Breast Cancer in Women: Incidence, Mortality and Treatment Management in Puerto Rico

by

Cristobal Cintron-Vargas

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor in Public Health
(Epidemiology Department)
The University of Michigan
2020

Doctorate Committee:

Professor Sioban Harlow, Chair
Professor Sofia D. Merajver
Associate Professor Rafael Meza

criscintron@umich.edu

ORCID ID: 0000-0002-7272-8450

© Cristobal Cintron-Vargas 2020

DEDICATION

This dissertation is dedicated to all perseverant students in Public Health. For those who think that today has to be the best day and for those who commit to a cause of building everlasting friendships. More specifically, I dedicate this work to my mother Victoria Mercedes Vargas Sánchez. A strong and lovely woman who believes in the power of education as a tool for the poor for having a better and happier life. She has never stopped teaching, even after her forty years' teaching career, now more than ever, over the last years during her latest battle against breast and ovarian cancers. My mother teaches whomever she talks to that cancer, as well as any other big struggle, needs to be fought from day one, without losing any time. Fight, always trusting that research and promptly systematic and unstopped action will work for patients regardless of age and gender. Thanks for being so courageous and teaching me by example, never to fear change, and always to trust that medicine is good as God is good.

ACKNOWLEDGMENTS

This Dissertation was written by Cristobal Cintron-Vargas. This work was supported by the Center of Midlife Science. Special gratitude to Carlos Cintrón and Dr. Diego Zavala from the Puerto Rico Central Cancer Center Special thanks to Dr. Raúl Montalvo (President) and Dr. Waldemar Ríos (Chief Medical Officer) of MSO of Puerto Rico, and Orlando González and Salvador Ayende from MMM Holdings. Special gratitude also to the Office of the President of the University of Puerto Rico and the partners at Advanced BMO, LLC for their support during my doctoral studies. Sincere gratitude to Dr. Roberto Varela, Dr. José Lozada, Dr. Cruz M. Nazario, Dr. Stephen Martin, Dr. Hale Toklu, and Dr. Mike Churuba for their motivation and influence towards completing this achievement. Thanks to the School of Public Health writing lab instructor, Dr. Kirsten Herold.

Special thanks to my mentor Dr. Sioban Harlow, who guided me over the years in this stage of my academic life, and finally, a special acknowledgment for my two faculty advisors, Dr. Rafael Meza, and Dr. Sofia, Merajver for their support and professional feedback for this dissertation. To my beloved wife Johanna and my two great sons Diego and Fabián for their support, trust, and patience over the years.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

ABSTRACT

Background: Data on trends in breast cancer incidence and mortality in Puerto Rico are limited, as is information on therapeutic services available to women with breast cancer on the Island. Such data is necessary to evaluate the success of the recent expansion in health insurance coverage and public health efforts to increase breast cancer screening and reduce breast cancer mortality. Expanding on reports from the Puerto Rico Central Cancer Registry (PRCCR), this dissertation analyzes breast cancer incidence and mortality trends in Puerto Rico for the period 2000-2013 by geographic health service region and clinical tumor characteristics, during which Medicare Advantage was introduced in Puerto Rico. It also evaluates therapeutic services provided over this period in one Medicare Advantage program.

Methods: Breast cancer cases data was obtained from the PRCCR and population data from the Puerto Rican State Planning Board tables. A total of 20,228 females in whom invasive breast cancer was diagnosed during 2000 and 2013 were analyzed by age group, health service region, and clinical characteristics, including histological type, the grade of tumor, and disease stage at diagnosis. Incidence rates were analyzed using Joinpoint analysis to study the trends during this period after age-adjusting to the female population of the United States. In addition, a utilization claims-based analysis was performed to document the frequency of medical and therapeutic services rendered in a Medicare Advantage Health Plan in Puerto Rico, MMM Holdings, from 2007 to 2016 after the introduction of the Medicare Advantage Program.

Results: Incidence rates significantly increased after 2007 with an Annual Percent Change of 3.6% (p-value <0.00016), reaching an incidence rate in 2013 of 81 per

100,000 females. Significant increases were found in rates of infiltrating duct cell carcinoma well and moderately differentiated tumors, in each stage of breast cancer. Mortality rates increased after 2007 with an Annual Percent Change of 2% (p-value = 0.2), reaching a rate in 2014 of 25 per 100,000 females. Increases in mortality were explicitly observed in ductal cell carcinomas and for poorly differentiated and moderately differentiated tumors. Medical and pharmacy services increased for the female Medicare breast cancer population in Puerto Rico. A higher proportion of services and prescriptions, including injectable treatments, were rendered by physicians from their office setting during this time.

Conclusion: The introduction of the Medicare Advantage Program in Puerto Rico has impacted the ascertainment of more breast cancer cases and improved documentation of clinical characteristics of tumors. These findings enhance the understanding of breast cancer in Puerto Rico and guide efforts to improve medical care quality, especially among elderly females with breast cancer. With this study methodology, we expect that describing breast cancer incidence and mortality rates by histological types, grade, and staging will become an integrated section in the reporting of future cancer publications in Puerto Rico. Another recommendation is to increase the awareness among medical providers of the relevance of histological type, the grade of the tumor, and staging when evaluating the preventive services and treatment in breast cancer patients. A detailed evaluation of treatment episodes can be suggested as a next step, complementing the claims-based and electronic medical record information in breast cancer patients in Puerto Rico.

CHAPTER I

Introduction

Studies of breast cancer in Puerto Rico are facilitated by the availability of data collected through the Census Bureau, Vital Statistic records, the Cancer Registry of Puerto Rico, and the CDC's Behavioral Risk Factors Surveillance System. Information concerning incidence and mortality rates is vital for creating awareness about the magnitude of the breast cancer burden in Puerto Rican women for health care providers and the population at large. However, publications describing rates by clinical classifications are scarce in Puerto Rico. This dissertation addresses this matter, thus facilitating patient management quality, based on the 2014's American Society of Clinical Oncology Guidelines for breast cancer.

More specifically, this dissertation focuses on describing the increasing incidence and stable mortality among patients with malignant breast cancer in Puerto Rico, the first and second objectives. We evaluated trends over time by age categories, geographical service region, histologic type, grading, and stage using data from the Puerto Rican Cancer Registry. Of particular interest was whether breast cancer patients were arriving late at diagnosis or with a higher prevalence of aggressive breast cancers, partly explaining the breast cancer mortality rates' stable behavior.

Given that insurance paid claims information provides the opportunity to evaluate diagnostic and treatment modalities, this dissertation's third main objective was to describe the degree of medical and pharmaceutical treatment received in women with breast cancer in Puerto Rico. Due to the absence of this information in the registry data, the methodology used for this aim was the most innovative and challenging aspect

of this dissertation. This chapter's findings and recommendations will contribute to a better understanding of the disease and guide efforts to improve the quality of medical care, especially among elderly females with breast cancer in Puerto Rico.

Dissertation Objective and Specific Aims

Objective

To describe the epidemiology of breast cancer incidence and mortality in PR women and treatment management of breast cancer in a segment of the population insured through Medicare.

Specific Aims

The specific aims of this dissertation were:

1. To describe the overall age-adjusted incidence and mortality rates for breast cancer in Puerto Rico women between 2000 and 2013, stratified by the Health Care Reform's geographical regions.
2. To evaluate trends of incidence and mortality rates between 2000 and 2013 by:
    a. Histologic types
    b. Tumor Grades and
    c. Stage at Diagnosis
3. To describe the frequency of services and treatment modalities among breast cancer patients seen by the Castellana's Medicare Advantage Independent Practice Association from 2007 to 2016.

Background and Significance

In the United States, Non-Hispanic Black and Hispanic women with breast cancer present with the most advanced stages compared to Non-Hispanic whites (American Cancer Society, 2020). Puerto Ricans in the mainland of the United States are 20% to 50% more likely to have received or elected a first course of surgical and radiation treatment not meeting the National Comprehensive Cancer Network standards and have a 20% greater risk of mortality after a breast cancer diagnosis compared to Non-Hispanic whites (Li CI, Malone, 2013).

On the island of Puerto Rico, the most recent state vital statistics report indicates that cancer was the second leading cause of death, with 5,008 cancer deaths occurring in 2008. These deaths represent an age-adjusted death rate of 117.7 per 100,000 inhabitants. Despite the magnitude of overall 2008 cancer mortality in Puerto Rico being lower than in the United States (175.7), mortality is slightly higher than the mortality of 114.8 per 100,000 reported for 2009 in the USA's Hispanic populations (American Cancer Society Report, 2012). Among cancers in women on the Island, breast cancer is the first cause of death, followed by lung cancer (Department of Health of PR (DOH, Vital Statistics Report, 2010).

These disparities in the US and PR cancer rates, especially breast cancer rates, are not clearly understood. In Puerto Rico, significant efforts have been made to promote screening tests. Between 77% and 81% of women over 50 years have a mammogram every two years, figures similar to the USA mainland population (BRFSS, 2018).

Only a limited number of scientific publications on breast cancer in Puerto Rico have addressed these topics, to some extent, as a result of the lack of and delay in published cancer incidence and mortality data from the Department of Health and the State Cancer Registry. The DOH is responsible for the publication of the annual vital statistics report. The most recent one, published on September 16, 2019, on the DOH's website, provides information on the state's 2015 and 2016 mortality experience. For this dissertation, the author was provided preliminary data through the year 2013 following a written request for this data. Thus, the data presented below for the post-2008 period were based on these preliminary data.

Cancer incidence official reports are published bi-yearly on the Island by the Puerto Rico Central Cancer Registry (PRCCR). Several gaps have occurred since SEER funding ended in 1989, and local funding only supported needed technology, personnel, and maintenance of physical facilities for this surveillance. It was not until 2001 that the PRCCR received continuous support from the CDC when generation and publishing responsibility were transferred to the Medical Sciences Campus. The next report was published in 2010, describing the 2000 to 2004 data period, followed by the latest 2015 publication describing the 2008-2012 rates.

For the first time in Puerto Rico, this dissertation conducted a population-based study using Medicare data from Health Insurance claims files of one of the most prominent Independent Practice Association called Castellana Physician Services. We analyzed the distribution of breast cancer cases seen within the Castellana system by year and the related pharmaceutical and medical services utilization during the study period. No study has described, to our knowledge, the pharmaceutical and medical treatment modalities

provided to breast cancer patients since the implementation of the Medicare Advantage program on the Island. Analyzing these patterns will help evaluate the extent of breast cancer treatment guidelines and help identify areas where there is an opportunity for improvement.

Overview

World

While breast cancer rates are higher among women in more developed regions, rates are increasing in nearly every region globally (WHO, 2018). Breast cancer mortality rates have been decreasing in high-income countries, despite increasing or stable incidence rates. The incidence of breast cancer has been increasing in the developing world due to increases in life expectancy, increased urbanization, and adoption of western lifestyles, and population adoption of screening (Nazario and colleagues, 2000). Early detection has been the primary public health strategy to improve survival and help control disease outcomes (WHO, 2018). Although some risk reduction might be achieved with early detection through mammography screening, it cannot eliminate the majority of breast cancer deaths in low- and middle-income countries where breast cancer is diagnosed at late stages.

A study using WHO data, found that 9 out of 32 countries with available data of incidence and mortality showed increasing incidence and reduction in mortality rates, mainly in Northern and Western Europe. Incidence and mortality have decreased in France, Israel, Italy, Norway, and Spain. Incidence and mortality show an increase in Colombia, Ecuador, and Japan. Only death rates have increased in Brazil, Egypt, Guatemala, Kuwait, Mexico, Mauritius, and Moldova (De Santis, 2015). Also, incidence rates have been rising in traditionally low-incidence Asian countries, particularly in

Japan, Singapore, and urban areas of China, as these regions transition toward a Western-style economy and patterns of reproductive behavior (Colditz, 2013).

Puerto Rico

Puerto Rico is a Caribbean Island, a territory of the United States of America with a total population of 3,725,789 based on the 2010 USA Census Bureau. Women represent 52% of the population. In 2010, there were 541,998 women older than 65 years representing 14% of the population. One out of every 11 women born will be diagnosed with cancer in their lifetime, with one-half of new cancer cases occurring in women aged 65 years and over (PRCCR, 2015). Recognizing the increasing cancer trends, public health officials in 1994 started a Health Reform initiative to increase access to services and reduce health disparities between the public and private healthcare sectors (DOH of PR, 2000, personal communication with Secretary of Health, Puerto Rico). More prevention strategies were targeted to the public sector to reduce the number of new cancer cases in the population and address other health-related conditions.

Furthermore, in 2006, the Island's Medicare population started receiving the benefits of the new Medicare Advantage (MA) program. By 2012, the Medicare Advantage program had succeeded in enrolling close to 80% of the Medicare population (Keyser, 2014). MA private companies are now locally administering screening services provisions and supporting health care providers in cancer treatment modalities for most Medicare beneficiaries. Data from the Behavioral Risk Factor Surveillance System suggests an improvement in breast cancer screening, as mammography prevalence increased from just 61% in 1996 to 79% in 2012 among women aged women 50 years and older (BRFS, 2015).

Although MA coverage is now widely available across the Island, a higher prevalence of low socio-economic disparities exists among the senior population who have had scarce health resources for decades (Oficina Procuradora de la Vejez, PR 2017). The program will seek to enhance access to services by having Medicare members access close to 10,000 providers from multiple specialties who now all implement Medicare guidelines when servicing this population.

Epidemiology of Breast Cancer in the USA and Puerto Rico

Epidemiology of Breast Cancer in the USA

Besides skin cancer, breast cancer is the most commonly diagnosed cancer among women in the United States, accounting for 250,520 new cases in 2017, or approximately 30% of all incident cancers (CDC, 2020). About 1 in 8 U.S. women (about 12%) will develop invasive breast cancer throughout their lifetime (Breast Cancer Org. 2020 and CDC Website). https://www.cdc.gov/cancer/breast/statistics/index.htm.

Regarding cancer deaths each year in the United States, about 42,170 women, or one in 39 women (3%), are expected to die of breast cancer, making it the second-leading cause of cancer deaths among American women (Breast Cancer Org. 2020) . Mortality rates have declined over the past 50 years, but since 2007, rates have remained steady (Breast Cancer Org, 2020). The lifetime risk of dying of breast cancer is approximately 3.4% (Colditz, 2013; and Breast Cancer Org, 2020). These decreases are attributable to treatment advances, earlier detection through screening, and increased awareness.

Puerto Rico

Breast cancer is the most commonly diagnosed cancer in Puerto Rican females and the second leading cause of death among females in Puerto Rico after cardiovascular diseases (DOH, Vital Statistics, 2010). The adjusted incidence of breast cancer has risen more than six-fold over the past sixty years. In 1950, fewer than 100 new cases of breast cancer were diagnosed in Puerto Rico. The average age-adjusted incidence rate for the 1950-1954 period was 12.8 per 100,000 females. In 2010, 1904, breast cancer cases were diagnosed for an age-adjusted incidence rate of 77.6 per 100,000 females. This represents a 506% increase in breast cancer risk (percent change) in 60 years. Although screening rates in Puerto Rico are increasing, there is evidence of poor compliance in following mammography guidelines among providers that manage low income-middle age women (Sanchez, 2002). Failure to screen may contribute to advanced stages of breast cancer at the time of diagnosis, resulting in higher mortality rates. Patient characteristics and system delays in receiving treatment after diagnosis significantly contribute to the observed differential in survival in medically under-served or impoverished patients (Caplan, 2014).

Breast Cancer Incidence

As stated above, 1,904 new breast cancer cases were diagnosed in 2010 for a crude incidence rate of 98.2 per 100,000. The age-adjusted incidence rate was 77.6 per 100,000 compared to 84.2 in the USA (Source, PRCCR as of August 2013). Breast cancer accounted for 29.7% of all female cancers between 2006 and 2010. Based on the incidence rates from 2006 to 2010, “8.6% of women born today will be diagnosed with cancer of the breast during their lifetime,” states the PRCCR report. Between 1987 and 2010, the incidence rate of invasive breast cancer increased an average of 1.3% a year

while the “in-situ” breast cancer rates increased 8.5% a year, possibly explained by the increase in early detection efforts with screening mammography (PRCCR, 2013).

