.5 million women living in the United States with a history of breast cancer, including survivors and those currently being treated (American Cancer Society, *Cancer Facts & Figures*, 2020; Barnard, Boeke, & Tamimi, 2015). For women who survive breast cancer, the risk of developing further comorbidities increases (Nechuta, Lu, Zheng, Cai, Bao, Gu, & Shu, 2013; Barnard, Boeke, & Tamimi, 2015; Herman, Ganz, Petersen, & Greendale, 2005). One of the negative health outcomes is an increased risk of heart failure (Nechuta, Lu, Zheng, Cai, Bao, Gu, & Shu, 2013; Mayo Clinic & Klein, 2018). Recent studies indicate that breast cancer patients who received treatment are more

than three times more likely to develop congestive heart failure when compared to patients without cancer (Mayo Clinic & Klein, 2018).

Heart failure has many risk factors, but the most common conditions which can lead to heart failure are high blood pressure, previous heart attacks, and coronary artery disease (American Heart Association, 2019). Certain medications, including statin therapy and those for diabetes, have been found to increase the risk of heart failure for some patients (Seicean, Seicean, Plana, Budd, & Marwick, 2012; American Heart Association, 2019). Sleep apnea, valvular heart disease, alcohol use, tobacco, obesity, congenital heart defects, diabetes, high pulse pressure, and irregular heartbeats have also been shown to increase the risk of heart failure (Bauters, Lamblin, Mc Fadden, Van Belle, Millaire, & De Groote, 2003; Chae, Pfeffer, Glynn, Mitchell, Taylor, & Hennekens, 1999; American Heart Association, 2019).

Specific to breast cancer survivors, several cardiotoxic factors have been shown to increase the risk of heart failure in these patients (Harrison, Pressler, & Friese, 2016; Patanè, 2014). Breast cancer treatment with Trastuzumab, Bevaciumab, and Anthracycline have been shown to increase risk of heart failure in breast cancer survivors (Chen, Long, Hurria, Owusu, Steingart, & Gross, 2012; Choueiri, Mayer, Je, Rosenberg, Nguyen, Azzi, & Schutz, 2011; Pinder, Duan, Goodwin, Hortobagyi, & Giordano, 2007).

Several of these risk factors for heart failure were included in this analysis as potential confounders of the association between age of breast cancer diagnosis and heart failure in breast cancer survivors. In this longitudinal cohort analysis, we assessed the risk of heart failure in breast cancer patients stratified by age of breast cancer

diagnosis. When stratified by adult women under and over 65 years of age at cancer diagnosis, we predict that the risk of heart failure for breast cancer survivors will be higher among older versus younger patients.

Methods

Study Population

This population was selected from a large cohort study of 103,333 adult cancer survivors, called the Young and Emerging Cancer survivors (YEA), treated at Northwestern Medicine Health System in Illinois. Data was collected from Electronic Health Records (EHRs) from patients within this healthcare system with a cancer diagnosis of any type. SAS version 9.4 was utilized to limit the cohort to 22,299 female breast cancer survivors.

Exposure & Outcome

The exposure of interest was age, which was recorded at the date of first cancer diagnosis. Age was categorized into two groups, under 65 years old (18-64), and 65+ years old. The outcome of interest was breast cancer survivors treated within the Northwestern Medical System who experienced heart failure.

Missingness

Prior to data cleaning, there were 22,299 observations and 71 variables when limited to female breast cancer survivors. After evaluating the exposure and outcome of interest, the remainder of this dataset was evaluated for missingness and normal distribution of variables. When re-coded, values missing from the original variables were kept in the analysis to evaluate for bias. Values which were outside the realm of biological probability and logical thresholds were re-coded as “missing” for this analysis.

Missing data was assessed for bias and was non-differential by outcome. Pulse pressure was dropped from the dataset due to its high biologic variability and that it was over 10% missing (Table 2). Diastolic Blood Pressure (DBP) was only recorded at baseline, and was missing for the most recent visit. Additionally, several clinical test measures such as Vitamin D, low-density lipoprotein (LDL) and high-Density Lipoprotein (HDL) cholesterol, glucose levels, fasting glucose, and C-reactive protein (CRP) marker variables were 100% missing. Other variables such as tobacco packs per day, ounces of alcohol per week were more than 30% missing. Values for an “alcohol comment” was over 50% missing, and contained values from an open text box in the EHR system. Due to the unformatted nature of this variable, this was excluded from analysis as the majority of values were unique. Variables that were 100% or over 30% missing were not included in the survival analysis, with the exception of smoking and alcohol use due to their known association with heart failure.

Data Cleaning

Continuous numeric variables were assessed for outliers and incorrect data through proc univariate statements. Clinical cut points were used to recode continuous numeric variables into categorical numeric variables based on biologic viability. For both baseline and most recent measures of Systolic Blood Pressure (SBP), acceptable values ranged from 74-238 mm Hg (Yi, Mok, Ohrr, Yi, Yun, Park, & Jee, 2016; Ovbiagele, Diener, Yusuf, Martin, Cotton, Vinisko, & PROFESS investigators, 2011). Based on categories of normal to high, $74 \leq x < 120$ mm Hg was coded as 0, $120 \leq x < 140$ mm Hg coded as 1, and $140 \leq x \leq 238$ mm Hg was coded as 2. For Diastolic Blood Pressure (DBP), only baseline measures were recorded. Acceptable

ranges for DBP were 60-134 mm Hg. Based on categories of normal to high, $74 \leq x < 90$ mm Hg was coded as 0, $90 \leq x < 134$ mm Hg coded as 1 (Park & Ovbiagele, 2017).

Body Mass Index (BMI) data was recorded at baseline and at the most recent follow up visit. For BMI, the acceptable range for biologically probable values was 10-60 kg/m² (Cody, Robert Wood Johnson Medical School, & SAS Institute, 2018). Three levels of BMI were coded based on normal, overweight, and obese definitions of BMI (Cody, Robert Wood Johnson Medical School, & SAS Institute, 2018). A BMI of $10 \leq x < 25$ kg/m² was coded as 0, $25 \leq x < 30$ kg/m² as 1, and $30 \leq x < 60$ kg/m² as 2 (Cody, Robert Wood Johnson Medical School, & SAS Institute, 2018).

Categorical character variables were assessed for coding errors through proc freq statements and re-coded into categorical numeric variables. Cancer type originally included leukemia, lymphoma, lumphoid, skin, bladder, urinary, colon, large intestine, anal, renal, liver, kidney prostate cancer, pancreatic, endometrial, testicular, thyroid, connective, and breast cancer. Cancer type was re-coded into individual binary variables for each individual cancer type, with 1 indicating that the patient was diagnosed with that type of cancer. Several outcomes were recorded, including Polycystic Ovarian Syndrome (PCOS), cardiovascular disease, Chronic obstructive pulmonary disease (COPD), diabetes mellitus, myocardial infarction, preeclampsia, hypertension, and heart failure. All outcomes were re-coded into individual binary variables for each individual outcome, with 1 indicating that the outcome occurred.

Ethnicity was re-coded into a categorical three level variable, with “Declined,” “Declined to answer,” and “Unable to answer” as 0. “Hispanic or Latino” was coded as 1, with “Not Hispanic or Latino” and “NOT Hispanic or Latino” as 2. For race, “White”

and “White or Caucasian” as 0, “Black or African American” as 1, “Asian” as 2, “Native Hawaiian or Other Pacific Islander,” “American Indian or Alaska Native,” “2 or more races” or “Other” as 3, and “Declined,” “Unable to Answer,” or “Unknown” as 4. “Native Hawaiian or Other Pacific Islander,” “American Indian or Alaska Native,” “Other,” and “2 or more races” were coded as one group due to small sample size for each category.

For the “Metastasized” variable indicating if the diagnosed breast cancer was metastatic, 0 was coded for “No” and 1 for “Yes.” For smoking status, “Never Smoker” was coded as 0. “Passive Smoke Exposure - Never Smoker” was coded as 1. “Former Smoker” was coded as 2. “Current Everyday Smoker,” “Current Some Day Smoker,” “Light Tobacco Smoker,” “Smoker, Current Status Unknown” were coded as 3. “Unknown If Ever Smoked” was coded as 4. Alcohol use was categorized into two levels: “Defer,” “Never,” “No,” and “Not currently” were coded as 0, and “Yes” was coded as 1.

For diabetes and hypertension medications, both were re-coded as 0 being no drug and 1 as the patient being treated with one or more drugs. Hypertension was re-coded as a three level variable, where 0 equaled no hypertension. Due to the large dataset, many patients received diagnosis of comorbidities prior to treatment at Northwestern Medicine. In this case, variables reading “01JAN1900” indicated that the diagnosis occurred prior to treatment within the Northwestern Medicine network. Therefore, patients with prior history of hypertension (i.e. “01JAN1900”) were coded as 1, and patients who were diagnosed with hypertension at Northwestern Medicine (diagnosis date after 01JAN1900) were coded as 2.

Assessment of Confounding and Effect Modification

Confounding is a distortion in the estimated association of an exposure-outcome relationship (Sullivan & LaMorte, 2019). For a variable to be considered a confounder, it must be associated with both the exposure of interest (age of breast cancer diagnosis) and outcome (heart failure). Two other conditions must be met for confounding to occur: the confounding factor must be distributed unequally among compared groups, and the confound cannot be an intermediary step on the causal pathway from the exposure of interest to the outcome of interest (Sullivan, & LaMorte, 2019). Effect modification is when the covariate of interest is only associated with the outcome (heart failure). Based on an extensive literature review, several variables were assessed for confounding or effect modification of the exposure (age of breast cancer diagnosis) and outcome (heart failure) relationship.

While several drugs used to treat cancer have been shown to be cardiotoxic, this analysis only assessed hypertension and diabetes medications as whole groups. Therefore, the following variables were assessed as potential confounders or effect modifiers: metastasis, hypertension, hypertension medications, diabetes medication, alcohol use, smoking, race, ethnicity, hypertension, myocardial infarction, diabetes mellitus, coronary artery disease, atrial fibrillation, systolic blood pressure (baseline and most recent) and diastolic blood pressure (baseline), and body mass index (baseline and most recent).

Chi-square analysis was used as the test of association for all variables of interest as potential confounders or effect modifiers were categorical 2-level or 2+ level variables in association with the exposure and/or the outcome (both categorical 2-level variables). An alpha-level of 0.05 was used to determine significance for all analyses.

Multiplicative effect modification was assessed using stratification for categorical variables. Confounding was assessed by analyzing whether covariates were significantly associated with the exposure (age of breast cancer diagnosis) and the outcome (heart failure). Analysis was conducted using SAS version 9.4 (SAS Institute, Cary, NC).

SAS Survival Analysis

Survival analysis was performed through Kaplan Meier and Cox regression. In order to perform survival analysis, a time variable was created indicating the amount of time from breast cancer diagnosis and to the date of heart failure. This value was then divided by 365.25. Proc lifetest was used to estimate the survival function from lifetime data. In medical research and the log likelihood.

Proc phreg was used to perform cox regression analysis for the crude hazard ratio of age and the adjusted hazard ratio for age as the exposure for heart failure. Age was adjusted for all variables considered confounders, effect modifiers, or independent predictors. Model fit statistics will be used to determine how well the proposed model represents the data.

GIS Study Population

Of the 22,299 breast survivor cohort, this population was further limited to patients living in Chicago, Illinois with zip codes. This was done in order to obtain a large enough sample size of patients per community area for a valid hotspot analysis. When limiting the dataset to breast cancer survivors in Chicago, only 7,193 patients were in the limits of Chicago with zip code data.

Geocoding

Geocoding was performed on 7,193 patients living in Chicago by matching to an “Address Locator” in US Addresses-Dual Ranges (Source: Street CenterLine file, Chicago Data Portal 2010). The SAS YEA dataset was limited to female breast cancer survivors limited to those living in Chicago (due to collection errors, all forms of Chicago were selected including "CHICAGO", "Chicago", "CHICAGP", "CHI", "CHGO", "CHICAG", "CHIAGO", "CHICGO", "cHICAGO", "chicago"). Collection errors in the spelling of “Chicago” were corrected in Excel and exported as a CSV file.

ArcMap Visualization of Cohort Data

Six selections were performed on the geocoding results: 1) total breast cancer cases per community area, 2) breast cancer cases per community area aged 18-64 at the time of diagnosis, 3) breast cancer cases per community area aged 65+ at the time of diagnosis, 4) total heart failure cases per community area, 5) heart failure cases per community area aged 18-64 at the time of diagnosis, and 6) heart failure cases per community area aged 65+ at the time of diagnosis. The geocoded breast cancer patient result files were joined to a United States Community Area file of Chicago, Illinois (Source: Chicago Data Portal, Community Areas 2010). The join was conducted by joining data from another layer based on spatial location to receive average attributes for each datafile, as well as the count per patient for each community area. This was performed to mask the individual patient data in compliance with The Health Insurance Portability and Accountability Act of 1996 and Northwestern University’s Institutional Review Board.

When trying to visualize heart failure per community area, there were only 369 heart failure cases matched to valid addresses in Chicago. Due to the small number of

cases in Chicago, these results were geocoded and joined to a Chicago Community Areas map instead of the Chicago Census Tract map (Source: Chicago Data Portal, 2010). This allowed for larger community areas in order to have more contiguous data, and a higher count per area to have a hot spot analysis of higher validity. Maps were created per community area of the following variables: 1) total breast cancer survivors, 2) breast cancer survivors by age, 3) total heart failure cases, 4) heart failure cases by age. Then, the rate of heart failure in breast cancer survivors was calculated per community area in total. A new numeric field was added to the joined datatable with the following formula to calculate the rate of heart failure per community area: $(\text{Total heart Failure per area} / \text{Total breast cancer survivors per area}) * 100$.

ArcMap Hotspot Analysis

For the datafile containing merged community area data and the YEA Breast Cancer Survivor data in Chicago, Illinois, a hot spot analysis (Getis-Ord Gi*) was performed on the rates of heart failure among breast cancer survivors. The geocoding result of the patient data was input, the input field was set to age category, conceptualization of spatial relationships was set to “Zone of Indifference” and the distance measure chosen was Manhattan Distance. Raster analysis was set to 100 for the cell size and to automatically convert units. The processing extent was set to the Community Areas file for Chicago (Top:1961363.743987, Left: 1085586.655876, Bottom: 1795140.613929, Right:120866.856971). Output coordinates were projected into the same projection as the dataframe, NAD_1983_StatePlane_Illinois_East_FIPS_1201_Feet.

Results

Study Population

The majority of patients in this cohort were white (75.14%), with 10.8% black, 3.92% asian, 5.38% other (other was an aggregate variable of 2 or more races, Alaskan or Native American Indian, and Pacific Islander based on sample size), and 4.25% unknown. In overall ethnicity, 5.23% were hispanic or latino. In comorbidities included in the evaluation, 0.96% of patients experienced myocardial infarction, 2.64% were diagnosed with diabetes mellitus, 2.98% were diagnosed with coronary artery disease, 4.36% experienced atrial fibrillation, and 5.56 were diagnosed with hypertension. In total, 38.40% of patients reported some type of alcohol use. Overall, 0.29% of patients reported passive smoke exposure, 22.84% were former smokers, 5.07% were current smokers, and 0.81% were unknown. Table 1 outlines the demographics of this breast cancer survivors population stratified by age. In patients aged 18-64 at the time of diagnosis of breast cancer, 71.3% had metastasized cancer compared to 28.7% aged 65+ at the time of diagnosis. In patients 18-64, 60.5% were diagnosed with hypertension, compared to 39.5%. In patients aged 18-64, more patients reported smoking and alcohol use than those over 65+.

Missingness of each covariate was assessed in table 2. Hypertension medications at baseline and most recently, diabetes medications at baseline and most recently, hypertension, myocardial infarction, diabete mellitus, coronary artery disease, atrial fibrillation were missing only 1 value, or 0.0045% of the data. Metastasized was missing 0.15%, race 0.52%, ethnicity 0.45%, systolic blood pressure at baseline 9.54%, systolic blood pressure most recently 1.96%, body mass index at baseline 9.12%, and body mass index at 1.31%. The largest percentage of missingness was bolded.

Diastolic blood pressure at baseline was 16.35% missing, pulse pressure at baseline was 16.34% missing, and smoking status was 21.23% missing. The covariate containing the most missing values was alcohol use, at 60.76% missing (Table 2).

As seen in table 3 the 2x2 table of heart failure in breast cancer survivors by age, 67.29% of the cohort were aged 18-64 and 32.71% were aged 65+. When looking at heart failure, there were 334 cases of heart failure (2.23%) in the population of breast cancer survivors diagnosed between the ages of 18-64, and 552 cases of heart failure (7.57%) in the population of breast cancer survivors diagnosed over the age of 65 (Table 3).

Confounding and Effect Modification

Table 4 outlines the assessment of covariates for confounding and effect modification. Variables were assessed in association with the exposure (age of breast cancer diagnosis) and outcome (heart failure). Metastasized cancer, hypertension medication at baseline, hypertension medication most recent, diabetes medication most recent, diabetes medication at baseline, smoking status, race, ethnicity, hypertension, myocardial infarction, diabetes mellitus, coronary artery disease, atrial fibrillation, SBP baseline, and BMI baseline were shown to confound this relationship. BMI most recent was only associated with the outcome, therefore, is an effect modifier of this relationship. SBP most recently and DBP Baseline were only associated with the exposure, therefore, are independent predictors of heart failure of breast cancer survivors. Only alcohol was shown to have no significant association with either age of breast cancer diagnosis or heart failure of breast cancer survivors.