Mortality

During 2010, 5,197 deaths were reported on the Island. Of these, 2,927 (56.3%) were among women. Breast cancer accounted for 18.1% percent of all deaths in women in that year. A total of 411 deaths of breast cancer in 2010 accounted for a crude mortality rate of 21.1 per 100,000. The age-adjusted rate was 15.9. Mortality rates have decreased an average of 0.1% a year from 1987 to 2010 (PRCCR, 2013). In 2008, the Vital Statistics Reports from the Department of Health reported 416 breast cancer deaths. The Cancer in Puerto Rico 2006-2010 report stated that an average of 412 women with breast cancer died from breast cancer each year during 2006 and 2010 for a crude death rate of 21.0 and an age-adjusted rate of 18.5 per 100,000 females adjusting for the USA population.

Total cancer deaths and breast cancer deaths among females occurred most often among older women in Puerto Rico, as observed in the USA mainland. Although rising slightly, breast cancer mortality rates remained lower in Puerto Rico than in the USA among all age groups.

It’s important to highlight that breast cancer is the leading cause of cancer death among Hispanic women in the USA (American Cancer Society, 2014). From 2000 to 2009, breast cancer death rates decreased by 1.6% per year among Hispanic women, and by 2% per year among non-Hispanic white women (American Cancer Society, 2014).

Even though progress has been made in reducing breast cancer mortality in Puerto Rico, a significant number of potentially preventable deaths are still occurring on

the Island, and significant effort is needed to reduce the rate and reach state health objectives.

Survival

United States survival rates for breast cancer have increased slightly since the mid-seventies. Data from 2019-2020 in the USA shows that survival rates in women diagnosed with breast cancer are 91% at five years after diagnosis, 84% after ten years, and 80% after 15 years (American Cancer Society, 2019).

The overall relative five-year survival rates for 2009-2015 were 92% in Whites versus 83% in Blacks over the same period. Some of the possible reasons for better survival in Whites are that Whites seek medical attention earlier than Blacks (Oii and colleagues, 2011). First, the time between symptoms and presentation seems to account for differences in survival rate or diagnosis stage. Secondly, less aggressive modes of treatment are used for Black than Whites. Third, a higher proportion of poorly differentiated tumors are found among Blacks who often have a poorer nutritional status, including high relative weight (Oii and colleagues, 2011). In contrast, White and Hispanic survival rates are similar, independent of the stage of disease and difference in tumor histology (Oii and colleagues, 2011).

Breast Cancer Survival in Puerto Rico

Only one study evaluated breast cancer survival in Puerto Rico, a hospital-based study in the Oncologic Hospital of Puerto Rico (Ortiz et al., 2013). Among patients with localized stage, women with Triple Negative (TN) breast cancer had a higher risk of death (adjusted hazard ratio [HR]: 2.57, 95% confidence interval [CI]: 1.29–5.12) as compared to those with Luminal-A status, after adjusting for age at diagnosis (Ortiz et

al., 2013). Among women with regional/distant stage at diagnosis, those with TN breast cancer (HR: 5.48, 95% CI: 2.63–11.47) and those with HER-2+, including HER-2 overexpressed and Luminal-B, (HR: 2.73, 95% CI: 1.30–5.75) had higher mortality. (Ortiz et al., 2013).

Histogenesis of Breast Cancer

To improve breast cancer patients' prognosis and avoid treatment failure, it is essential to understand the relationship between pathologic tumor characteristics such as histologic class, nuclear grade, and disease staging. Pathologists classify tumor cells by cell growth and their microscopic features to classify them on aggressiveness and the potential to metastasize. There are four types of prognosis categories according to histologic types (Rosa,1981):

Type I (Noninvasive):
- Ductal Carcinoma NOS
- Lobular carcinoma in situ (LCIS-lobular neoplasia)

Type II (Invasive, circumscribed margins, rare metastasis):
- Pure mucinous carcinoma
- Tubular Carcinoma
- Invasive Papillary Carcinoma
- Medullary Carcinoma

Type III (Invasive, moderately metastasizing):
- Invasive ductal carcinoma NOS
- Intraductal carcinoma with invasion
- Invasive lobular carcinoma

Type IV (Invasive, undifferentiated carcinoma):
- Tumors indisputably invading blood vessels regardless of the type

The relative proportions of each tumor type have been estimated in various studies (Page and Anderson, 1987; Elis et al., 1992 and Fisher et al.,1993). The vast

majority are adenocarcinomas, of which most are classified as infiltrating ductal cell carcinomas. Slight variation is seen among different ethnic groups, with medullary carcinomas occurring more frequently in Hispanic, Black, and Chinese women than in white women (Kelsey, 1993; Li, 1993). All the above histologic subgroups can exist in combination with ductal carcinomas NOS; coexistence has been estimated to occur in some 17% to 30% of cases.

Tumor Grade

A well-known quotation summarizes the importance of tumor grade: “The more atypical the structure, the better the prognosis” (Ashikari, et al, 1974). The tumor grade is a score that tells us how pathologically different the tumor cells are from a normal and healthy breast cell. The correlation between the microscopic differentiation of tumors and the tumor’s clinical behavior was first observed by Duncan (quoted in Azzopardi,1979). Bloom and Richardson used the pattern of tubular arrangement, the nuclear pleomorphism, hyperchromasia, mitotic ratio, and axillary lymph node status to independently assess a grading category (Bloom and Richardson, 1957):

- Well-differentiated (Grade 1 or low grade),
- Moderately differentiated (Grade 2 or intermediate grade),
- Poorly differentiated (Grade 3 or high grade) and
- Undifferentiated (Grade 4 high grade).

This gradient of aggressiveness is also found within these breast cancer subtypes. The higher the grade, the faster and the more disorganized is the growth in new cancer cells.

Staging at Diagnosis

The stage of the disease has been identified as an important predictor of patient survival. Staging refers to the classification of breast cancer by its anatomical extension. The rationale is that cancers progressively extend, and progression is related to prognosis (Donegan, 1995). Staging facilitates treatment selection and comparison of treatments across similar cases. The USA SEER Cancer Registry structures stages in the following categories:

- In situ
- Localized
- Regional by direct extension only
- Regional lymph nodes only
- Regional by BOTH direct extension AND lymph node involvement
- Distant site(s)/node(s) involved.
- Benign/borderline
- Unknown if extension or metastasis (un-staged, unknown, or unspecified)

Using this gradient of aggressiveness facilitates understanding the distribution of these breast cancer subtypes, focusing on higher grades with faster and more disorganized growth in new cancer cells. Based on the SEER database, the American Cancer Society reported that the USA's 5-yr survival rates were 99% for localized tumors, 86% for regionalized, 27% for distant tumors, and all stages combined 90% (American Cancer Society, 2020). However, the 5-yr survival rates are not stratified systematically by the SEER registry. Historically, a 1971 study reported a 5-yr survival rate of 81% among breast cancer patients with Grade I, 50% percent among patients with Grade II, and 35% among patients with Grade III (Bloom, 1971). In more recent years, the research has identified the benefits of linking the information of grade of the tumor and the patients' stage at diagnosis, which can better predict the survival outcomes in breast cancer patients (Henson and colleagues, 1991).

Medical Care Access in Puerto Rico

In the 1970s, Puerto Rico's government-funded public health system began to weaken while the private sector began to grow (Arbona and Ramírez de Arellano, 1978). The public health system became increasingly decentralized and fragmented. Early evaluation of Puerto Rico's Medicaid program showed that approximately 12 percent of participating physicians billed for 43 percent of all Medicaid visits (Arbona and Ramírez de Arellano 1978). Access to health services in Puerto Rico changed significantly starting in 1994 when the Government established a Health Reform giving health insurance companies an essential role in administering health service provisions to the medically indigent population. By 2000, the Medicare Advantage program had successfully penetrated close to 80% of the Medicare population. These Advantage companies were locally administering screening services and supporting health care providers in cancer treatment modalities for most of the Medicare Population. This dissertation analyzes the incidence and mortality rates by service region.

Methods

Overview

For Aim 1 and 2, we obtained de-identified data from all breast cancer cases from the Puerto Rico Central Cancer Registry (PRCCR) from 2000 to 2013. The information included age, gender, the township of residence at the time of diagnosis, and the following clinical characteristics: stage at diagnosis, histology, and tumor grade. Date of diagnosis and information on vital status, including death date for deceased cases, were also obtained. Information on the population size and age structure of the Puerto Rican population was obtained from the US census.

The Puerto Rico government has designated eight service health regions recognized by the health plans that serve the indigent population. Age-adjusted incidence and mortality were calculated overall and by these services regions to provide a more familiar geographical analysis for government and private companies administering services to the population. Lastly, incidence and mortality trends were stratified and analyzed by histologic type, tumor grade, and stage at diagnosis.

Registry Study

In Part I, we used de-identified data provided by the Cancer Registry. The Data was requested from the PRCCR using their standard protocol forms *"APPLICATION TO ACCESS PRCCR DATA" (see Appendix 1 & 2)*. The request was considered Level II, which stands for "Data files containing individual, record-level data with personal identifiers, to be used for purposes of record linkage, either electronic or manual, but not direct patient contact. Once the record linkage was complete, the personal identifiers were removed from the data set. The following variables were obtained from the PRCCR: Patient Sex, Age at Diagnosis, Cancer type, Date of diagnosis, Date at death, Township of Residence, and the following disease clinical characteristics: Stage at diagnosis, Histologic Type, and Grade of the tumor.

The Puerto Rico population census estimates and specific female estimates by municipality were downloaded from the Census Publicly available files in the USA Census website: https://www.census.gov/popest/data/datasets.html. Population estimates from the State Planning Board public available files by municipality for the 2000 data files were used to generate regional and total population for the Island by age.

Incidence and mortality rates were generated using information from new cases from the Cancer Registry over the population estimates obtained from the Planning Board [Junta de Planificación]. Cancer Registry data were weighted with USA Census population estimates for Puerto Rico to standardize rates and make them comparable to the USA rates. Annual age-adjusted incidence and mortality rates adjusted to the USA 2000 population were calculated using counts from the PRCCR data and population size based on the US census, for all cases and by clinical characteristics for the whole island and by health region using SAS 9.4. Trends for the Island as a whole and each health region were graphed over time to assess temporal trends using NCI's Joinpoint Regression Program (Version 4.1.0).

Services and Treatment Modalities in breast cancer

This dissertation's third aim was to perform a ten-year utilization profile of Medicare breast cancer patients in Puerto Rico. To achieve this, we analyzed breast cancer patients in Puerto Rico. We analyzed patient characteristics and their related pharmaceutical and medical services utilization from 2007 to 2016.

To address this aim, demographic, medical, and pharmacy claims files were analyzed for a Medicare Advantage Independent Practice Associations (IPA) in Puerto Rico called Castellana Physician Services (see Appendix 2 & 3). Castellana is an Independent Physician Network of almost 400 Primary Care Physicians in Puerto Rico. The Provider's groups are mainly General Practitioners with specialties in General Medicine, Family Medicine, and Internal Medicine. The providers are grouped into four Regions of the Island: Northeast, East, Metronorth, and Southeast. These providers exclusively provided services to close to 60,000 members enrolled in the two Medicare

Advantage Health Plans on the Island (MMM and PMC Medicare Choice). The Castellana Central Office provides administrative support to each of the 400 providers, with a group of Regional Medical Directors and the nursing and administrative staff facilitating the communication with the Health Plan's administration. For January 2014, Castellana's membership consisted of 55,219 active members distributed in four Island regions, of which approximately 30,000 were female members. Each of the members received services from these Primary Physicians and used the Health Plan Contracted Specialists and/or other Providers' Networks to obtain additional clinical services. Findings in this study population thus likely represent the best healthcare standards in Puerto Rico for the elderly population.

This is the first study of claims data using an IPA specific Medicare population from the only NCQA certified Health Plans in Puerto Rico (MMM and PMC). Castellana served MMM and PMC exclusively, and Castellana's population represents a significant segment of the market and the biggest IPA. The study's findings apply to the Health Reform Regional distribution, which the government uses to allocate the funding for state funds for health insurance companies. Health plans and government decision-makers will be able to use the results as benchmarks for future surveillance.

Chapter II presents breast cancer incidence and mortality trends by geographic region. Chapter III presents the trends by the clinical characteristics of the disease. Chapter IV presents the analysis of the Castellana claims data. Chapter V discusses the main findings, discusses the policy implications of these findings, and makes recommendations for future research needs.

References

Althuis M, Dozier J, Anderson W, et al. Global trends in breast cancer incidence and mortality 1973–1997. International Journal of Epidemiology 2005; 34:405–412.

American Cancer Society. Cancer Facts & Figures for Hispanics/Latinos 2012-2014. Atlanta: American Cancer Society, 2012

American Cancer Society. Breast Cancer Facts & Figures 2019-2020. American Cancer Society, January 2020

American Cancer Society. Survival Rates for Breast Cancer; https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-survival-rates.html; January 2020.

Arbona, Guillermo and Ramirez de Arellano Anette: Regionalization of Health Services: The Puerto Rican Experience; Oxford University Press, 1978.
Ashikari, R., Park K., Huvos A.E, et al. Paget Disease of the Breast; Cancer 26;680, 1974.

Azzopardi, J.G Problems in Breast Pathology. Philadelphia. W.B Saunders, 1979.

Banegas M, Leng M, Graubard D et al., The risk of developing invasive breast cancer in Hispanic women. Cancer 2013;(7): 1373-1380.

Becerra J., Atrash H, Perez N, and Saliceti J. Low birthweight and Infant Mortality in Puerto Rico. American Journal of Public Health.Vol. 83, No. 11, 1993.

Bloom, HJG, and Field JR. Impact of tumor grade and host resistance on the survival of women with Breast Cancer. Survival in Breast Cancer, September 1971.

Bloom and Richardson, 1957. Histologic grading and prognosis in breast cancer. A study of 1709 cases of which 359 have been followed for 15 years. Br. J Cancer, 2:253,1957.

Breast Cancer Org. U.S. Breast Cancer Statistics | Breastcancer.org. *June 25, 2020.*

Brouckaert O, Wildiers H, Floris G et al. Update on Triple-Negative breast cancer: prognosis and management strategies. 2012; International Journal of Women's Health. Open Access to Full Article.

Burstein H, Temin S, Anderson H et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. Journal of Clinical Oncology. 2014; 32(21):2255-2269.

Bush E., Kemeny M, Fremgen A, et al.; Patterns for breast cancer care in the elderly. Cancer July 1, 1996; Volume 78, No 1.

Caplan L. Delay in breast cancer: implications for stage at diagnosis and survival. Frontiers in Public Health. Review Article. 2014.

Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health. BRFSS Prevalence & Trends Data [online]. 2018. [accessed Dec 20, 2020].
URL: https://www.cdc.gov/brfss/brfssprevalence/.

Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health. BRFSS Prevalence & Trends Data [online]. 2015. [accessed Dec 20, 2020].
URL: https://www.cdc.gov/brfss/brfssprevalence/.

Centers for Disease Control and Prevention and National Cancer. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2019 submission data (1999-2017): U.S. Department of Health and Human Services, Institute; www.cdc.gov/cancer/dataviz, released in June 2020.

Cokkinides V. Bandi P, Siegel R. Cancer-related risk factors and preventive measures in US Hispanics/Latinos. CA A Journal for Physicians**;** 62(6) 353-363.

Chiriko T, Lopéz-García J, Cintrón-Vargas C, et.al. Evaluation of Breast Cancer care under Puerto Rico's Health Care Reform. Journal of Health Care for the Poor & Underserved 2007; 18(1): 116-38.

Colditz G, Breast Cancer Epidemiology, and Risk Factors. 2013.
http://emedicine.medscape.com/article/1697353-overview#aw2aab6b3.

Colditz G and D Craig A. Breast cancer Epidemiology and Risk Factors, Medscape 2013. http://emedicine.medscape.com/article/1697353-overview.

Colon E, Reyes J, González-Keelan C et al. Prevalence of steroid receptors and HER 2/neu in breast cancer biopsies of women living in Puerto Rico. Puerto Rico Health Sciences Journal 2002; 21(4): 299-303.

Department of Health of Puerto Rico. 2010. Vital Statistics Report. San Juan, Puerto Rico.

Department of Health of Puerto Rico. Title V Block grant application, San Juan Puerto Rico 2000.