SAS Survival Analysis

When looking at the Kaplan Meier output in figure 9, the product-limit survival estimates cross twice before 0.2, once at 1.5, and at 13.5 (units being the duration variable created from the time of cancer diagnosis to the event of heart failure). In the log of negative log of estimated survivor functions, the two age groups cross at -4, -3.5, 0, and at 3 (Figure 9). This indicates that the law of proportional hazards had been violated. For the Kaplan Meier output, the test of equality over strata log-rank Chi-Square test statistic was 15.4657 with a p-value of $<.0001$, indicating that the age groups have significantly different survival rates.

The model fit statistics for the cox regression were 7182.434 without covariates and 7166.840 with covariates for -2 LOG Likelihood. The AIC statistics for the regression including all covariates of interest were 7182.434 without covariates and 7168.840 with covariates. The likelihood ratio for this regression had a Chi-Square value of 15.5944 with a p-value of $<.0001$ without adjustment for covariates, indicating that there is a significant difference in survival for breast cancer survivors under and over age 65 at the time of diagnosis (Table 5). Without adjustment for covariates, the hazard ratio was 1.377 (95% confidence interval 1.173-1.616). This indicates that breast cancer survivors aged 65+ at the time of diagnosis are 1.377 times more likely to experience heart failure than patients diagnosed under 65.

When adjusted for covariates, the Chi-square test statistic was 4.6144 with a p-value of 0.0317. This indicated that although there is still a significant difference in survival for breast cancer survivors under and over age 65 at the time of diagnosis. The hazard ratio for age (adjusted for metastasized cancer, hypertension medication at baseline, hypertension medication most recent, diabetes medication most recent,

diabetes medication at baseline, smoking status, race, ethnicity, hypertension, myocardial infarction, diabetes mellitus, coronary artery disease, atrial fibrillation, SBP baseline, BMI baseline, BMI most recent, SBP most recent, and DBP Baseline) was 1.291 with a 95% confidence interval of 1.023-1.629. This can be interpreted that breast cancer survivors aged 65+ at the time of diagnosis are 1.291 times more likely to experience heart failure than patients diagnosed under 65. The fit statistics for this adjusted model are -2 log likelihood of 4315.750 without covariates, and 4254.942 with covariates. The AIC statistic is 4315.750 without covariates, and 4292.942 with covariates. The SBS fit statistic is 4315.750 without covariates, and 4369.976 with covariates. This indicates that between the two models, the model adjusted for the several covariates of age is a better fit for the data.

Geocoding Results

Out of 7,193 patients in the Northwestern Medicine care network designated as living in Chicago, 4,891 breast cancer survivors (68%) were matched to valid addresses in Chicago, IL. When the dataset was further limited to patients with both “Chicago” as their listed city and a zip code, 4,854 out of 5219 were successfully matched to a valid address (93%). Due to the larger number of matched points, the dataset was limited to patients living in Chicago, even for those missing zip code values.

ArcMap Visualizations

In figure 1, the demographics of the Breast Cancer survivors from the YEA dataset can be seen to have the highest count in the Near North Side (373-849), followed by Lakeview and Lincoln Park (214-372). This is expected as the major hospital in the Northwestern care network, Northwestern Memorial Hospital, is located

in the Near North Side community area of Chicago. There are a higher number of breast cancer survivors (80-213 patients) on the North side of the city in the communities surrounding Near North Side (Logan Square, West Town, Near West Side, Loop, Near North Side, Edgewater, Uptown, and West Ridge). Several areas on the far South Side and the West Side of the city have the least amount of patients (2-33; Figure 1).

The second map, figure 2, displays breast cancer survivors aged 65+, which again shows the highest concentration of patients in the Near North Side (108-376), with the second highest number of cases in the surrounding areas of Lincoln Park, Lakeview, Loop, and Edgewater (49-107). There are slightly higher amounts of patients on the South Side of Chicago in Great Grand Crossings, South Shore, Auburn Gresham, Washington Heights, Calumet Heights, Chatham, Hyde Park and Kenwood (17-48). Several areas on the far South Side and the West Side of the city have the least number of patients (0-7; Figure 2). Similar trends to figure 2 are seen in figure 3, which displays counts of breast cancer survivors aged 18-64. The highest counts of cases are in Lakeview, Lincoln Park, and Near North Side (135-473), and the least amount of cases are seen on the far South Side and West Side of the city (1-19; Figure 3).

In figure 4, the total heart failure cases among breast cancer survivors per community area are visualized. There are the highest number of cases in the Near North Side (12-62), followed by Edgewater, Uptown, Lakeview, Lincoln Park, Loop, Douglas, Austin, and Roseland (7-11). The smallest number of cases is seen on the far South Side of the city (Figure 4). Austin and Roseland are notable community areas in this visualization, as they are far from Northwestern Memorial Hospital.

When stratified by age, figure 5 shows the heart failure cases among breast cancer survivors per community area aged 65+. The highest number of cases are seen in the Near North Side (9-45), with the second highest number of cases in the community areas of Edgewater, Uptown, Near South Side. Austin and Roseland have a higher number of cases than surrounding West or South Side communities (Figure 5). Figure 6 shows similar distribution of heart failures cases among breast cancer survivors aged 18-64 (Figure 6).

Figure 7 shows the density of rates of heart failure (%) among breast cancer survivors per community area. Interesting, the highest rates of heart failure were on the South and West sides of town. The highest rates of heart failure among breast cancer survivors are between 19-33% in Fuller Park, Roseland, and South Lawndale communities. The second highest rates of heart failure among breast cancer survivors were seen in the surrounding community areas, such as West Garfield Park, Washington Park, Douglas, Englewood, Austin, Humboldt Park, Brighton Park, Lower West Side, Armor Square, Calumet Heights, and South Deering.

Hot Spot Analysis

Hot spot analysis shown in figure 8 depicts the cluster of the highest rates of heart failure among breast cancer survivors in the city, as well as a cluster of the lowest. The highest rates of heart failure were on the South side clustered around Armor Square (13%) with 99% Confidence. Douglas had a heart failure rate of 18% among breast cancer survivors, with 95% confidence. Bridgeport had a 3% heart failure rate and Grand Crossing had a heart failure rate among breast cancer survivors of 7% with

95% significance. Near South Side had a 6% rate of heart failure among breast cancer survivors with a confidence interval of 90%.

The cold spots identified by this analysis were on the North side of the city. Lakeview (2% rate of heart failure) and Lincoln Square (7%) had the highest confidence of the cold spot at 95%. 90% confidence was determined for the cold spots in Uptown (6% rate of heart failure), North Center (1% rate of heart failure), North Park (7% rate of heart failure), Jefferson park (3% rate of heart failure), and Logan Square (9%).

Discussion

Implications

Breast cancer survivors over 65+ have a 1.291 times higher risk of heart failure than patients diagnosed under 65. This was expected, as age is a known risk factor for heart failure and for many other comorbidities. This was a strong retrospective cohort study with a large study population in one of primary hospital care networks in the state of Illinois. The majority of patients were not lost to follow up (only 0.15% of patients did not have a value for death status or last known follow-up). The data collection methods from electronic health records were consistent throughout the study.

The data collected from the overall cohort of patients treated within Northwestern Medicine, which led to high clustering of breast cancer survivors and heart failure cases near the hospital system. The highest amount of breast cancer survivors and heart failure among breast cancer survivors were, therefore, seen in the Near North Side. The far South Side and West Side communities consistently had the least number of cases for both breast cancer survivors and heart failure, most likely due to the distance from

the hospitals (other hospital systems such as University of Chicago Medicine or Advocate Health Systems in these areas).

Limitations

In this large cohort, there were a limited number of heart failure cases under 40. When stratified by ages 18-39, 40-65, 65+, there were only 11 cases of heart failure in the youngest age group (18-39). For this reason, age was analyzed as a dichotomous categorical variable (above 65 or below) due to sample size concerns. This limited the study analysis to the influence of only two age categories on heart failure in breast cancer survivors. Additionally, the majority of breast cancer survivors in this population were white, which may have biased the results of the survival analysis.

Additional limitation was that this cohort was limited to patients who received care and cancer diagnosis at Northwestern Medicine. This is limited to either patients who have private health insurance, or Medicare/Medicaid. External validity for populations outside of the Northwestern Medicine care network is therefore limited. Due to the clustering of patient data on the North side and downtown area of Chicago, there were large clusters of breast cancer patients on the North side and central downtown areas of Chicago. This may not be representative of the entire breast cancer survivor population of Chicago.

Additionally, even though the majority of cases of breast cancer survivors were concentrated downtown and on the North side of the city, the highest rates of heart failure among breast cancer survivors were among the West and South sides of the city. This is representative of literature on overall heart failure in Chicago (higher rates of heart failure on the South and West sides due to a combination of structural racism and

many studies showing higher rates of negative health outcomes in these community areas; Cromley & Cromley, 2009; Orsi, Margellos-Anast, & Whitman, 2010; Berkman, Sheridan, Donahue, Halpern, & Crotty, 2011). Due to the small amount of heart failure cases per community area in Chicago, hot spot analysis could only be conducted for total heart failure cases, not stratified by age. When stratified by age, many community areas had 0 cases of heart failure for the 18-64 age group.

Another limitation was the geocoding capability of the dataset. Data was collected from Electronic Medical Records (EHRs) from Northwestern, which had several imputation errors. Many patients were missing either the city as “Chicago,” state as “Illinois,” address lines, or zip code. In the first geocoding attempt, only 33.49% of 22,299 breast cancer survivors were successfully matched to a geographic location. Additionally, for hotspot mapping, patient count per area must be high enough to perform an analysis (e.g. at least 1 patient per area). Therefore, the breast cancer survivor cohort had to be further limited to those Chicago, Illinois with zip codes for a large enough sample size of patients per community area for a valid analysis.

Of the patients living in Chicago, 2,315 were unable to be geocoded due to either address collection errors or missing values for zip codes. While 4,878 patients were matched to valid locations in Chicago, this may not be entirely representative of the Northwestern cohort population as well as the breast cancer survivors in Chicago. Due to time constraints, further geocoding of the dataset through python, R, or through commercial mapping software such as Geocodio were not able to be performed. A variety of collection errors and missingness limited the ability of ArcMap to geocode the

majority of the dataset without manual entry of Chicago and Illinois in a consistent format readable by ArcMap software.

Collection errors or missing data also limited this analysis. DBP, for example, was only collected at baseline. Smoking is a known confounder of heart failure, but was missing for 21.76% of the data. While smoking status was included in survival analysis as a potential confounder, this may not be representative of the true relationship in this dataset due to the large amount of values missing. This is the same assumption applied to alcohol use, as 60.76% of the values were missing. Imputations were not performed on missing data, which has the potential to not be entirely representative of the sample of Northwestern Medicine breast cancer survivor population. While several variables contained missing values, the sample size was large enough where survival analysis could be conducted without imputations. The fit statistics of the Cox regression indicate that while age adjusted for the listed covariates is a better fit to the data than unadjusted age, this model is not the best overall fit for the data. With the large number of variables included in the model, there were concerns for overfit. Additionally, the law of proportional hazards was violated, indicating that results must be interpreted with caution.

Future Directions

Future directions of this work could be to further gather data on breast cancer survivors of the age group 18-39 in order to perform a survival analysis with three separate age categories, as 18-39 and 40-64 could have significantly different risks of heart failure. Further work could be done to geocode this dataset in its entirety, either the 7,193 breast cancer survivors living within Chicago, or all 22,229 breast cancer

survivors. Missing data should be either re-collected from electronic databases, imputed based on appropriate averages, or dropped from the dataset for further analysis. When looking at the fit statistics of the Cox regression analysis performed in this study, the created model is not the ideal fit for the data. Another potential model that could be considered is a multilayer, fully connected neural network due to the large number of covariates included in this analysis. Future analysis will include looking at time varying covariates (like change in diabetes status, meds, etc.).

This study was limited to cancer patients within the Northwestern Medicine network, which biases the population to a higher concentration of cases nearer to Northwestern Medicine. Even with this clustering of cases in the Central and North sides of Chicago, higher rates of heart failure were seen in the South and West sides of the city. To further explore these results, future studies could partner with other hospital networks like the Advocate Health Care system with more locations on the South and West sides of Chicago. This would increase the geographic distribution of patients to be more representative of all Chicago, as well as increase the amount of breast cancer survivors in the age range of 18-39 for further analysis.

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Appendix

Table 1. Demographics of Breast Cancer Survivors by Age Group (18-64, 65+)

Covariate	Aged 18-64 N (%) ^b	Aged 65+ N (%) ^b	Chi-Square (P value) ^a
Metastasized (N)	14981	7284	
No	12004 (66.7)	6084 (33.6)	37.12(<.0001)
Yes	2977 (71.3)	1200 (28.7)	
Hypertension (N)	15004	7294	
No	13600 (68.9)	6135 (31.1)	241.93(<.0001)
Prior diagnosis	654 (49.4)	670 (50.6)	
Yes	750 (60.5)	489 (39.5)	
Most Recent Hypertension Medications (N)	15004	7294	
No	9431 (80.8)	2235 (19.2)	2041.82(<.0001)
Yes	5573 (52.4)	5059 (47.6)	
Baseline Hypertension Medications (N)	15004	7294	
No	11139 (78.4)	3065 (21.6)	2203.43(<.0001)
Yes	3865 (47.8)	4229 (52.3)	
Most Recent Diabetes Medications (N)	15004	7294	
No	13855 (68.5)	6370 (31.5)	146.09(<.0001)
Yes	1149 (55.4)	924 (44.8)	
Baseline Diabetes Medications (N)	15004	7294	
No	14226 (68.4)	6584 (31.6)	163.06(<.0001)
Yes	778 (52.3)	710 (47.7)	
Smoking Status (N)	11396	6168	
No	7648 (68.9)	3446 (31.1)	410.93(<.0001)
Passive Smoke Exposure	48 (73.9)	17 (26.2)	
Former Smoker	2732 (53.6)	2361 (46.4)	
Smoker	830 (73.4)	301 (26.6)	
Unknown	138 (76.4)	43 (23.8)	
Alcohol Use (N)	5910	2841	
No	119 (63.0)	70 (37.0)	1.84(0.1747)
Yes	5791 (67.6)	2771 (32.4)	
Race (N)	14920	7264	
White	11043 (65.9)	5712 (34.1)	74.90(<.0001)
Black	1655 (68.7)	754 (31.3)	
Asian	654 (74.7)	221 (25.3)	
Other ^c	896 (74.7)	303 (25.3)	
Unknown	672 (71.0)	274 (29.0)	

Ethnicity (N)	14934	7269	
Unknown/Declined	947 (71.0)	386 (29.0)	88.40(<.0001)
Hispanic or Latino	920 (78.9)	246 (21.1)	
Not Hispanic or Latino	13067 (66.3)	6637 (33.7)	
Atrial fibrillation (N)	15004	7294	
No	14725 (69.1)	6600 (31.0)	689.20(<.0001)
Yes	279 (28.7)	694 (71.3)	
Coronary Artery Disease (N)	15004	7294	
No	14733 (68.1)	6900 (31.9)	219.29(<.0001)
Yes	271 (40.8)	394 (59.3)	
Diabetes Mellitus (N)	15004	7294	
No	14698 (67.7)	7011 (32.3)	64.44(<.0001)
Yes	306 (52.0)	283 (48.1)	
Myocardial Infarction (N)	15004	7294	
No	14918 (67.6)	7166 (32.5)	72.10(<.0001)
Yes	86 (40.2)	128 (59.8)	
BMI Baseline (N)	14824	7183	
10-24.9	5741(67.8)	2730(32.23)	121.36(<.0001)
25-29.9	4438(66.4)	2251(33.7)	
30-60	4645(67.8)	2202(32.2)	
BMI Most Recent (N)	13802	6463	
10-24.9	5472(72.8)	2044(27.2)	4.49 (0.1059)
25-29.9	4061(65.3)	2158(34.7)	
30-60	4269(65.4)	2261(34.6)	
SBP Baseline (N)	13575	6597	
10-24.9	5398(80.5)	1311(9.5)	1201.83(<.0001)
25-29.9	5728(66.9)	2829(33.1)	
10-24.9	2449(49.9)	2457(50.1)	
SBP Most Recent (N)	14713	7150	
25-29.9	6217(77.7)	1786(22.3)	880.15(<.0001)
25-29.9	5950(66.0)	3062(34.0)	
25-29.9	2546(52.5)	2302(47.5)	
DBP Most Baseline (N)	12591	6063	
60-89.9	11354(67.0)	5591(33.0)	20.46(<.0001)
90-140	1237(72.4)	472(27.6)	

^a Data presented as N (%), with Chi-squared test as all are categorical 2-level or 2+ level variables.

^b Percentages calculated from total not including missing values; total population of N=22,229.

^c "Other" race includes "Native Hawaiian or Other Pacific Islander," "American Indian or Alaska Native," "2 or more races" or "Other" due to sample size.