DeSantis, Carol E. Bray Freddie, Ferlay, Jacques, et al., International Variation in Female Breast Cancer Incidence and Mortality Rates. Cancer Epidemiology, Biomarkers & Prevention, 2015.

Donegan, William, Staging and Primary treatment. Cancer of the Breast. W.B Sanders Company. Page 375, 1995.

Dutil J, Colon-Colon J, Matta J, et al. Identification of the prevalence BRCA1 and BRCA2 mutations in the female population of Puerto Rico. Cancer Genetics 2012; 205(5): 242-248.

Elis et al., 1992; Prognostic factors in breast cancer. Histopathology, 20:479,1992.

Fisher et al., 1993: Pathologic findings from the national surgical Adjuvant Breast Project. Cancer, 76:2507,1993.

Giraldo-Jimenez M, Cabanillas F, Negron V, et al. Triple Negative breast cancer: a retrospective study of Hispanics residing in Puerto Rico. Puerto Rico Health Sciences Journal 2012; 31(2): 45-51.

Habel L. and Stanford. Hormone Receptors and Breast cancer. Epidemiologic Reviews: 1993 15(1) 209-219.

Henry Keyser Foundation, 2014. https://www.kff.org/medicare/issue-brief/a-dozen-facts-about-medicare-advantage-in-2020/

Henson DE, Ries L, Freedman LS, and Carriagal M. Relationship among outcome, stage of disease, and histologic grade for 22,616 cases of breast cancer. The basis for a prognostic index; Cancer 1991 Nov 15;68(10):2142-9.

https://gis.cdc.gov/Cancer/USCS/DataViz.html

Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin*. Mar-Apr 2008;58(2):71-96.

Kelsey J. Breast Cancer epidemiology: summary and future directions. Epidemiologic Reviews 1993, 15(1) 256-263.

Kelsey Jennifer and Horn-Ross Pamela; Breast Cancer: Magnitude of the Problem and Descriptive Epidemiology. Volume 15. No 1. Epidemiologic Reviews; 1993.

Knight WA, Livingston RB, Gregory EJ, et. 1977; Estrogen receptor as an independent prognostic factor for early recurrence in breast cancer. Cancer Research (12): 4669-71.

Li C, Malone KE, and Daling JR. Differences in breast cancer Stage and Treatment and Survival by Race and Ethnicity. Arch Intern Med. 2003: 163(1):49-56.

Nazario CM, Figueroa-Valles N, Rosario R. Breast Cancer Patterns and Lifetime risk of developing breast cancer among Puerto Rican Females. Puerto Rico Health Sciences Journal 2000; 19(1): 7-13.

Oficina de Procurador de la Vejez, Perfil demográfico de la Población de 60 años o más en Puerto Rico, 2017.

Ooi SL, Martínez ME, Li CI. Disparities in breast cancer characteristics and outcomes by race/ethnicity. Breast Cancer Res Cancer Res Treat. Jun 2011;127(3):729-738.

Ortiz A, Calo, Figueroa, Suarez; Disparities in breast cancer in PR among Hispanics, Non-Hispanic Whites and non-Hispanic Blacks, in the USA 1992-2004. 2010: Breast Journal 16(6):666-8:

Ortiz A, Frías O, Perez J, et al.; Breast cancer molecular subtypes and survival in a hospital-based sample in Puerto Rico; Cancer Medicine, 2013 343-350.

Page and Anderson, Diagnostic histopathology of the Breast. NY Churchill Livinston, pp 188-205.

Peredo, R. Sastre G Serrano J et al, Her-2/neu oncogene expression in Puerto Rican females with breast cancer. 2001: Cellular & Molecular Biology. 47(6):1025-32.

Perez-Mayoral J, Pacheco-Torres A, Morales L, et al. Generic Polymorphisms in RAD23B and XPC modulate DNA Repair capacity and breast cancer risk in Puerto Rican women. 2013: Molecular Carcinogenesis. 52 Suppl 1: E127-38.

Richman, Eli. Medicare Advantage enrollment soared in Puerto Rico. Now it's starving the island's healthcare system, Aug 8, 2018. Interview with the President of the Puerto Rico Medicare Advantage Coalition. https://www.fiercehealthcare.com/payer/puerto-rico-s-medicare-advantage-participation-through-roof-but-program-s-low-reimbursement

Rosai J., Ackerman's Surgical Pathology. 6th edition. St Louis, C.V. Mosby, 1981.

Sańchez Ayéndez M, Davila AL, Bustillo M, Nazario CM, Larriuz MC, Martínez-Paz G. Análisis cualitativo sobre el cumplimiento con mamografía de cernimiento de mujeres de edad mediana en Puerto Rico [Qualitative analysis on screening mammography compliance among middle-aged women in Puerto Rico]. P R Health Sci J. 2002 Sep;21(3):221-31. Spanish. PMID: 12243113.

Tortolero-Luna G, Zavala-Zegarra D, Pérez-Ríos N et al (2013). Cáncer en Puerto Rico, 2006-2010. Puerto Rico Central Cancer Registry. San Juan, PR.

WHO, Breast cancer, Early Diagnosis and Treatment, 2018. https://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en/

Wittliff J, Hormone, and Growth Factors Receptors. Cancer of the Breast. Edited by Donegan & Spratt. W.B. Saunders Company, Philadelphia; 1995.

CHAPTER II

Age-adjusted incidence and mortality rates for malignant breast cancer in Puerto Rico between 2000 and 2013, stratified by geographical regions of the Health Care Reform

Introduction

Breast cancer incidence in Puerto Rico has been significantly increasing by 1.5% during the period of 1987 to the year 2012, while for the same period, mortality decreased by 0.1% a year (Zavala 2015). *Cancer in Puerto Rico 2008-2012*, the most recent published report, states that breast cancer is the most commonly diagnosed cancer among females with an average of 1,971 new malignant cases every year. Breast cancer accounted for 29.6% of all cancers in women and 19% of all cancer deaths, with an average of 423 deaths per year. Similarly, an independent study on patterns of lifetime risks on breast cancer reported that the age-adjusted breast cancer incidence rate (per 100,000) in Puerto Rico increased from 15.3 in 1960-1964 to 43.3 in 1985-1989. The age-adjusted breast cancer mortality rate (per 100,000) increased from 5.7 to 10.6, comparing the same two time periods (Nazario, 2000). Despite the government's and private health insurance companies' efforts to promote awareness of early detection and availability of screening and treatment options among different stages of diagnosis, the number of breast cancer cases has been increasing with a minimal effect on the reduction of breast cancer deaths in the Island.

Puerto Rico (PR), a territorial Caribbean island of the United States of America, has a total population of 3,725,789 based on the 2010 USA Census Bureau (USA Census 2010). Women represent 52% of the population. In 2010, 305,577 women were older than 65 years, representing 8% of the population. The proportion of women in this age

group in 2010 increased by 31% compared to the 2000 Census (US Census 2010). Based on the most recent published data from the Puerto Rico Central Cancer Registry (PRCCR), 1 out of every 11 women born will be diagnosed with cancer in their lifetime, with one-half of new cancer cases occurring in women aged 65 years and over. Recognizing the increasing cancer trends, public health officials needed a new prevention strategy to reduce the number of new cancer cases in the population and address other health-related conditions.

The health system in Puerto Rico consists of two components. On one side, private hospitals, pharmacies, and local providers offer a fee-for-service model. In parallel, the public sector -- with public hospitals, emergency centers, clinics, and secondary and tertiary hospitals that provide free service across the Island -- serves the poverty-level indigent population. The government's substantial cost, high levels of bureaucracy, and complaints of long waits for specialty services contribute to dissatisfaction with the public health system (DOH, Title V Block Grant, 2017).

In 1994, PR started a Health Reform initiative, which refers to the territory's Medicaid plan that is a subset of the larger governmental healthcare delivery system, as a strategy to increase access to services and to reduce health disparities, such as infant mortality rates, between the public and private healthcare sectors. For example, the infant mortality for the Puerto Rico birth cohorts 1986/1987 through 1989/1990 for the public sector was 16.5 per 1,000 live births as compared to 7.5 per 1,000 live births for the private sector (Becerra,1993). The Health Reform initiative had three objectives: (1) reduce PR's healthcare footprint by selling tertiary and secondary health facilities to the private sector; (2) increase the Department of Health's (DOH) promotion and prevention

strategies for healthy lifestyles and early cancer detection and treatment; and (3) delegate the administration and managed care activities to the private sector under the oversight of a new government agency called “Administración de Seguros de Salud” (ASES) (DOH-Title V Block Grant, 2017)

Briefly, the Health Reform initiative started its implementation in 1994 in the east region and concluded in 2000 in the San Juan Region (Figure 2.1). The government grouped Puerto Rico’s 78 municipalities into ten (10) service regions. Each region was assigned to a different health insurance company to increase competition, improve access to care, control costs, and avoid monopolizing the services within the Island.

In 2006, the new Medicare Advantage (MA) program arrived on the Island. By 2012, the Medicare Advantage program had succeeded in enrolling close to 80% of the Medicare population, a total of 483,978 individuals (Henry Keyser Foundation, 2014). These MA private companies are now locally administering screening services provision and supporting health care providers in cancer treatment modalities for most of the Medicare beneficiaries.

Although MA coverage is widely available across the entire Island, socioeconomic disparities among this senior population persist in some geographical regions, for example in the Southeast region. Politicians and community leaders have called the Southeast region the “Ruta del Hambre” (i.e., the Hunger Route), given that the government and private sector have not invested in this area for decades (“El nuevo día” and Medicaid and Medicare Advantage Products Association of PR 2015).

Puerto Rico Cancer Registry

The Puerto Rico Cancer Registry was established in 1951 and is one of the oldest cancer registries in Latin America (Tortolero-Luna 2013). It attained many achievements, including becoming part of the U.S. Surveillance, Epidemiology, and End Results (SEER) Program from 1973 to 1989. However, in 1989, the registry lost its SEER membership due to its inability to keep up with the SEER's technology requirements. From 1989 to 1997, the registry operated with limited government funds, resulting in sparse publications of statistical reports. It was not until 2001 that the new Puerto Rico Central Cancer Registry (PRCCR), under the University of Puerto Rico Medical Sciences Campus administration, began receiving continuous support from the U.S. Centers for Disease Control and Prevention (CDC) for systematic operation. In 2012 PRCCR started bi-annual publishing reports with crude 5-year cancer incidence rates for PR and its 78 municipalities (Figure 2.1).

Studies of breast cancer in Puerto Rico are facilitated by the availability of data collected through the Census Bureau, the vital statistics records, and the PRCCR. Information concerning incidence and mortality rates is essential for creating awareness about the magnitude of the breast cancer burden among Puerto Rican women and health care providers at large. This paper describes the malignant breast cancer incidence rates and mortality rates for the period of 2000 to 2013, overall and by health insurance regions. Stratifying rates by health insurance regions presents a novel approach that may improve how public health stakeholders identify areas to prioritize for services and education. Further, we investigate whether the geographical distributions used to define the new Health Reform had health outcome differences, given how funds

were allocated with differential access to health services between 2000 and 2013. This paper aims to expand the breast cancer incidence and mortality information so that local health administrators can evaluate the efficacy of their prevention efforts both in the government and private health sector. The study hopes to understand better how funding allocations could impact the rate of cancer incidence and mortality and improve PR women's health outcomes with breast cancer. We expect to observe higher incidence rates of breast cancer. Still, declining mortality had increased awareness in preventive screening in the Medicare Advantage Populations, especially after 2006, when Medicare Advantage started on the Island.

Methods

Data Source and Data Management

For this analysis, PRCCR supplied a data file containing the information necessary to study a total of 29,750 breast cancer cases from 2000 to 2013. The variables provided for each case included: encrypted case number, diagnosis date, last contact date, gender, age at diagnosis, diagnostic city, primary site, histologic type, grade, SEER Staging, vital status, and cause of death diagnostic code.

Incidence Trend Analysis

Overall crude rates were electronically computed using the total frequencies of new breast cancer cases over the entire female population. Next, we calculated the regional rates using the total numbers of new breast cancer cases by region over the female population estimates by age group and municipality of residence from the State Planning Board (Junta de Planificación de Puerto Rico, 2015). Finally, age-adjusted

rates were calculated using the U.S. 2000 Census female population estimates by age group as the standard population to control the aging population. Age-adjusted incidence rates for PR females from 2000 to 2013 using the U.S. Census 2000 Standard Population were calculated (PR Census Profile, 2010). Cancer incidence rates were then analyzed in the Joinpoint Regression Program (National Cancer Institute, 2020). Joinpoint regression allows for breaking the incidence trends into time segments to identify years in which there was a statistically significant change in trend ("joinpoints"). For each time segment, the analysis estimates the annual percentage change (APC) in the incidence/mortality rates during that period and determines whether the APC is statistically different from zero (no trend) at an alpha level equal to 0.05.

Recoding and Categorization

Recoding and categorization of the PRCCR data were done using the SAS 9.4 software. The variables that required recoding were: “year of diagnosis,” “age categories,” “primary tumor site,” “patient vital status,” “health region,” and “gender.” A key variable that was defined for the mortality analytical purposes was the “year of death” based on the “last seen date” information.

The inclusion criteria were established in the following order: only females, breast cancer as the primary diagnosis, Puerto Rico residents, known age at diagnosis, no in-situ diagnosis, and non-borderline status. A total of 9,522 did not meet the selection criteria for a final study population of 20,228 cases with malignant breast cancer from the provided data.

The following groups were excluded:

- 260 males
- 5,783 breast cancer cases with more than one primary site to limit breast cancer selection only and breast cancer as the primary malignancy.
- One case living outside of Puerto Rico.
- 25 cases with unknown age at diagnosis.
- 38 SEER breast cancer cases were excluded given Hodgkin and Non-Hodgkin Lymphomas of All Sites not related to breast cancer diagnostics based on the SEER breast cancer criteria for histologic codes: 9590, 9596-9663, 9673-9679, 9687-9698, 9716-9719, 9725-9726, 9735, 9737-9738. https://staging.seer.cancer.gov/eod_public/schema/1.1/lymphoma/
- 3,405 in situ cases
- One case with a tumor morphology in a Borderline status.

Results

Table 2.1 summarizes the total counts of breast cancer patients by health service region and presents the start year for the health care reform regions. Female population estimates by region are listed, and the 2000- and 2013-years incidence rates and increment percent by region are displayed. Annual percent change adjusted death rates, and percent increases are also demonstrated in this summary table. The San Juan and North West regions of the Island showed the highest breast cancer incidence rates for 2013. The South East, the Northwest, and the East regions presented the greatest increases compared to the year 2000. Regarding mortality rates, the West and

the San Juan Region presented the highest age-adjusted death rates on the Island. The Northwest, the Central, and Northeast showed the highest increase compared to the year 2000 death rates.

Incidence of Malignant Breast Cancer in Puerto Rico

Our results show that Puerto Rico incidence rates were lower than the U.S. rates and the U.S. Hispanic rates for the study period (Figure 2.2). The malignant breast cancer incidence age-adjusted rates for Puerto Rico increased from 70 cases per 100,000 females in 2010 to 81 cases per 100,000 females in 2013. The rates remained lower than the overall U.S. rate but approached rates in the U.S. Hispanic population.

Joinpoint analysis

The age-adjusted malignant breast cancer incidence rate increased from 63.04 in 2000 to 81.03 cases per 100,000 person-years in 2013, at an average annual percent change of 2.1 per year. The Joinpoint analysis (Figure 2.3) showed that in the first part of the period, 2000 to 2006, there was a small and non-significant annual percent change in the incidence rates (APC= 0.08%; p-value 0.8616). The incidence started to increase in the year 2006 and showed a high and statistically significant annual percent change of 3.63 for the period 2007 to 2013 (p-value <0.00016).

Breast Cancer Incidence Rates for Females by Age Categories

Incidence rates increased for all-female groups under 40 years of age, 40 to 59 years of age, and 60 years of age or older in the study period. However, there are some important key differences in age-group trends. The adjusted breast cancer incidence

rates for women under 40 years of age (Figure 2.4, Table 2.3) consistently increased and almost doubled for the period. The rates increased from 6.63 in 2000 to 12.31 cases per 100,000 person-years in 2013, representing a statistically significant 3.2% annual percent change (APC) for the period (p-value <0.0273).