Table 2. Assessing the Missingness of Breast Cancer Survivor Covariates

Covariate	Count Missing (N)	Percent Missing (%)^a	Total (N)
Metastasized	34	0.15	22,299
Hypertension Medication Most Recent	1	0.0045	22,299
Hypertension Medication Baseline	1	0.0045	22,299
Diabetes Medication Most Recent	1	0.0045	22,299
Diabetes Medication Baseline	1	0.0045	22,299
Alcohol Use^b	13548	60.76	22,299
Smoking Status^b	4735	21.23	22,299
Race	115	0.52	22,299
Ethnicity	96	0.43	22,299
Hypertension	1	0.0045	22,299
Myocardial Infarction	1	0.0045	22,299
Diabetes Mellitus	1	0.0045	22,299
Coronary Artery Disease	1	0.0045	22,299
Atrial Fibrillation	1	0.00	22,299
Systolic Blood Pressure Baseline	2127	9.54	22,299
Systolic Blood Pressure Most Recent	436	1.96	22,299
Diastolic Blood Pressure Baseline	3645	16.35	22,299
Pulse Pressure Baseline^b	3643	16.34	22,299
Body Mass Index Baseline	2034	9.12	22,299
Body Mass Index Most Recent	292	1.31	22,299

^a Percent missing calculated from total female breast cancer cohort population of N=22,299.

^b Covariates containing more than 10% missing data bolded.

Table 3. 2x2 Table of Age by Heart Failure

AGE (N, %) ^a	HEART FAILURE (N, %) ^a		
	No	Yes	Total
18-65	14670 65.79 97.77 68.51	334 1.50 2.23 37.70	15004 67.29
65+	6742 30.24 92.43 31.49	552 2.48 7.57 62.30	7294 32.71
Total	21412 96.03	21412 3.97	21412 100.00

Frequency Missing=1

^a Data ordered by frequency (N), percent, row percent, and column percent.

Table 4. Assessment of Covariates for Confounding and Effect Modification

Covariate	Association with Age (p-value) ^a	Association with Heart Failure (p-value)	Confounder, Effect Modifier, or none?
Metastasized	37.12(<.0001)	33.9(<.0001)	Confounder
Hypertension Medication Most Recent	2041.82(<.0001)	922.8(<.0001)	Confounder
Hypertension Medication Baseline	2041.82(<.0001)	778.7(<.0001)	Confounder
Diabetes Medication Most Recent	146.09(<.0001)	415.42(<.0001)	Confounder
Diabetes Medication Baseline	163.06(<.0001)	294.32(<.0001)	Confounder
Alcohol Use	1.84(0.1747)	1.06(0.3)	None
Smoking Status	410.93(<.0001)	38.65(<.0001)	Confounder
Race	74.90(<.0001)	150.16(<.0001)	Confounder
Ethnicity	88.40(<.0001)	15.89(0.0004)	Confounder
Hypertension	241.93(<.0001)	33.91 (<.0001)	Confounder
Myocardial Infarction	72.10(<.0001)	394.72(<.0001)	Confounder
Diabetes Mellitus	64.44(<.0001)	34.81(<.0001)	Confounder
Coronary Artery Disease	219.29(<.0001)	355.74(<.0001)	Confounder
Atrial Fibrillation	689.20(<.0001)	1210.85(<.0001)	Confounder
SBP Baseline	880.15(<.0001)	56.43(<.0001)	Confounder
SBP Most Recent	1201.83(<.0001)	4.80(0.09)	Independent Predictor
DBP Baseline	20.46(<.0001)	3.36(0.07)	Independent Predictor
BMI Baseline	121.36(<.0001)	82.27(<.0001)	Confounder
BMI Most Recent	4.49 (0.1059)	25.15(<0.001)	Effect Modifier

^a Type 3 Analysis of Effect Chi-Squared Test^b Confounding was determined if the covariate had a significant association with both the exposure (age of breast cancer diagnosis) and outcome (heart failure). Effect modification was determined if the covariate had significant association with

Table 5. 2x2 Cox Regression of Age and Heart Failure

Parameter	Parameter Estimate	Standard Error	Chi-Square	Pr>ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age, Crude	0.31956	0.08171	15.2961	<.0001	1.377	1.173	1.616
Age, Adjusted	0.25517	0.11879	4.6144	0.0317	1.291	1.023	1.629

^a Age adjusted for the covariates metastasized cancer, hypertension medication at baseline, hypertension medication most recent, diabetes medication most recent, diabetes medication at baseline, smoking status, race, ethnicity, hypertension, myocardial infarction, diabetes mellitus, coronary artery disease, atrial fibrillation, SBP baseline, BMI baseline, BMI most recent, SBP most recently, and DBP Baseline.

Figure 1: Total Heart Breast Cancer Cases per Community Area

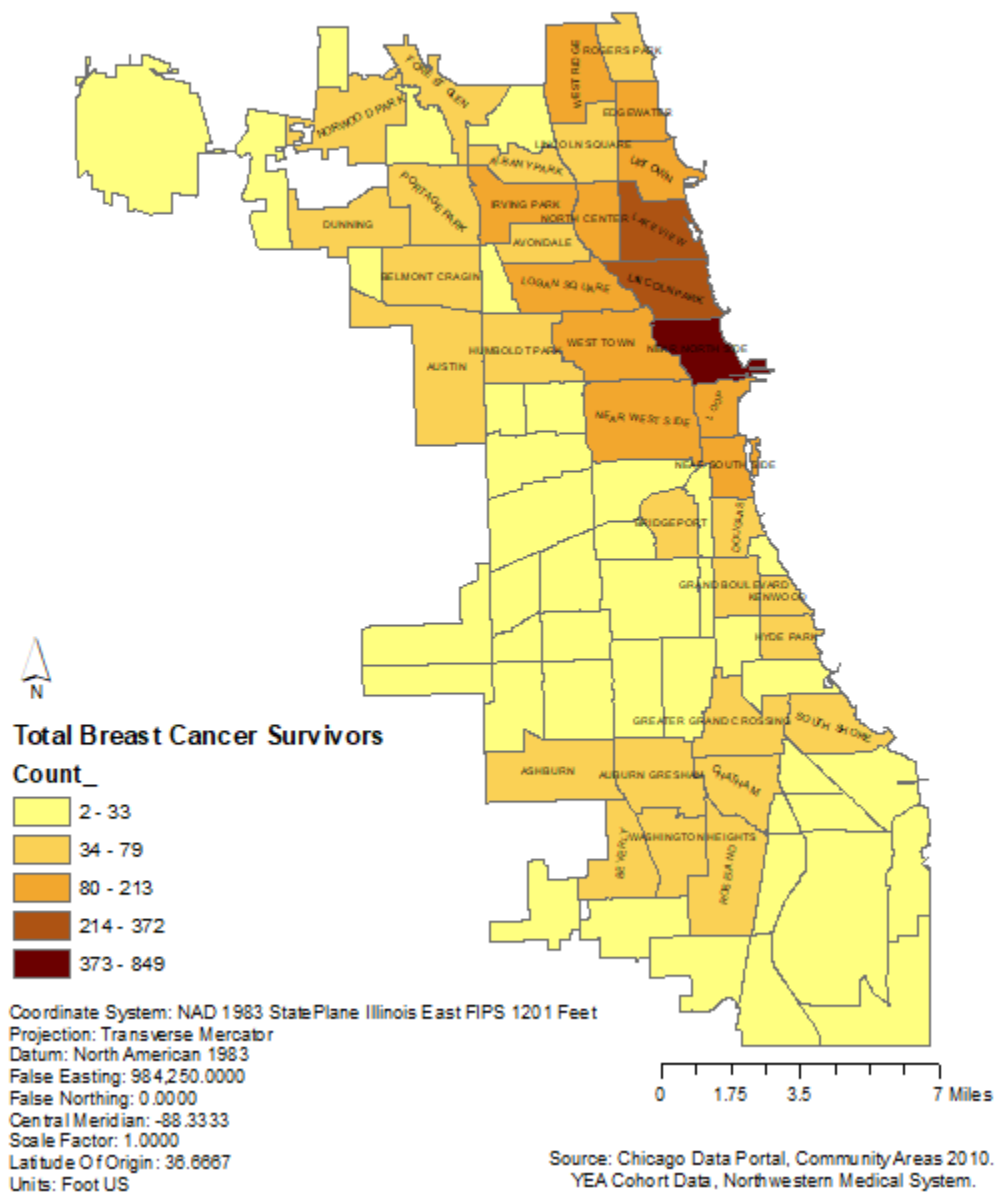


Figure 2: Total Heart Breast Cancer Cases per Community Area (Aged 65+)