For the PR female group 40 to 59 years of age, the adjusted breast cancer incidence rate increased from 111.61 in 2000 to 145.24 cases per 100,000 person-years in 2013 (Figure 2.5). A non-significant increment in the incidence was observed for this age group during the 2000 to 2007 period with an APC of 0.01% (p-value of 0.9945). However, starting around 2007, the incidence began to increase at a statistically significant APC of 4.22% (p-value<0.0217).

Finally, the age-adjusted breast cancer incidence rates for women over 60 years of age increased from 184.7 in 2000 to 229.6 cases per 100,000 person-years in 2013 (Figure 6). The Joinpoint analysis showed a non-significant reduction in the rates for the first part of the period from 2000 to 2003 (APC= -3.61%). However, there was a statistically significant increase in the rates for the remaining portion of the period 2003 to 2013 with an (APC=3.35%; p-value of 0.026) (see Figure 2.6).

Breast Cancer Incidence Rates by Health Service Regions

We next analyzed the age-adjusted incidence rates for the 2000-2013 period by the ten Health Reform geographical regions. The presentation order of these sections below is based on the magnitude of the rates, not the order in which the regions entered the government health reform.

The age-adjusted breast cancer incidence rates for the San Juan region show a statistically significant decrease for the period of 2000–2004 with an annual percent

reduction of almost 7% per year (APC= -6.84; p-value<0.0429) (Figure 2.7). Starting in 2004, an increase in the incidence rates was observed for the remainder of the period with a statistically significant annual percent change of close to 2% (APC=2.18% p-value<0.0349). The incidence rate for the year 2000 was 97.8, and the rate for the year 2013 was 91.4.

The North-Metro region presented the highest incidence rate on the Island (Figure 2.8). The analysis shows a non-significant decrease for the period 2000 to 2013, with an annual percent change of almost 1% (APC=0.92; p-value of .2270). The incidence rate for the year 2000 was 102.4, and the rate for the year 2013 was 100.8.

The Northeast region age-adjusted incidence showed a significant statistical increase o for the period, with an annual percent change of 2.71 per year (p-value of 0.0004) (Figure 2.9). The incidence rate for the year 2000 was 71.5, and the rate for the year 2013 was 89.96.

The age-adjusted incidence rates in the North region presented a statistically significant increase for the period of 2000 to 2013 with an annual percent change of nearly 4% per year (APC= 3.78; p-value < 0.000011) (Figure 2.10). The rate in the year 2000 was 57.1 cases per 100,000 persons and 84.2 cases per 100,000 person-years in 2013.

The East region age-adjusted incidence rates presented a statistically significant increase for the period with an annual percent change of just over 4% per year (APC=4.32%; p-value of 0.000012). (Figure 2.11). The rate in the year 2000 was 50.2 cases per 100,000 persons and 92.5 cases per 100,000 person-years in 2013.

Similarly, the Central region age-adjusted incidence rates showed a significant statistical increase for the 2000 to 2013 period with an annual percent change of nearly

4% per year (APC=3.89; p-value of 0.000065) (Figure 2.12). The rate for the year 2000 was 42.8 in 2000 to 65.4 cases per 100,000 person-years in 2013.

In the Southeast region, the age-adjusted incidence rates presented a statistically significant increase for the year 2000 to 2013 with a 6% annual percent change per year (APC= 6.02; (p-value of 0.000016) (Figure 2.13). The rate for the year 2000 was 17.5 in 2000 to 48.3 cases per 100,000 person-years in 2013.

The Northwest region age-adjusted incidence rate showed a non-statistically significant increase with an annual percent change of slightly over 2% per year (APC=2.36; (p-value of 0.0931) (Figure 2.14). The rate for the year 2000 was 36.7 in 2000 to 58.4 cases per 100,000 person-years in 2013.

The Southwest Region's age-adjusted incidence presented a statistically significant increase in the annual percent change close to 2% per year (APC=2.26; (p-value of 0.00021) (Figure 2.15). The rate for the year 2000 was in 2000 to 54.4 cases per 100,000 person-years in 2013. The West Region age-adjusted breast cancer incidence rates were stable during the years 2000 to 2013. The annual percent change was not statistically significant and close to zero (APC-0.03; p-value of 0.94) (Figure 2.16). The rate for the year 2000 was 37.5 2000 and 41.32 cases per 100,000 person-years in 2013. The rates for cases with an unknown residence or unknown region showed a statistically significant reduction in the age-adjusted incidence rates for the 2000 to 2013 period with a negative annual percent change close to 11% (APC = –10.90 per year; p-value of 0.0004) (Figure 2.17). A summary of the annual percent changes, incidence rates, and volume of cases is detailed in Table 2.1 to better inform public and private health strategies.

Mortality

Out of the total of 20,228 patients from the PRCCR Data, a total of 5,764 had died as of the date that the data was provided. Out of the 5,764 deaths, a total of 3,790 (65.3%) were caused by breast cancer based on the diagnostic codes. The total and adjusted death rates by age are described in Figure 2.18 and Table 2.2. The mortality rate trend for Puerto Rico was higher than the overall U.S. breast cancer rate as well as higher than the U.S. Hispanic rate for the 2007 to 2014 study period (U.S. rates source: SEER Registry data)

Mortality by Geographical Regions

Mortality was evaluated by the member residence's geographical location based on geographical areas defined by the government entity responsible for the managed care of the Medicaid population. A total of 3,472 breast cancer deaths were reviewed for the study period. Regarding total deaths counts, the San Juan region and the East region had more deaths, and the Southeast and the West presented a lower number of deaths (Figure 2.19).

To control for the effect of demographic changes, mortality rates adjusted by age were calculated. Figure 2.20 presents the age-adjusted mortality rates by Health Reform Region by year. For the geographical distribution of mortality rates, the West and the Southwest showed an increase in the study period. The West's mortality rate presented a spike in 2012 compared to the rates of the other regions see Figure 2.20.

The regions with the highest death rates were the West Region, with an adjusted death rate of 25.11, followed by the San Juan Region with a death rate of 21.36 for the 2013 year. The two regions with the highest increase in death rates compared with the

year 2007 were the Northwest and Central Regions. Joinpoint regression analysis was not performed to evaluate trends in mortality rates by regions given the relatively small number of deaths reported each year in each region and the lack of information on death information for the beginning of the period.

Discussion

This study describes an observed change in the incidence trend starting in 2007, suggesting a possible impact of the Medicare Advantage Program on the breast cancer diagnosis in Puerto Rico. This central finding was observed when analyzing the incidence rates for malignant breast cancer and mortality rates stratified by Health Reform Region for 2000 to 2013. We investigated whether the geographical distributions of breast cancer cases and deaths across regions defined by the new Health Reform and documented that the incidence and death patterns varied by region. Such differences may reflect how funds were allocated or differential access to health services between 2000 and 2013.

The first goal of the study was accomplished when we described the trends in incidence rates for Puerto Rico between the years 2000 to 2013. The increase in the incidence rate observed starting around the year 2006 suggests an impact of the federal Medicare Advantage (MA) program, which began in 2006. The population that enrolled in a MA plan was able to receive, from their primary care physicians, more referrals for preventive services, earlier referrals to specialists, and diagnostic testing and early treatment options now paid by the program. Given that more diagnostic testing was done to screen the female population better, faster documentation of cases resulted in the cancer registry. Increases in rates since 2003 documented for the older population

might be related to the Health Reform initiative and increased MA coverage penetration among PR beneficiaries since 2007. Notably, although incidence rates were lower in Puerto Rican women than in US women or US Hispanic women, mortality rates were higher, with increases in mortality observed through 2012. Improvements in the health services access model allowed Puerto Rican females to receive earlier breast cancer screening, earlier diagnostic testing, and access to treatment, which might account for the observed decrease in breast cancer mortality after 2011.

The Southeast region observed the most remarkable percentage change in its incidence, and one of the lowest increases in mortality among the regions. The Southwest region deserves more study given its elevated mortality rates figures,

Like all ecological analyses of population-level data, this study is subject to several limitations. First, given the ecological nature of the analysis, no conclusions can draw regarding causal factors behind the observed trends not having the information on the type of health insurance, e.g., Medicare, Medicaid, Commercial types, within the registry data limited the analysis options for the specific source of the funding program. Efforts to obtain and document the insurance type in the registry will enhance future studies' analytical opportunities. Potential bias, common to cancer registry-related studies, might have occurred if local health providers reported incomplete case ascertainment and/or not all Cancer Registry cases. Significant efforts to improve breast cancer surveillance obtaining information on new cases activity reported to the health insurance companies could complement the cases reported to the Cancer Registry by medical providers. Having access to information on new cases is important

for local health and state administrators to better coordinate early treatment efforts both in the government and private health industry.

The data presented here suggest that implementing these reforms from the state and federal governments resulted in earlier diagnosis, which may increase the incidence and the observed declines in mortality rates in the Island for the study period. The Joinpoint analysis conducted in this study demonstrates that the increase in malignant breast cancer presented during the year 2000 to 2017 started specifically around 2007 when the Medicare Advantage Program became available on the island, which this author will expound on in Chapter III.

All service regions presented increases in the incidence rates, especially the South East, East, and Central regions (Table 2.3). The highest increment in incidence was observed in the 65-year-old female population, and mortality age-adjusted rates increased from 2007 to 2013 in all service regions. The most evident accomplishment of the government Health Reform and the Medicare Advantage Program was to provide more access to services. This resulted in better and faster documentation of new cases in the health service regions. This translates to earlier treatment, reducing early mortality in more aggressive types of tumors, especially among patients in advanced stages of the disease unaware of their diagnosis, which will be expounded in Chapter III.

Figure 2.1 Puerto Rico Health Reform Implementation Period 1994-2000

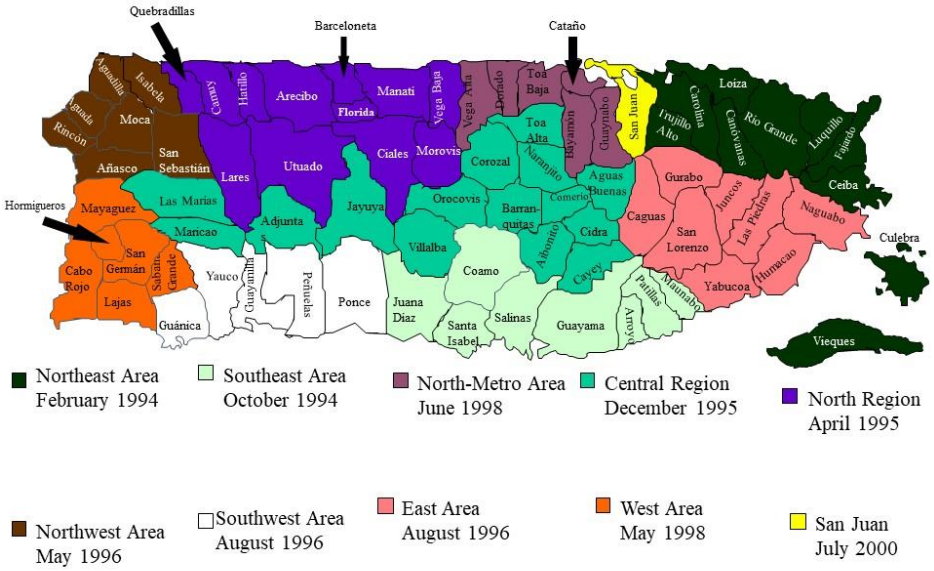


Figure 2.2 PR, the USA, and USA Hispanics, Malignant Breast Cancer adjusted rates

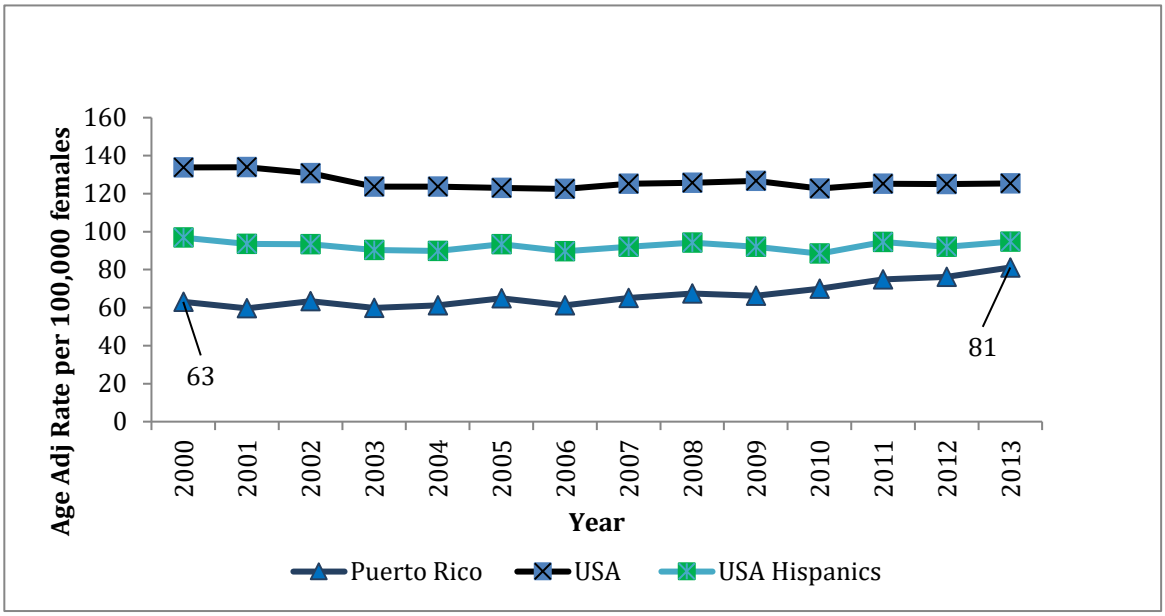
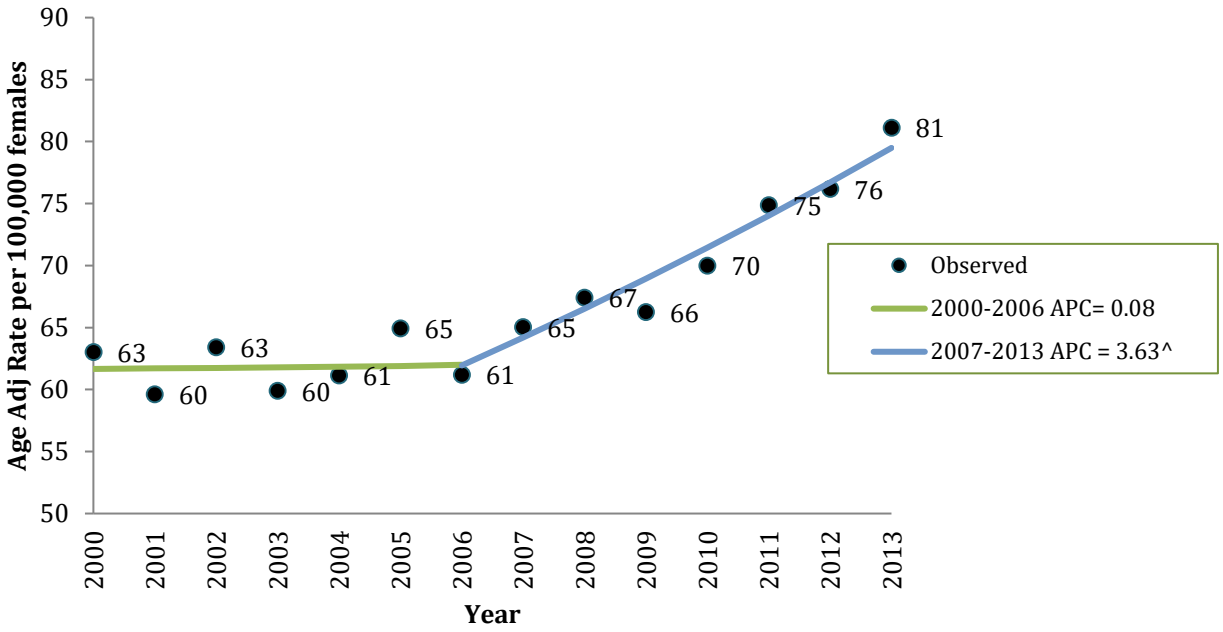
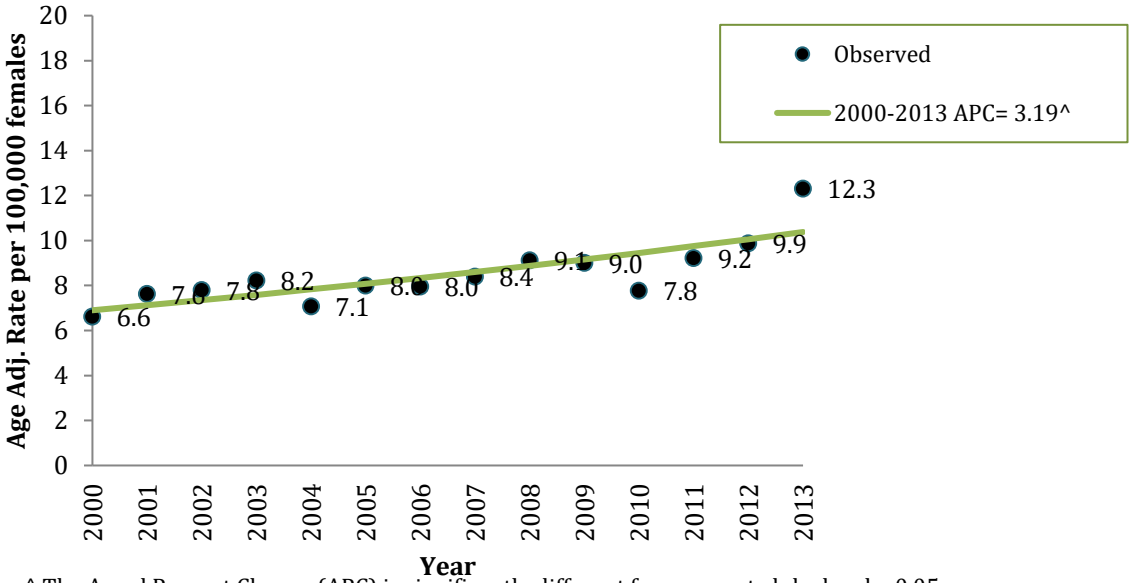


Figure 2.3 Puerto Rico Malignant Breast Cancer Age-Adj Rates



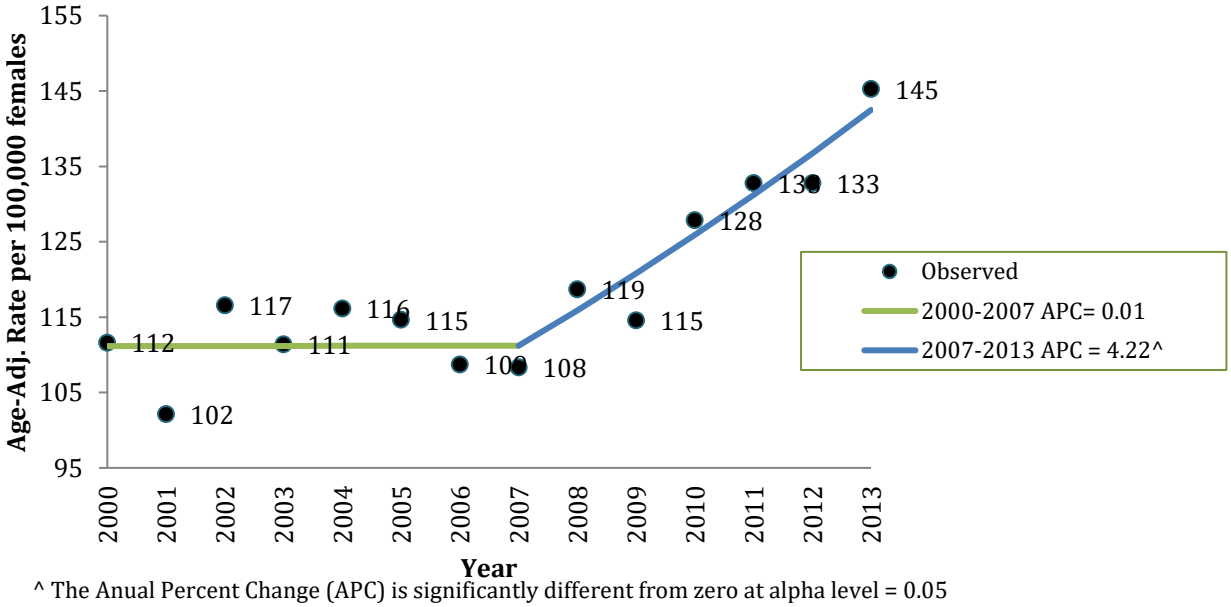
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 1 Joinpoint.

Figure 2.4 Malignant Breast Cancer Age-Adj Rates for females under 40 years



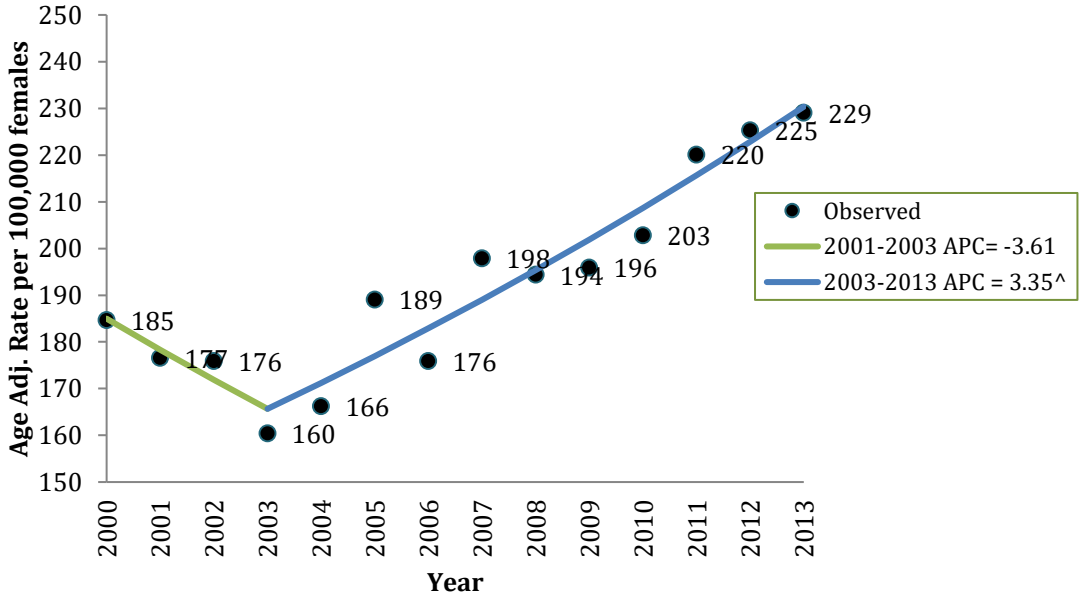
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 2.5 Malignant Breast Cancer Age-Adj Rates for females 40-59 years



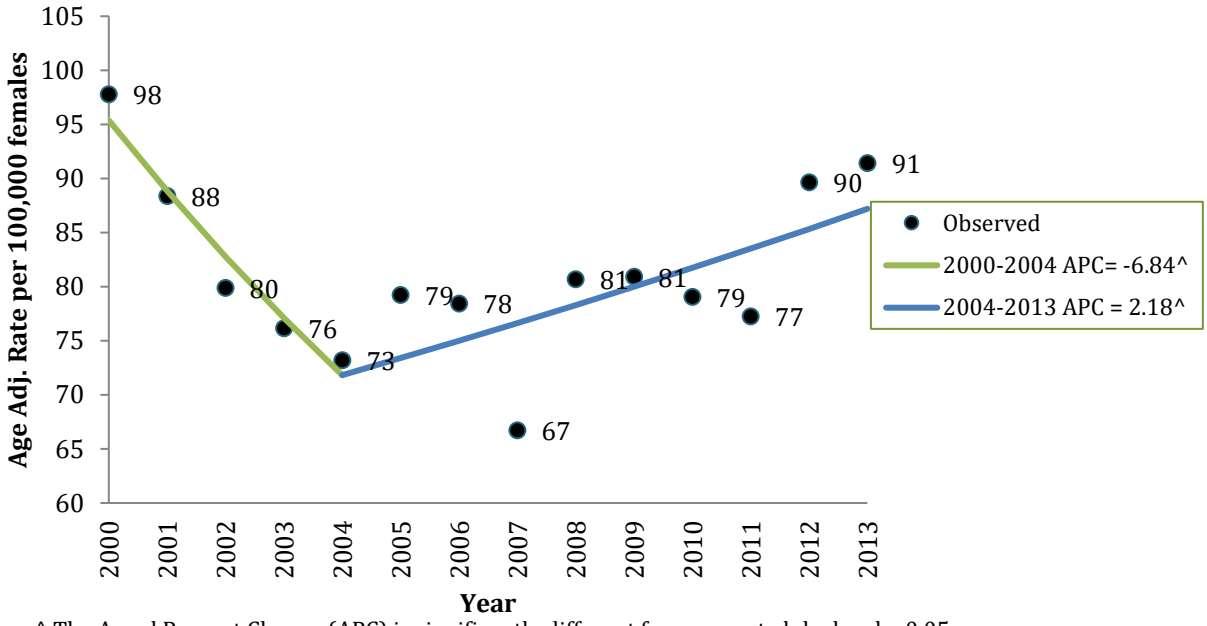
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 1 Joinpoint.

Figure 2.6 Malignant Breast Cancer Age-Adj Rates for females 60 years and older



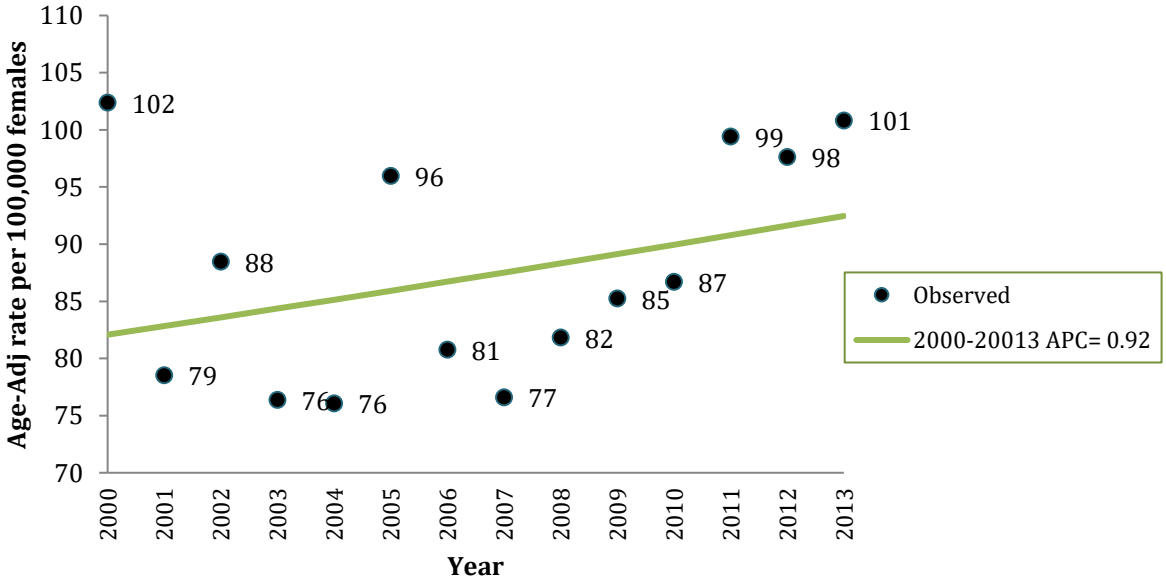
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 1 Joinpoint.

Figure 2.7 Malignant Breast Cancer Age-Adj Rates in the San Juan Region



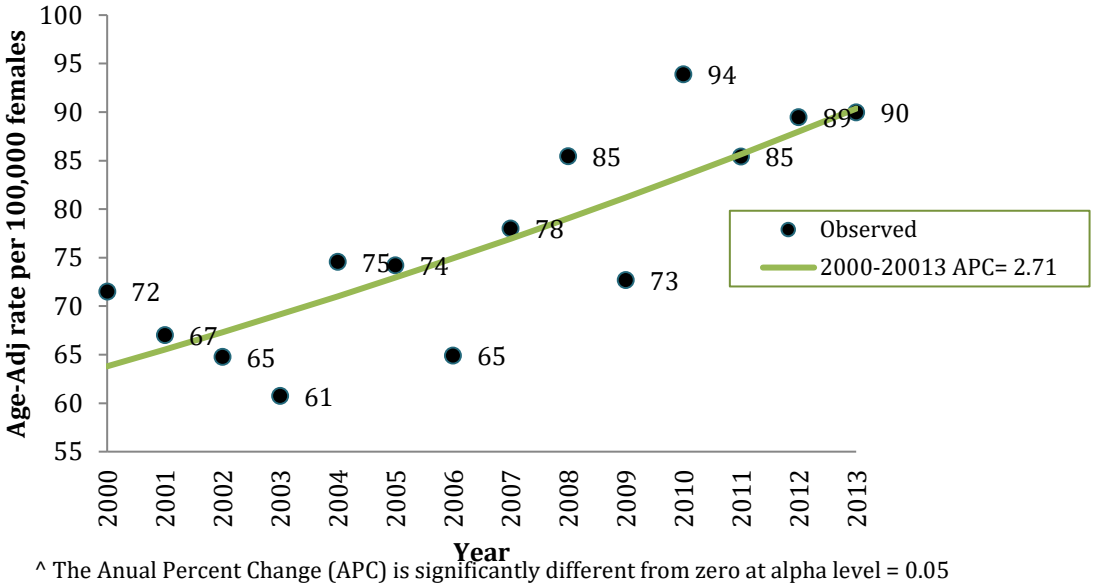
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 1 Joinpoint.