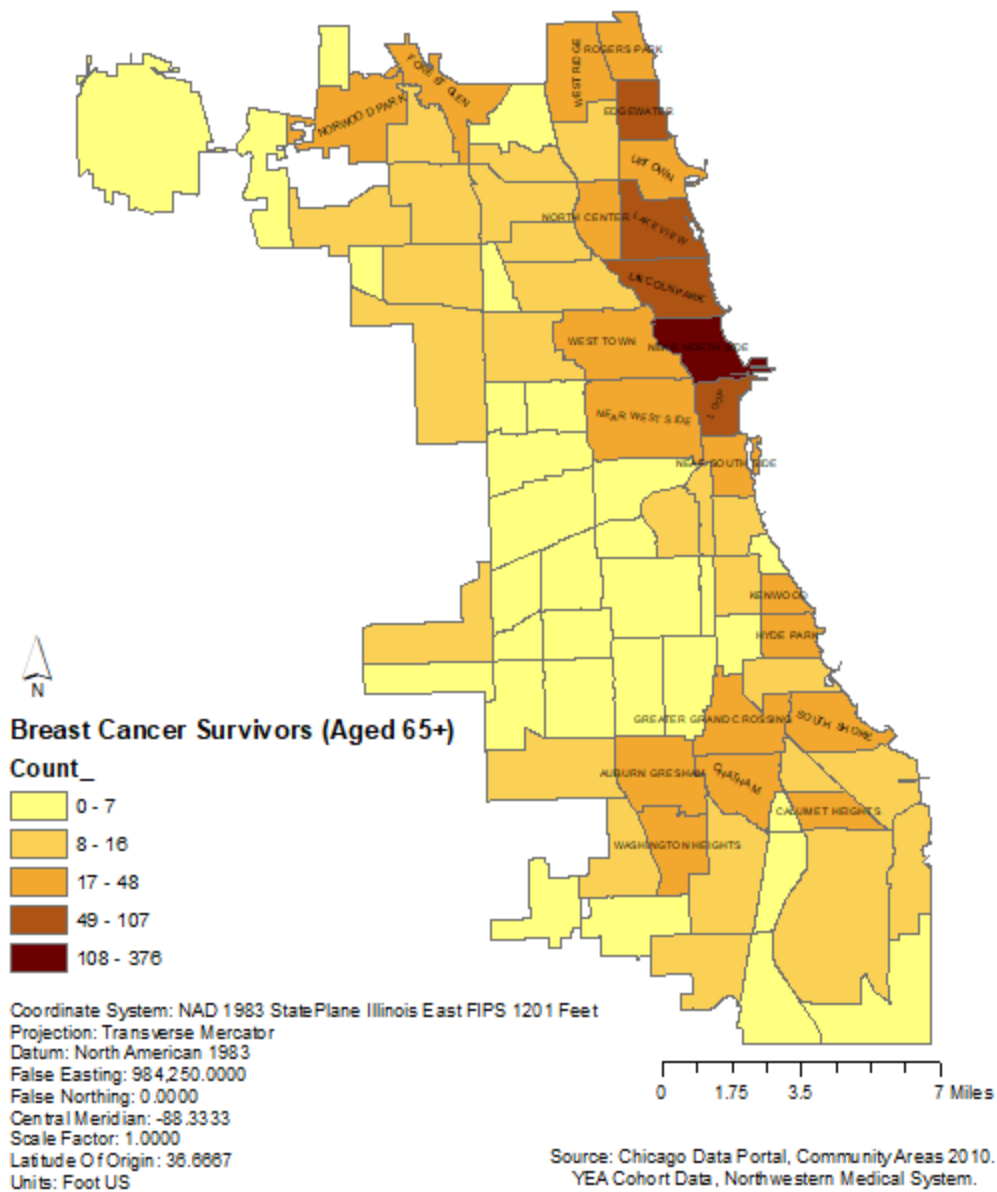


Figure 3: Total Heart Breast Cancer Cases per Community Area (Aged 18-64)

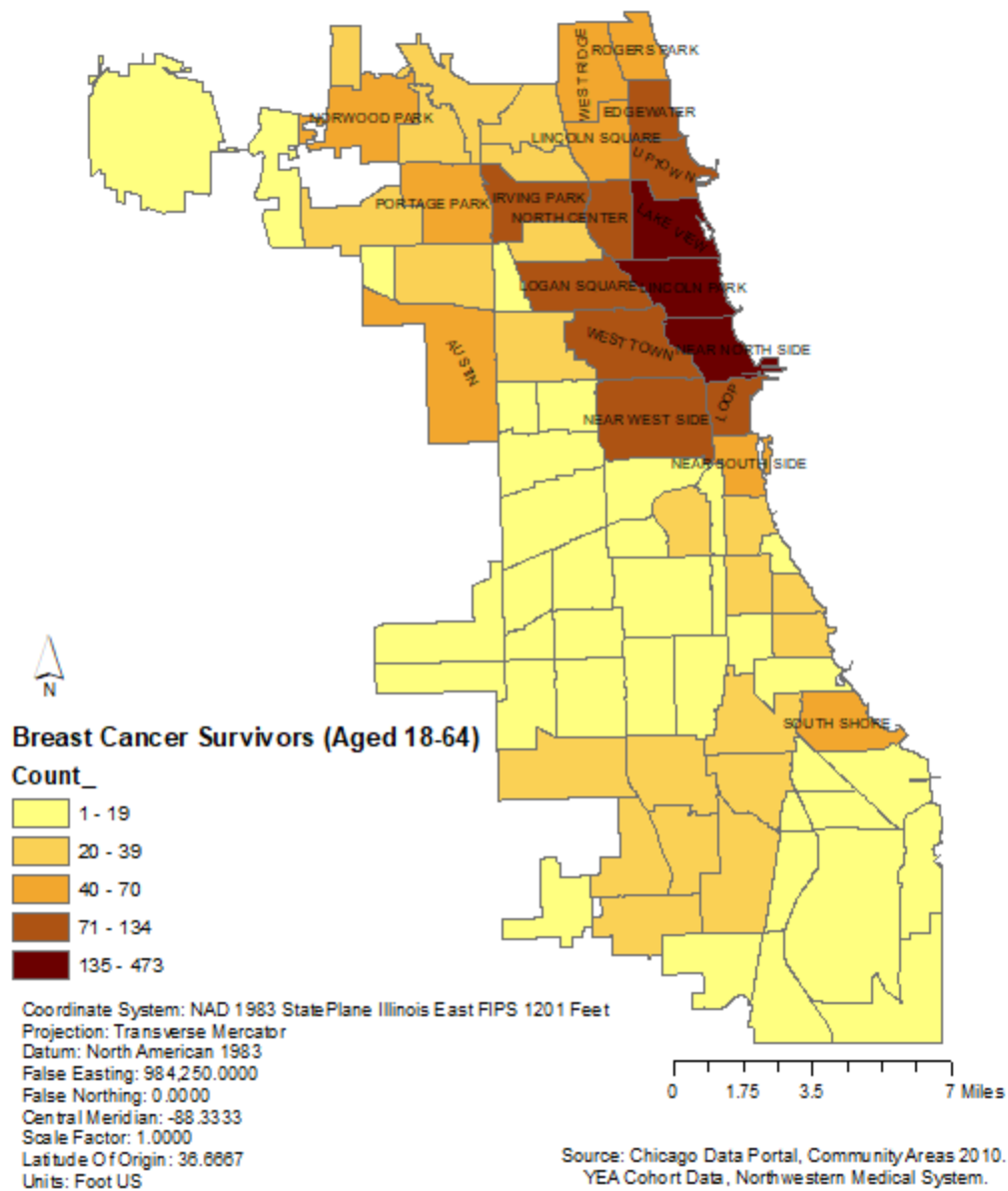


Figure 4: Total Heart Failure Cases Among Breast Cancer Survivors per Community Area

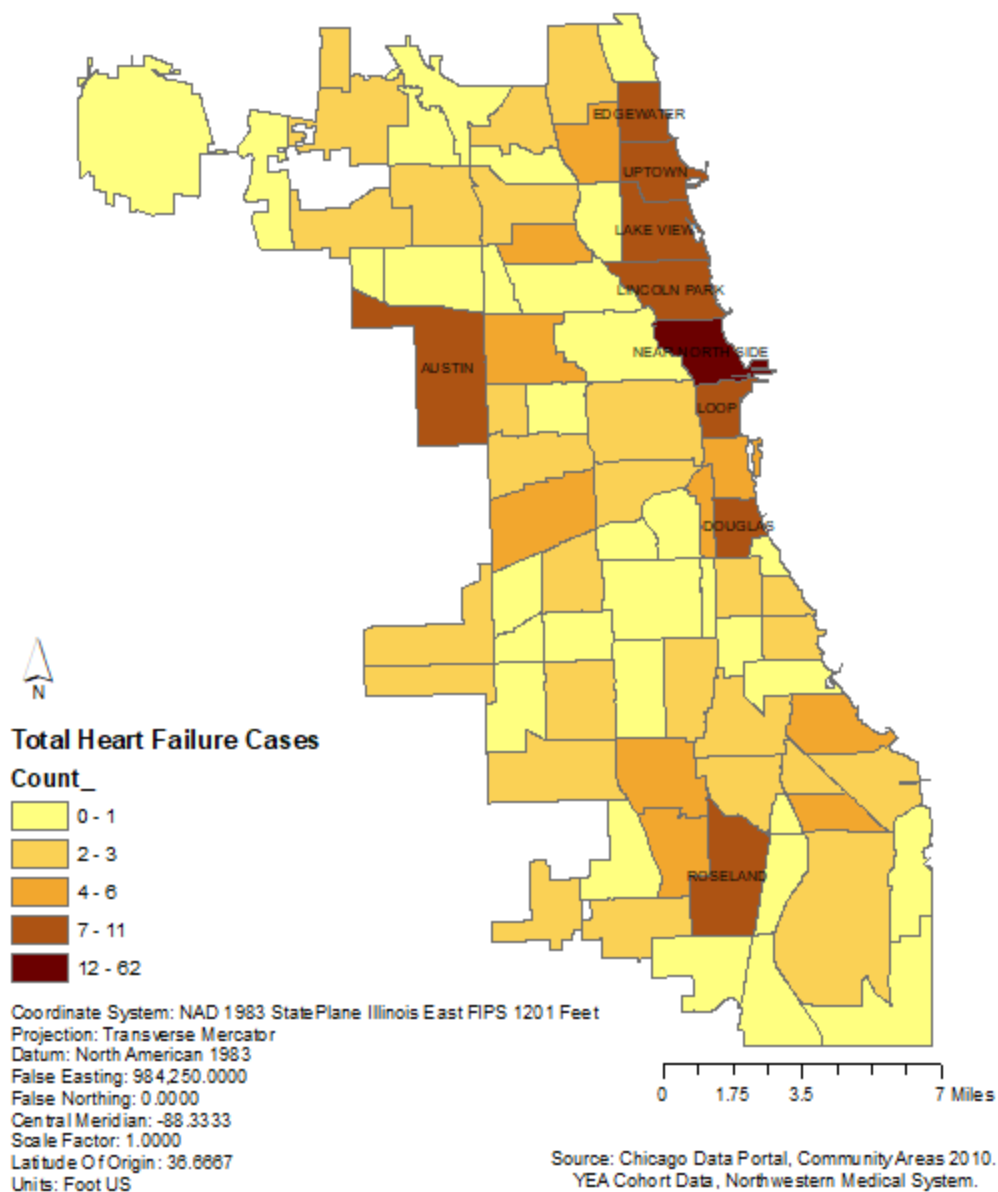


Figure 5: Total Heart Failure Cases Among Breast Cancer Survivors per Community Area (Aged 65+)

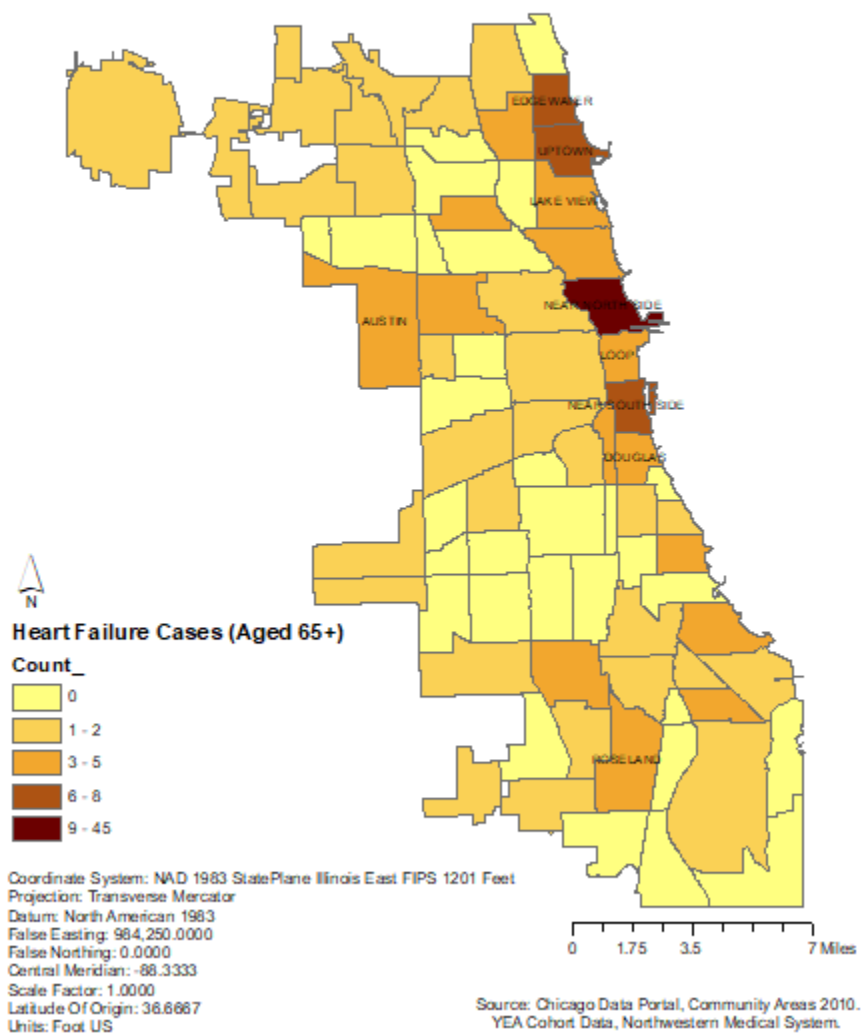


Figure 6: Total Heart Failure Cases Among Breast Cancer Survivors per Community Area (Aged 18-64)