Figure 2.8 Malignant Breast Cancer Age-Adj Rates in the Northmetro Region



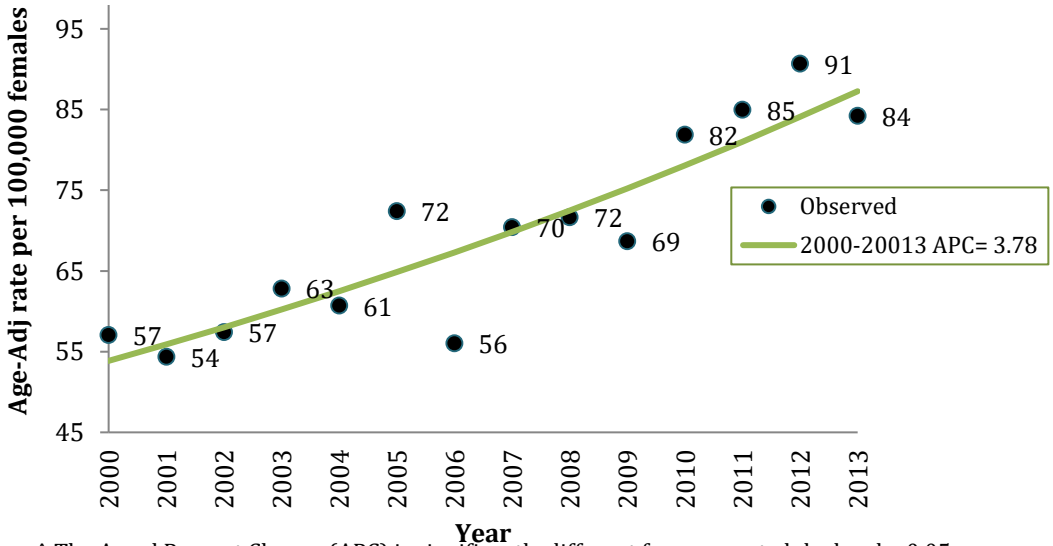
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 2.9 Malignant Breast Cancer Age-Adj Rates in the Northeast



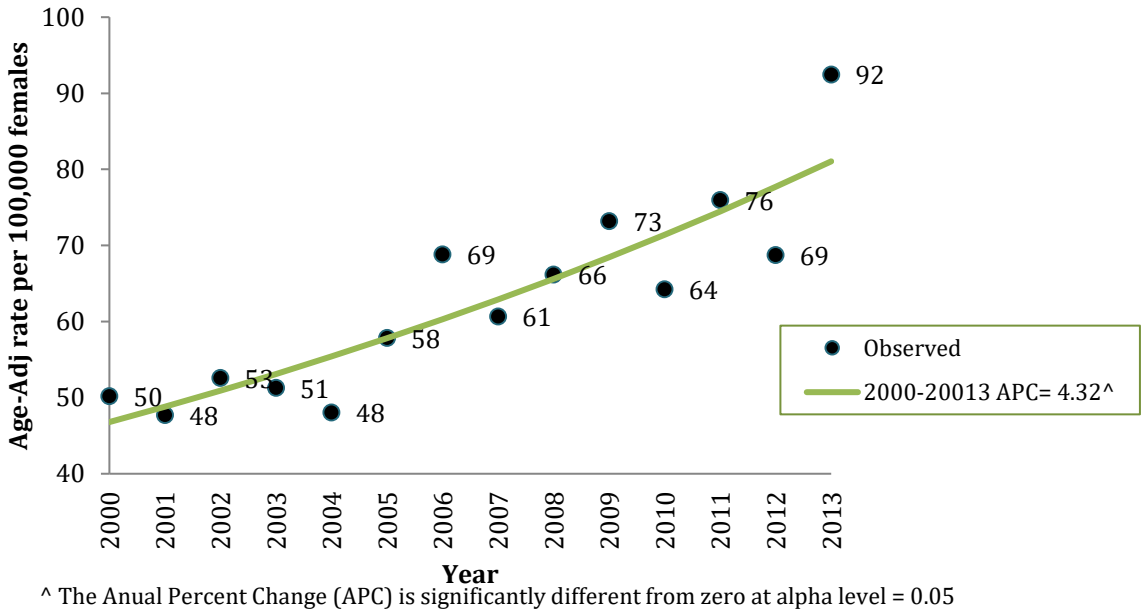
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 2.10 Malignant Breast Cancer Age-Adj Rates in the North



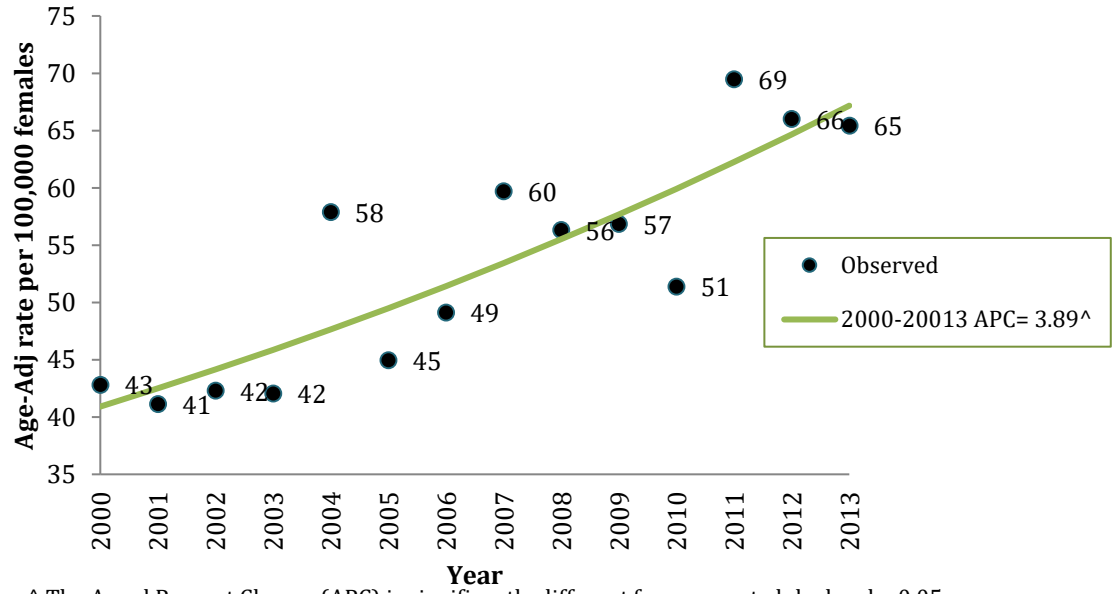
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 2.11 Malignant Breast Cancer Age-Adj Rates in the East Region



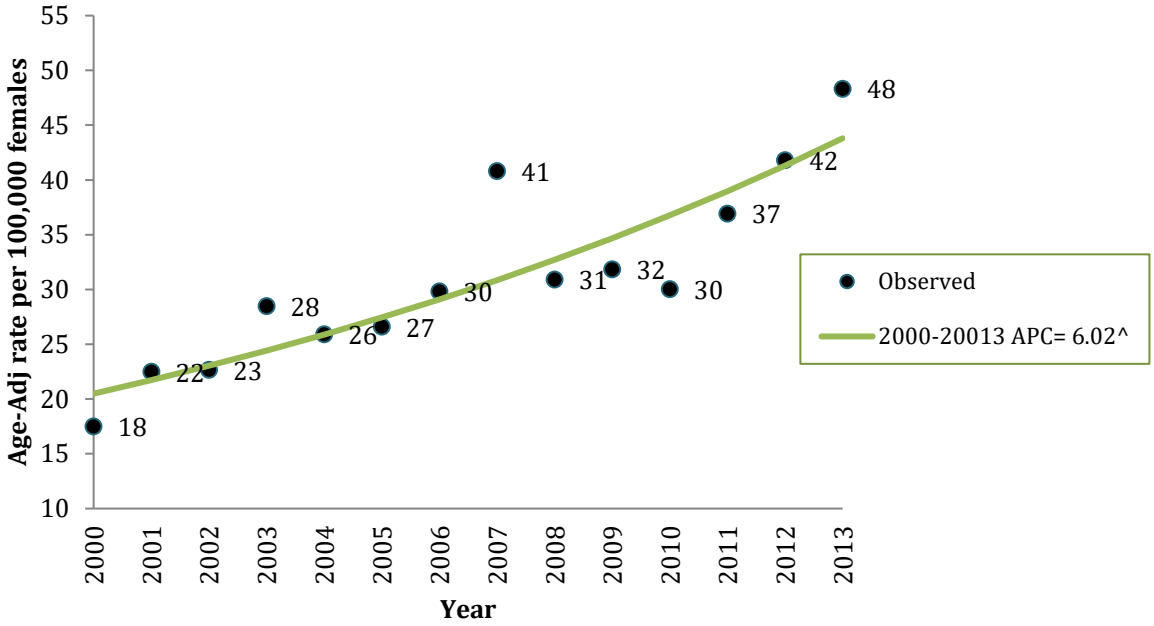
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 2.12 Malignant Breast Cancer Age-Adj Rates in the Central Region



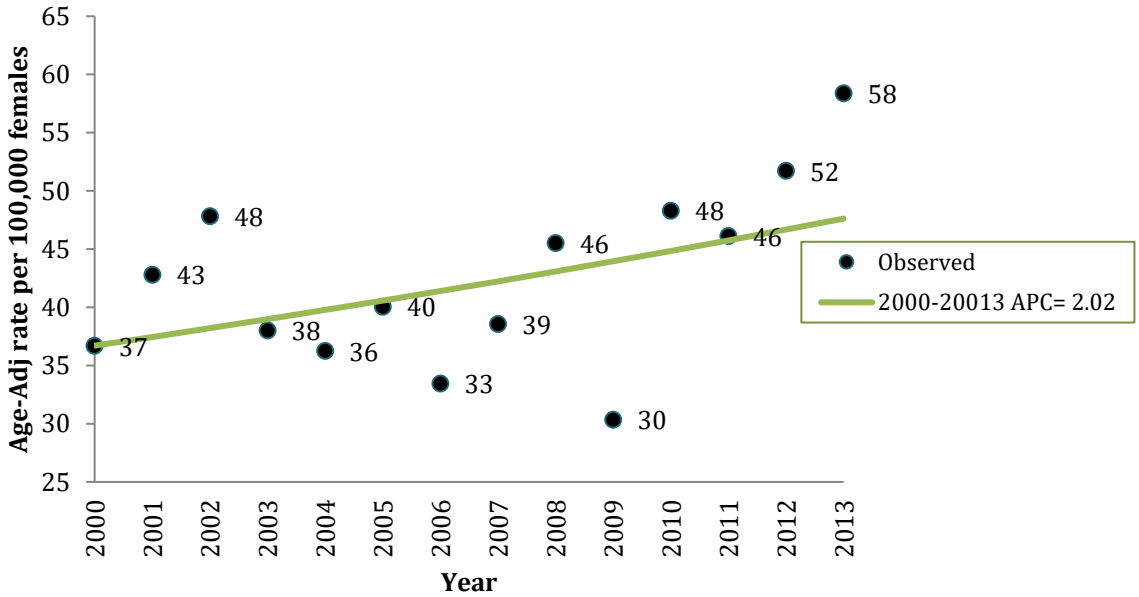
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 2.13 Malignant Breast Cancer Age-Adj Rates in the Southeast Region



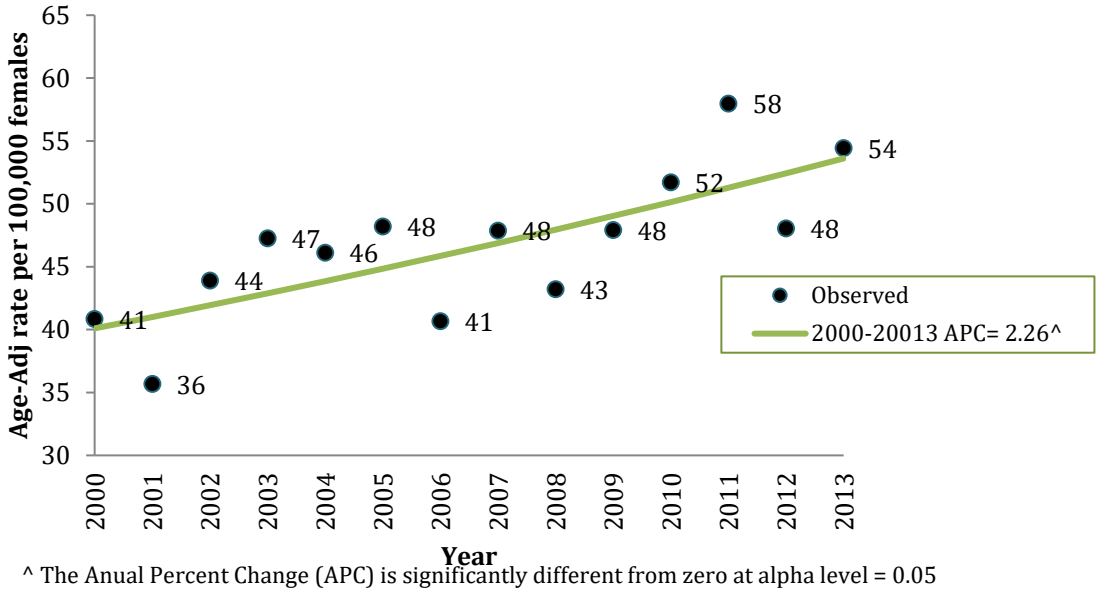
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 2.14 Malignant Breast Cancer Age-Adj Rates in the Northwest Region



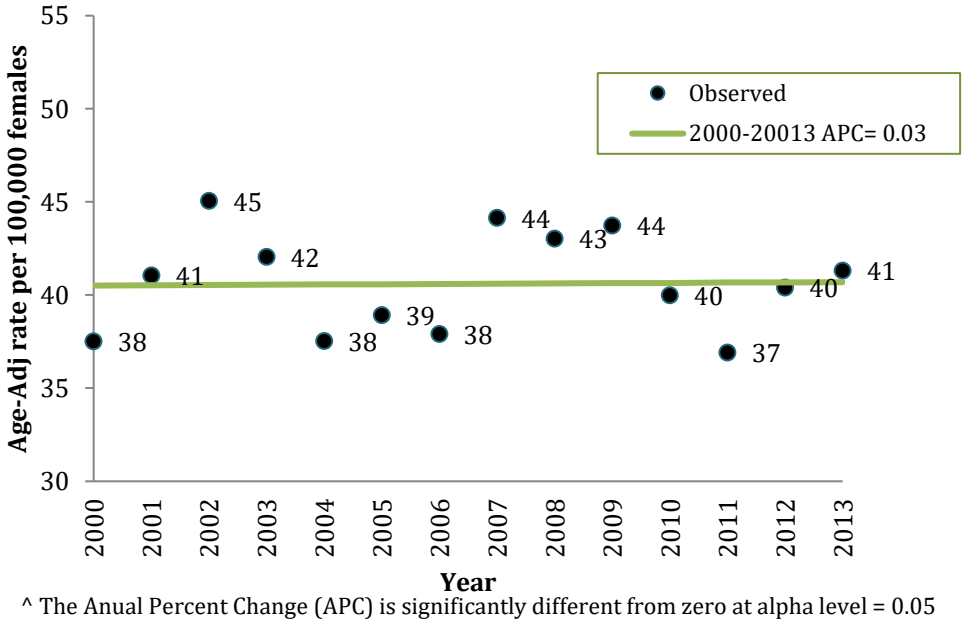
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 2.15 Malignant Breast Cancer Age-Adj Rates in the Southwest Region



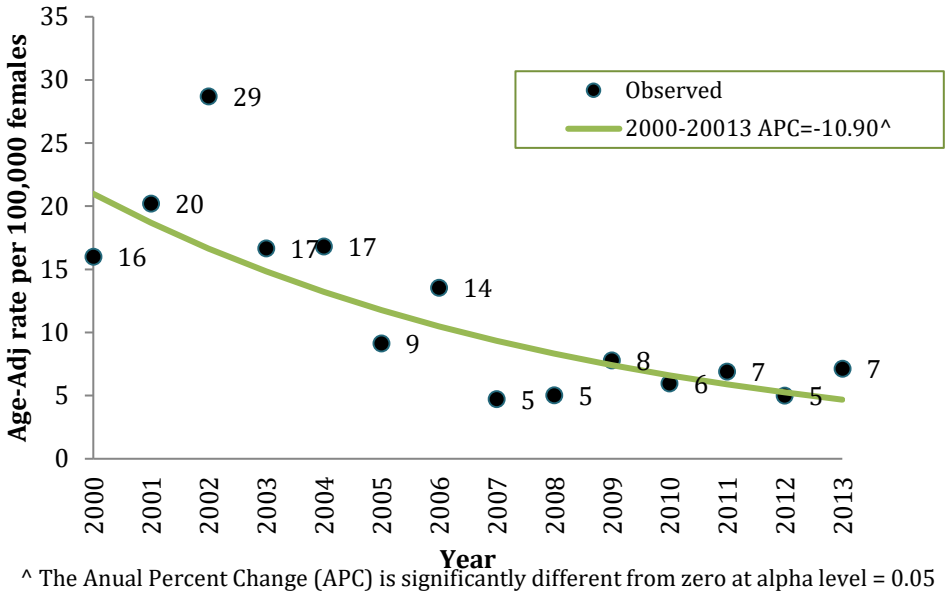
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 2.16 Malignant Breast Cancer Age-Adj Rates in the West Region



^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 2.17 Malignant Breast Cancer Age-Adj Rates with Unknown Region



^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 2.18 Breast cancer Age Adjusted mortality rates for PR and USA 2007 to 20014

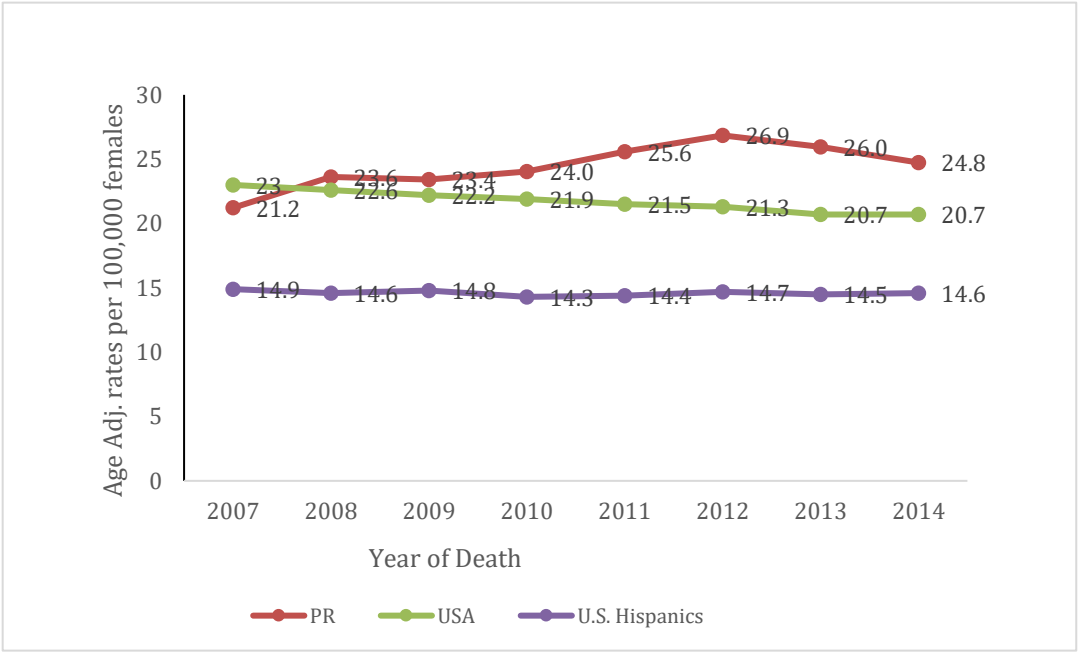


Figure 2.19 Total Breast Cancer Deaths and Rates by Health Reform Regions for 2000-2014

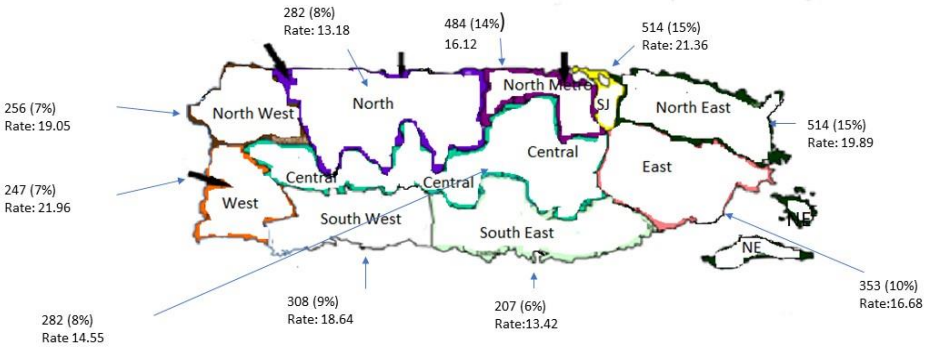


Figure 2.20 Age Adjusted Death Rates by Health Reform Regions

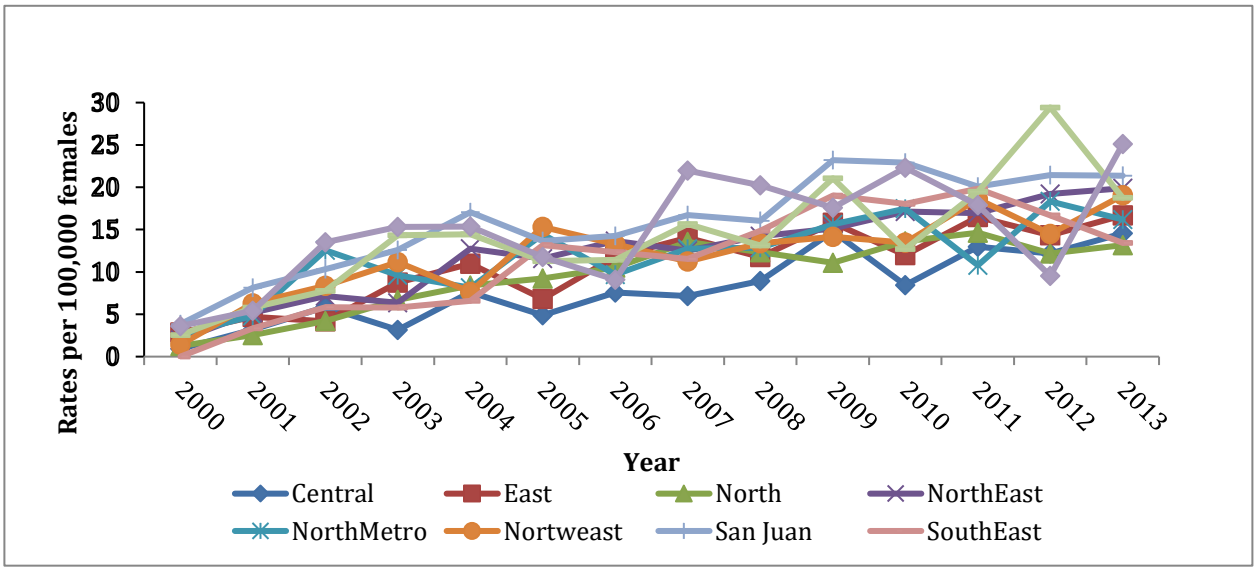


Table 2.1 Summary Table Incidence and Mortality Rates for Puerto Rico Malignant Breast Cancer Patients for Study Population

Health Reform Region	Malignant BC Cases	Started on the Health Reform	Female Pob	Inc. Rate 2000	Inc Rate 2013	Increment in Rate	Annual % Change	Adj Death Rate 2007	Adj Death Rate 2013	Increement in Death Rate
South East	1039	1994	122,016	31.2	102.5	71.3	5.9*	11.54	13.42	1.88
East	2101	1996	225,291	50	105.5	55.5	4.6*	14.05	16.68	2.63
North	2326	1995	234,959	52	91	39	3.9*	13.53	13.18	-0.35
Central	1764	1995	224,675	42.1	75	32.9	3.9*	7.15	14.55	7.4
North East	2598	1994	245,259	61	98	37	2.8*	12.52	19.89	7.37
San Juan	2717	2000	213,694	89.9	116.7	26.8	2.4*	16.72	21.36	4.64
North West	1421	1996	141,085	54.1	111.04	56.94	2.4*	11.72	19.05	7.52
South West	1581	1996	141,604	55.5	107.2	51.7	2.2*	15.67	18.74	0.53
North Metro A	2916	1998	263,267	81.6	99.6	18	0.9	12.77	16.2	3.43
West	1388	1998	107,629	74.1	105.3	31.2	0.01	21.96	25.11	3.15

Note: Unknown Region: 377

Table 2.2 Breast cancer mortality rates per 100,000 females

	2007	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
PR crude mortality rate	21.74	24.62	25.06	25.84	27.72	29.44	28.99	27.79
PR age adjusted mortality rate	21.22	23.62	23.41	24.04	25.58	26.85	25.95	24.75
U.S. age-adjusted mortality rate	23.00	22.60	22.20	21.90	21.50	21.30	20.70	20.70
U.S. Hispanics age-adjusted mortality rate	14.90	14.60	14.80	14.30	14.10	14.70	14.50	14.60

Table 2.3. Joinpoint Analysis Results; Observed Incidence for Malignant Breast Cancer, PR 2000-2013

			Jointpoint Trend 1		Jointpoint Trend 2		Avg. APC
	Age Category	**Cases**	**Years**	**APC**	**Years**	**APC**	**2009-2013**
Age at Diagnostic	All ages						
	Under 40 years	1,252	2000-2013	3.2^			3.2^
	40 to 59 years	8,399	2000-2007	0.01	2007-2013	4.2^	4.2^
	60 and older	10,577	2000-2003	-3.6	2003-2013	3.4^	3.4^
Health Reform Region	All Regions						
	Southeast	1,039	2000-2013	5.9^			5.9^
	East	2,101	2000-2013	4.4^			4.4^
	North	2,326	2000-2013	3.9^			3.9^
	Central	1,764	2000-2013	3.9^			3.9^
	Northeast	2,598	2000-2013	2.7^			2.7^
	San Juan	2,717	2000-2004	-6.9^	2004-2013	2.2^	2.2^
	Northwest	1,421	2000-2013	2.4^			2.4^
	Southwest	1,581	2000-2013	2.2			2.2
	NorthMetro	2,916	2000-2013	0.9			0.9
	West	1,388	2000-2013	0.01			0.01
	Unknown	377	2000-2013	-11.6^			-11.6^

Note: The APC and the AAPC are significantly different from zero at α=0.5

References

Addressing Puerto Rico's Medicare Crisis and Implementing an Urgent Path to Recovery from the Medicaid and Medicare Advantage Products Association of PR, 2015.

Department of Health of Puerto Rico. Title V Block grant application, San Juan Puerto Rico 2000.

Henry Keyser Foundation. Medicare Advantage Report, 2014.

http://www.elnuevodia.com/Xstatic/endi/template/imprimir.aspx?id=761428&t=3.

https://www.finance.senate.gov/imo/media/doc/Puerto%20Rico%20Healthcare%20Community%20(Attachment%201).pdf

Junta de Planificación, Programa de Planificación Económica y Social, Oficina del Censo; 2015. Proyección de población por género grupo de edad y municipios. https://jp.pr.gov/Econom%C3%ADa/Censo.

National Cancer Institute. Joinpoint Trend Analysis Software, 2020. https://surveillance.cancer.gov/joinpoint/

Nazario CM, Figueroa-Vallés N, Rosario RV. Breast cancer patterns and lifetime risk of developing breast cancer among Puerto Rican females. Puerto Rico Health Sciences Journal. 2000 Mar;19(1):7-13.

Puerto Rico 2000, Census 2000 Profile. U.S. Department of Commerce Economics and Statistics Administration U.S. CENSUS BUREAU; November 2002, C2KPROF/00-PR.

Tortolero-Luna, Guillermo. Presentation: Puerto Rico Central Cancer Registry, April 13, 2013.

USA Census Bureau, 2000 Census.

USA Census Bureau, 2010 Census of Population and Housing, updated every 10 years. Decennial Census Datasets. Population, Census, April 1, 2010.

Zavala-Zegarra D, Tortolero-Luna G, Torres-Cintrón CR, Alvarado-Ortiz M, Traverso-Ortiz M, Román-Ruiz Y and Ortiz-Ortiz KJ. Cáncer en Puerto Rico, 2008-2012. Registro Central de Cáncer de Puerto Rico; 2015.

CHAPTER III

Age-adjusted incidence and mortality rates for malignant breast cancer in Puerto Rico between 2000 and 2013, stratified by histologic type and stage of disease

Introduction

Puerto Rico's breast cancer incidence rates are increasing, and mortality rates for Puerto Rican (PR) females are higher than those for U.S. females and US Hispanic females, warranting analysis of breast cancer rates by other clinical indicators. Describing Puerto Rican breast cancer incidence and mortality rates by factors that influence prognosis, such as by histologic types, the grade of the tumors, and staging of the disease at diagnosis will confirm whether these clinical indicators, typically accompanied by a gradient of aggressiveness within breast cancer subtypes, explain the high mortality rates in PR females. Given the aging of the Puerto Rican population, it is expected that more advanced stages of the disease will become more prevalent among diagnosed breast cancer cases, as other researchers have described for the US population (Bush, 1996). Assessing the magnitude of the problem of diagnoses occurring in advanced stages will suggest strategies for improving outcomes, including increasing funding allocation for enhancing primary prevention efforts, screening efforts in high-risk groups, and improving access to treatment in the initial stages of breast cancer.

Our previous analysis in chapter II of the Puerto Rico Central Cancer Center (PRCCC) data demonstrated that the age-adjusted mortality rates were higher among PR females than U.S. females overall and U.S. Hispanic females. Additionally, the breast cancer incidence rate for PR females, which has been historically lower

compared to that for U.S. females, has been moving closer to the U.S. level since 2007, with breast cancer mortality rising through 2013.

Improvements in the health services access model allowed Puerto Rican females to receive earlier breast cancer screening, earlier diagnostic testing, and access to treatment, which might account for the simultaneous increase in incidence since 2006 and the flattening of the breast cancer mortality curve after 2011. However, given the lower incidence and mortality rates among the USA Hispanic population compared to other ethnic groups (Power, 2018), research is needed to explain possible explanations for the higher mortality in Puerto Rican women.

To our knowledge, no recent study has described trends in the distribution of histologic types and tumor grade of breast cancer in Puerto Rico. Such data would help local administrators evaluate governmental and medical providers' efforts to ensure responsible allocation of resources better, reduce the incidence and mortality, and improve women's health outcomes with breast cancer in Puerto Rico. The objective of this paper is to evaluate trends of breast cancer incidence and mortality rates between 2000 and 2013 by stage of the disease at diagnosis, histology tumor type, and tumor grades to develop a better understanding as to how to improve prevention strategies aimed at reducing new breast cancer cases and deaths in PR females.

Methodology

PRCCC provided a file with 29,750 records of breast cancer cases for the period between 2000 and 2013. The data file included basic demographic information and the following variables: Year of Diagnosis, Primary Site, Vital Status, Tumor Grade, Histological Tumor Type, and Stage of Disease at Diagnosis. A total of 9,522 cases did not meet the selection criteria below for a final study population of 20,228 malignant breast cancer females.

The following groups were excluded:

- 260 males
- 5,783 breast cancer cases with more than 1 primary site to limit breast cancer selection only and breast cancer as the primary malignancy.
- One case living outside of Puerto Rico.
- 25 cases with unknown age at diagnosis.
- 38 SEER breast cancer cases were excluded given Hodgkin and Non-Hodgkin Lymphomas of All Sites not related to breast cancer diagnostics based on the SEER breast cancer criteria for histologic codes: 9590, 9596-9663, 9673-9679, 9687-9698, 9716-9719, 9725-9726, 9735, 9737-9738. https://staging.seer.cancer.gov/eod_public/schema/1.1/lymphoma/
- 3,405 in situ cases
- One case with a tumor morphology in a Borderline status.

New breast cancer cases by clinical categories were calculated based on female population estimates by age group and municipality of residence using data from the

State Planning Board (Junta de Planificación de Puerto Rico, 2015). Finally, age-adjusted rates were calculated using the U.S. 2000 Census female population estimates by age group as the standard population to control the aging population. Age-adjusted incidence rates for PR females from 2000 to 2013 were calculated using the U.S. Census 2000 Standard Population (PR Census Profile, 2010). Cancer incidence rates were then analyzed in the Joinpoint Regression Program (National Cancer Institute, 2020). Joinpoint regression allows for breaking the incidence trends into time segments to identify years in which there was a statistically significant change in trend ("joinpoints"). For each time segment, the analysis estimates the annual percentage change (APC) in the incidence/mortality during that period and determines whether the APC is statistically different from zero (no trend) at an alpha level equal to 0.05.

Mortality cases were identified using the binary type Vital Status field from the Registry data file. Causes of death related to women's breast cancer diagnoses were determined using the breast cancer ICD-10 codes for each identified death. Breast cancer mortality analysis was restricted to breast cancer-related deaths with breast cancer-specific ICD-10 codes identified as the cause of death.

Results

Table 3.1 describes the clinical characteristics of the 20,228 breast cancer patients identified for this study. Sixty-eight (68%) percent of the tumors were from Ductal cell carcinomas, followed by Lobular cell carcinomas (11%). Thirty-five (35%) of the tumors were poorly differentiated (G3), followed by 31% of moderately differentiated (G2), 3.4% of well-differentiated (G1) tumors, and 1.8% presented undifferentiated

tumors (G1), and almost thirty percent of the tumors had not determined cell types (29%).

In Puerto Rico, 10,767 cases (53%) were classified with a localized stage at diagnosis, and twenty-two percent (22%) were classified with a Regional to lymph node stage at diagnosis. A total of 6,199 cases (30%) reported the upper outer quadrant as the tumor site at diagnosis. Fourteen percent (14.6%) manifest overlapping sites for the tumor at diagnosis. Thirty-two (32%) percent of the cases presented Breast (Not Specified) sites. Out of the total of 20,228 breast cancer patients, 5,764 cases were dead at the time of identification by the Registry, and 3,472 (17%) died from a breast cancer-related cause.