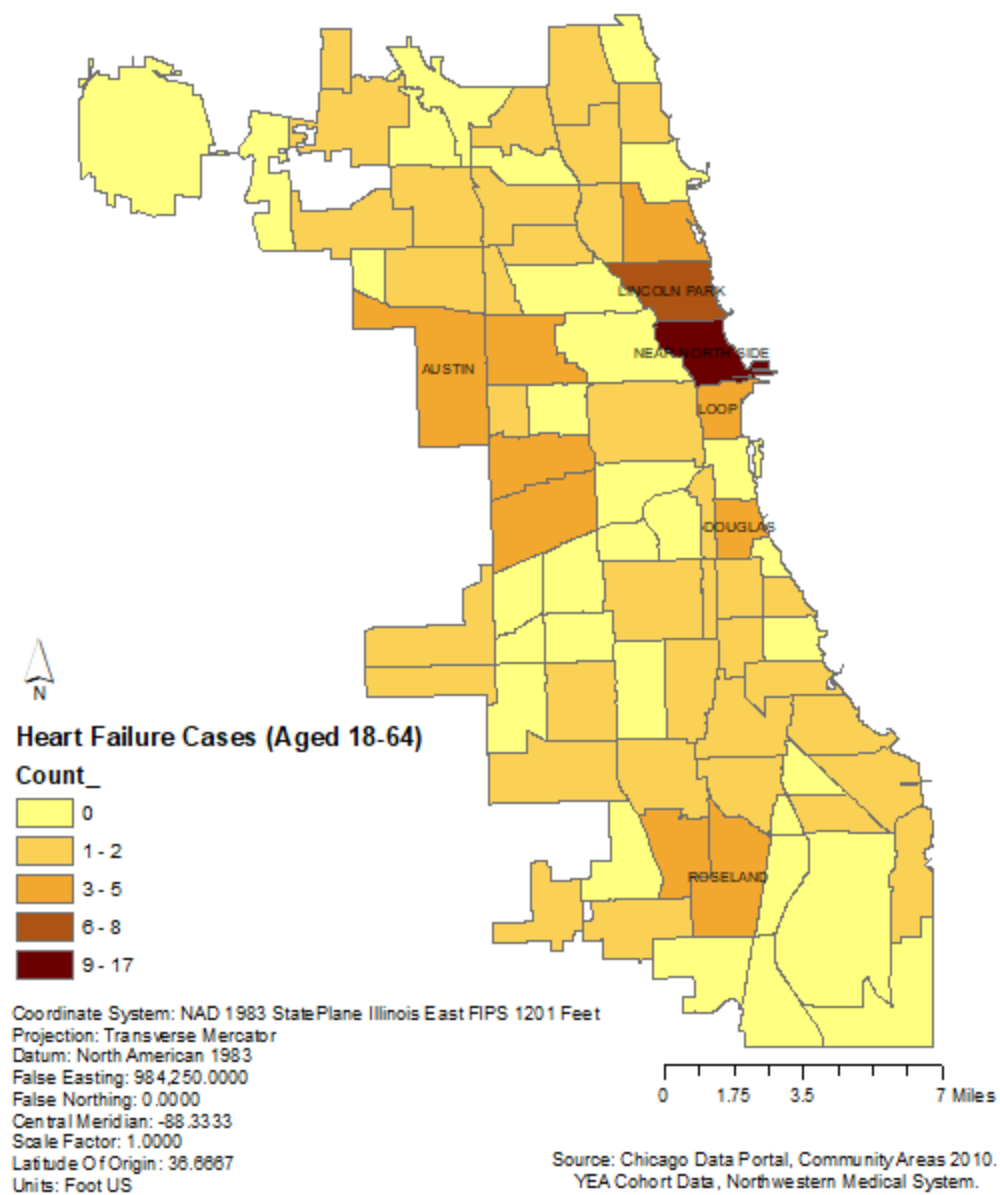


Figure 7: Heart Failure Rates of Breast Cancer Survivors
per Community Area

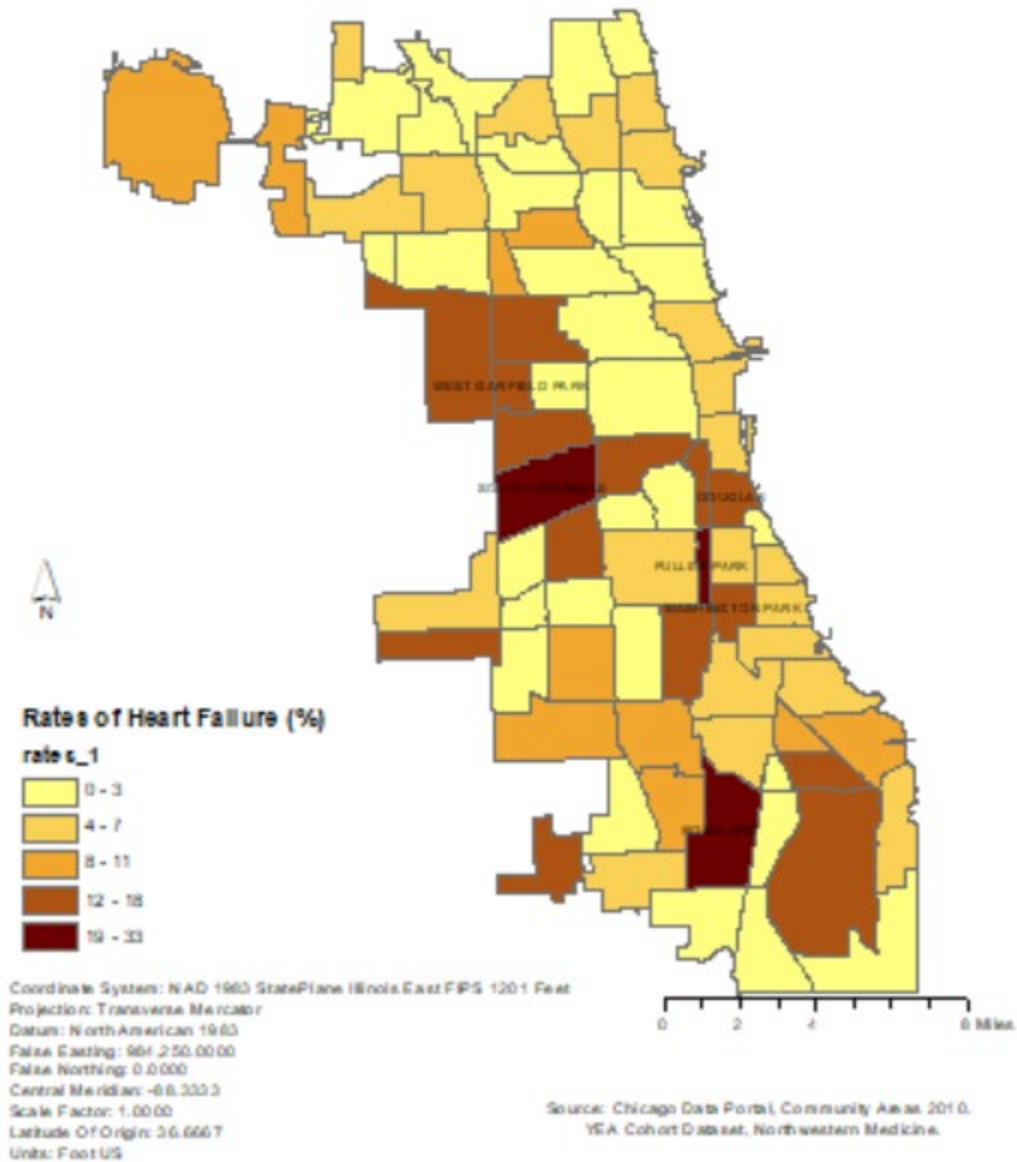


Figure 8: Hot Spot Analysis of Heart Failure Rates of Breast Cancer Survivors

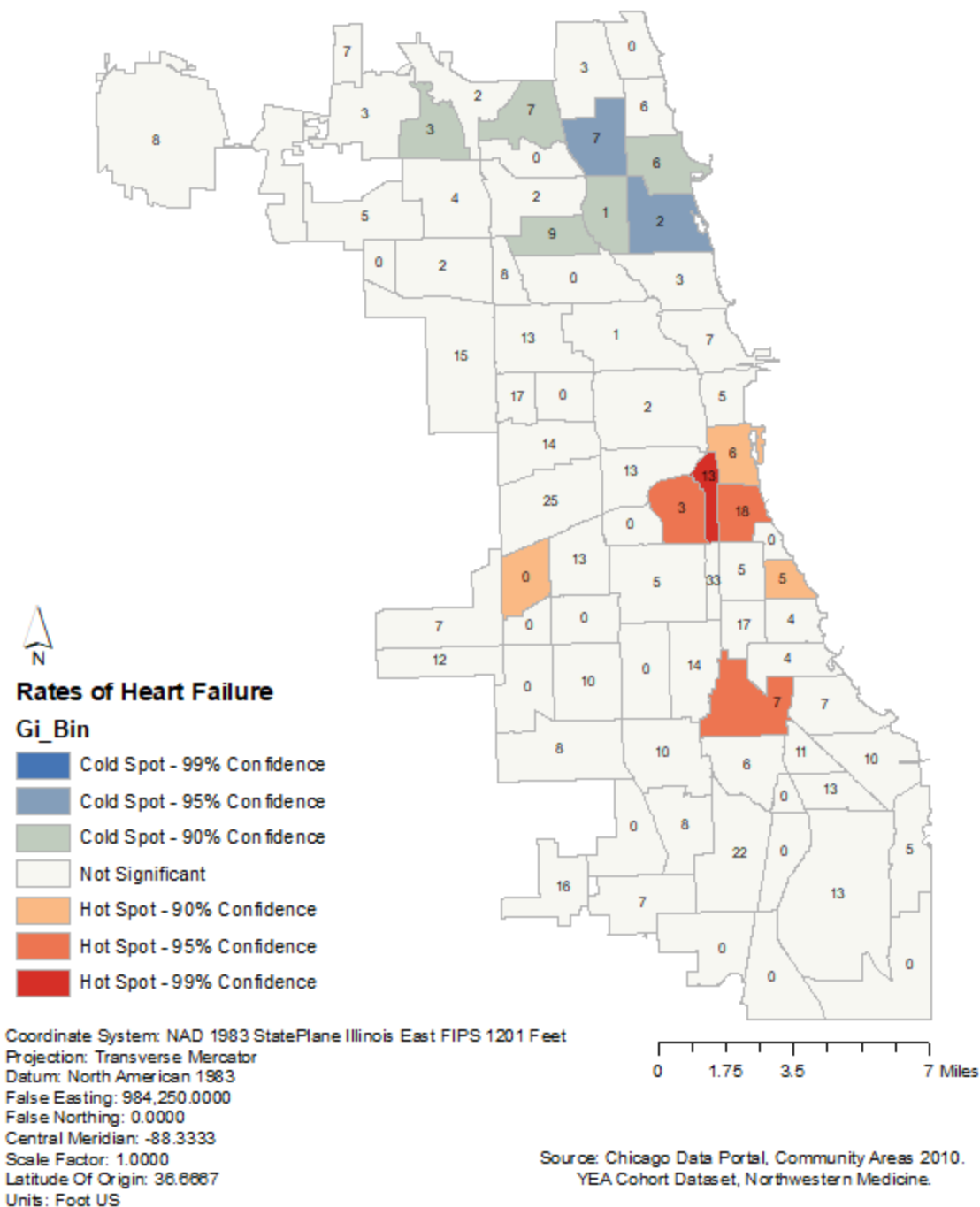


Figure 9: Kaplan Meier Output for Age of Breast Cancer Diagnosis and Heart Failure (above and below 65)