Overall Breast Cancer Incidence Rates in PR

As shown in chapter II, the adjusted malignant breast cancer incidence rate in Puerto Rico increased from 63.04 in 2000 to 81.03 cases per 100,000 person-years in 2013, an annual percent change of 2.1 per year. Incidence rates started to increase in 2006 and rose through 2013 with a statistically significant annual percent change close to 4% (APC=3.63; (p-value <0.00016) (Figure 3.1).

Breast Cancer Incidence by Histologic Type

The most prevalent reported histology among the Puerto Rico breast cancer cases for the period was infiltrating ductal cell carcinoma (Table 3.1). Ductal cell-specific incidence rates slightly increased between the years 2000 to 2009. A non-significant annual percent change of close to 1% per year (APC=1.2%; (p-value of 0.07). The incidence rate was 44.7 in 2000 to 47.96 cases per 100,000 females in the year 2009. For the second part of the period, ductal cell carcinomas rates reflected a

sharp increase between the 2009 to 2013 period with a statistically significant increase of 7% annually (APC=6.7; p-value of 0.0151). The rate increased from 48 cases per 100,000 females in 2009 to 62 cases per 100,000 females in 2013. These patterns are illustrated in Figure 3.2 and Table 3.2.

For the patients with “Lobular and other ductal carcinomas,” the rates showed a slight and statistically significant increase of approximately 2% per year (APC=1.87%; (p-value of 0.0021) (Figure 3.3). The incidence rate increased from 7.1 new cases per 100,000 females in 2000 to 8.3 new cases in 2013.

Incidence rates for patients with Mucinous histological types carcinomas show a small but statistically significant increase close to 3% annually (APC= 3.11%; p-value of 0.0177) (Figure 3.4). The incidence rate was 1.40 per 100,000 females in 2000 and 1.61 per 100,000 females in 2013.

Incidence rates for breast cancer cases with the Medullary histological type carcinomas presented a statistically significant reduction of close to 10% per year (APC=9.6%; p-value of 0.0005) (Figure 3.5). The rates rose from 1.19 per 100,000 females in the year 2000 to 0.34 per 100,000 females in 2013.

Incidence rates for breast cancer cases with Papillary histological type were showed a non-significant annual percent change close to 3% per year (APC=2.71%; p-value of 0.41) (Figure 3.6). The rate was 0.47 per 100,000 females for the year 2000 and 0.47 in 2013.

Breast cancer cases with rare histological types presented a small but not statistically significant increase in the incidence rates with an annual percent change close to 1% per year (APC=1.34%; p-values of .55 for the period (Figure 3.7). The rate

in the year 2000 was 0.89 per 100,000 females in the year 2000 and 0.84 per 100,000 females in the year 2013.

Breast cancer cases with “Other” histological types presented a slight, non-statistically significant decrease in the incidence from 2000 to 2013, APC=0.08%; p-value of 0.94 (Figure 3.8). The rate in the year 2000 was 7.28 per 100,000 females in the year 2000 and 7.37 per 100,000 females in the year 2013.

Breast Cancer Incidence by Tumor Grade

Breast cancer incidence rates for patients with “Well-differentiated” tumor grades presented a statistically significant increase during the study period with an annual percent change of 5% per year, APC= 4.78; p-value of 0.00002 (Figure 3.9 and Table 3.2). The incidence was 5.74 per 100,000 for 2000 and 9.44 per 100,000 females in 2013.

Incidence rates for cases with the “Moderately differentiated” types were stable between 2000 and 2009. The annual percent chance for the first part of the period was close to 0% (APC=0.24; p-value of .77). The incidence rate for the year 2000 was 22.56 per 100,000 and 23.97 per 100,000 females for the year 2013. However, in 2010, there was a statistically significant increase that continued through 2013. An annual percent change of 7% (APC=7.31%; p-value of 0.0176) (Figure 3.10). The incidence rate for the year 2010 was 22.89 per 100,000 and 30.11 per 100,000 females for the year 2013.

Breast cancer incidence rates for patients with “Poorly differentiated” tumor grades presented a statistically significant increase with an annual percent change close to 2% (APC= 2.16% with a p-value of 0.0029 (Figure 3.11). An observed

incidence rate of 15.12 per 100,000 females in the year 2000 per 100,000 and 20.23 per 100,000 in 2013.

Incidence rates for cases with undifferentiated cell types presented a non-significant decrease during the years 2000 to 2013 with a negative annual percent change close to 3% APC=-3.06%; p-value of 0.2 (Figure 3.12). An incidence rate of 1.05 per 100,000 for the year 2000 and a rate of 0.028 per 100,000 females for 2013.

Cases with undetermined grade presented a "U" shape curve for the incidence trend. A non-statistically significant decrease was first observed from 18.57 per 100,000 in the year 2000 and 13.30 per 100,000 in 2002 (APC= -17.02; p-value of 0.1929). Then, a stable segment trend was observed from 2002 to 2011. Subsequently, the trend showed a non-significant increase in incidence from 11.92 per 100,000 and 21.08 per 100,000 from 2011 to 2013. The annual percent change observed was 28.97%, with a p-value of 0.0625 (Figure 3.13).

Breast Cancer Incidence by Stage

Breast cancer incidence rates for patients with Localized State at Diagnosis presented a statistically significant increase between 2000 and 2014. The annual percent change was close to 3% per year (APC= 2.97%; p-value of 0.00008) (Figure 3.14 and Table 3.2). The observed incidence rate for the year 2000 was 29.70 per 100,000 females and 41.42 per 100,000 for the year 2013.

The observed breast cancer incidence rates for patients with the "Regional to Direct extension" stage showed a statistically significant increase from 2000 to 2009, with an annual percent change close to 9 percent per year (APC=9.42; p-value of .0012), (Figure 3.15). An observed incidence rate of 1.71 per 100,000 females in the year 2000

and 4.93 per 100,000 females in the year 2008. In contrast, starting in 2009, there was a statistically significant decrease that lasted until 2013. The negative annual percent change was close to 24% (APC=-23.93%; p-value of 0.0041). An observed incidence rate of 5.29 per 100,000 was observed in 2009 and 1.94 per 100,000 in 2013.

Incidence rates for breast cancer patients with the “Regional to Lymph node” stage were stable between 2000 and 2009. The annual percent change during this period was close to cero APC=-0.43%; p-value of 0.60. An incidence rate of 13.50 per 100,000 females was observed for the year 2000 and a rate of 11.5 per 100,000 females for the year 2013. However, in 2010, there was a statistically significant increase with an annual percent change close to 10% per year (APC=10.25%; p-value of 0.0032) (Figure 3.16). The observed rate for 2010 was 15.32 per 100,000 and 19.71 per 100,000 for the year 2013.

The observed breast cancer incidence rates for patients with “DE and lymph node” stages also showed a statistically significant increase from 2000 to 2008, starting with an incidence rate of 1.71 per 100,000 and 1.94 per 100,000, respectively. The annual percent change observed was 7.53%, with a p-value of 0.0243. In contrast, there was a statistically significant decrease starting in 2008. The annual percent change was 13.37% with a p-value of 0.0012 (Figure 3.17).

Breast cancer incidence rates for patients with “Distant Stage” reflected a non-statistically significant increase for the 2000 to 2013 period. The annual percent change in the period was close to 2% (APC=1.55%; p-value of 0.0738) Figure 3.18. The incidence rate observed for the year 2000 was 2.61 per 100,000 in 2000 and 4.40 per 100,000 in 2013.

Cases with an unknown stage at diagnosis presented a “U” shaped curve for the incidence trend. A statistically significant decrease was observed from the year 2000 to the year 2002. The negative annual percent change is close 40% (APC= -40.43%; p-value of 0.03). A rate of 12.92 per 100,000 females was observed for 2000 and a rate of 4.18 per 100,000 in 2002. Subsequently, a stable segment from 2003 to 2011 was observed (APC=0.97%; p-value of 0.7113). A rate of 4.53 per 100,000 females for the 2003 year and a rate of 4.19 per 100,000 females during 2010. From 2011 to 2013, though, the incidence rates showed a non-significant increase from 4.03 per 100,000 to 10.92 per 100,000, respectively. The annual percent change observed was close to 50% per year (APC=49.19%; p-value of 0.06), Figure 3.19.

Overall Mortality Rates for Breast Cancer

Out of a total of 20,228 breast cancer patients, 5,764 cases (28.5%) were dead at the time of identification by the registry, and 3,472 (17%) died from a breast cancer-related cause. The age-adjusted malignant breast cancer mortality rate in Puerto Rico increased from 3.6 deaths per 100,000 females in 2000 to 24.8 deaths per 100,000 females in 2014. After 2007, mortality rates increased with an annual percent change of 2% (p-value = 0.2), reaching a rate in 2014 of 25 per 100,000 females. The Puerto Rican age-adjusted mortality was higher than the USA age-adjusted mortality and the USA Hispanics' age-mortality rates (Figure 3.20). The age-adjusted mortality rates for Puerto Rico decreased from 26.85 deaths per 100,000 females in 2012 to 24.7 deaths per 100,000 females in 2014.

Mortality Rates by Histologic Type

Out of 3,274 reported breast cancer deaths, 2,346 deaths (68%) were attributable to infiltrating duct cell carcinomas. Notably, this was the only histologic type showing a significant increase compared to the other types during the study period (Figure 3.21). Six hundred and forty-three (643) deaths from lobular and other types of ductal carcinomas represented 11% of the deaths for that period. Rare subtypes of histological types accounted for 3% of the deaths, while mucinous adenocarcinomas and medullary carcinomas each represented 1% of the breast cancer deaths on the Island (Table 3.1).

The mortality rates for Infiltrating ductal cell carcinomas increased from 0.42 deaths per 100,000 females in 2000 to 10.1 deaths per 100,000 in 2014. Lobular cell carcinomas' mortality rate increased from 0.11 deaths per 100,000 females in 2000 to 1.17 deaths per 100,000 in 2014. The mortality rate for Mucinous adenocarcinomas, Medullary carcinomas, and Papillary carcinomas remained stable throughout the study period. For Mucinous adenocarcinomas, the rates increased from 0 in 2000 to 0.15 deaths per 100,000 females in 2014. The mortality rate for Medullary carcinomas increased from 0 in the year 2000 to 0.15 deaths per 100,000 females in 2014 and for papillary carcinomas from 0.6 to 0 in 2014. The other subtypes category decreased from 1.55 deaths per 100,000 to 0.

Breast Cancer Mortality by Grade

Out of 3,472 breast cancer-related deaths, 1,210 (34.9%) were attributable to “poorly differentiated” (Grade 3 tumors). A total of 1,070 (30.8%) deaths were attributable to “moderately differentiated” (Grade 2 tumors) tumors. Sixty-two deaths

(1.8%) were attributable to undifferentiated tumors (Grade 4). For 1,013 deaths (29%), the grade was not determined for the tumors' cell types (Table 3.1). The trend in the mortality rates for poorly differentiated (Grade 3) increased more for the period followed by moderately differentiated (Grade 2) tumors, which also increased consistently during the study period (Figure 3.22).

Mortality Rates by Stage

Out of 3,472 breast cancer-related deaths, 1,564 (45%) deaths were identified with a localized stage. A total of 794 (23.9%) were identified at a regional stage, and 562 deaths (16.2%) were diagnosed at a distant stage. There was also a total of 552 deaths (15.9%) that were either unstaged, unspecified or with an unknown stage at diagnosis (Table 3.1).

The percent distribution of deaths by stage of the disease at diagnosis and year is summarized in Table 3.3. Summarized age-adjusted mortality rates trends by stage and stage were graphically summarized in Figure 3.23. For breast cancer cases with a regional stage at diagnosis showed the highest mortality in the study period. A sharp increase was observed in the adjusted death rates starting with 0.15 per 100,000 females in the 2000 year to 6.78 deaths per 100,000 females in 2014. The age-adjusted death rates for patients with a localized stage at diagnosis increased from 0.1 deaths per 100,000 females to 3.24 deaths per 100,000 in 2014.

The third highest mortality trend line was for patients with distant metastasis increasing from a rate of 0.28 in 2000 to 1.73 in 2014. Finally, those patients with an unknown stage at the time of diagnosis showed a slight reduction in the study period trend. Table 3.2 summarizes the Joinpoint analysis.

Like all ecological analyses of population-level data, this study is subject to several limitations. First, given the ecological nature of the investigation, no conclusions can be made regarding potential causal factors behind the observed trends Selection bias, common to cancer registry-related studies, might have occurred if local health providers reported incomplete case ascertainment and/or not all cases to the Cancer Registry. The mortality information for cases identified by the registry was less documented in the early years of the study period, which correlates to the first years of the registry's re-implementation.

To our knowledge, no recent publication has described trends in the distribution of breast cancer cases by histologic types, tumor grade, and stage of the disease in Puerto Rico. It concerns that female breast cancer in PR shows a statistically significant increase in Type III histological types (Infiltrating ductal and lobular carcinomas). This finding correlates with a similar increase in more aggressive tumor types, Grade 2 (Moderately differentiated) and Grade 3 (Poorly differentiated), and may underlie the observed increases in mortality.

The increase in localized tumors likely reflects the success of screening efforts in earlier identification of the disease. More research is needed to understand better the reasons for the observed increases in mortality associated with Type III and Grade 2 cancers. More research is also necessary to understand the reasons for the rise in cases and mortality in the Regional to Lymph Nodes stage in the most recent period (2009 - 2013).

Discussion

The objective of this paper was to evaluate trends of incidence and mortality rates between 2000 and 2013 by stage of the disease at diagnosis, histology tumor

type, and tumor grades to provide a better understanding as to how to improve prevention strategies aimed at reducing new cases and deaths in PR females for breast cancer. To our knowledge, no recent publication has described trends in the distribution of breast cancer cases by histologic types, tumor grade, and stage of the disease in Puerto Rico. The data presented here provide vital information for public health stakeholders to better understand breast cancer cases' clinical profile and improve resource allocation to reduce the incidence and mortality of women with breast cancer in Puerto Rico. A total of 20,228 malignant breast cancer cases in Puerto Rico were analyzed for the 2000 to 2014 period. Regarding incidence, the analysis showed a sharp and significant increase in the incidence of infiltrating ductal cell carcinomas. The use of newer and more sophisticated diagnostic modalities among pathologists might have resulted in a more straightforward and more precise identification of histological types. With the new resources made available through the Health Reform and the Medicare Advantage programs, more cases may also have been referred for pathological evaluation. Incorporating more resources from the University of Puerto Rico, now administering the Registry, might have improved these clinical details. However, the possibility that environmental exposures may account for the observed increases cannot be discarded. Statistically significant increases were documented for lobular and Mucinous cell carcinomas for the study period. In contracts, Medullary carcinomas showed a statistically significant reduction in rates for the study period. Papillary carcinomas showed a statistically insignificant increase for the period, and other and rare subtypes rates remain stable for the period.

Similar to infiltrating ductal cell carcinomas, new cases with moderately differentiated tumors were stable from 2000 to 2009, but a sharp and statistically significant increase was observed from 2009 to 2014. Similar to infiltrating ductal carcinomas, this observed increase may be attributable to the use of newer and more sophisticated diagnostic modalities among pathologists, further resources from the Health Reform and the Medicare Advantage programs leading to more referrals for pathological evaluation, the improved abstraction of clinical details from the medical record, or to as yet unknown environmental factors. Malignant breast cases with well-differentiated and poorly differentiated tumors increased steadily for the whole period. The incidence of breast cancer with undifferentiated type tumors decreased for the study period.

Regarding the disease stage and similar to infiltrating ductal cell carcinomas, cases with a Regional to lymph node stage were stable from the year 2000 to 2009, with a sharp and statistically significant increase from 2009 to 2014. Localized tumors like tumors with well and poorly differentiated grades showed a constant rise in incidence rates for the whole period. Given the increase in incidence and mortality rates on poorly differentiated tumors (Grade 3) more attention needs to be allocated to patients in early stages with more aggressive tumors to receive targeted chemotherapy, to help destroy any cancer cells that may have spread as a result of the cancer being faster growing (Breast Cancer Now Org, 2020).

More aggressive tumors and tumors with a regional to lymph nodes stage increased after 2009, which is correlated with the increase in combined estrogen and progestin hormone replacement therapy (CHRT) in older women, which has been

documented since 2002 to increase breast cancer risk (Lee and colleagues, 2003). However, this correlation has not been investigated in Puerto Rican women.

This study had two main limitations. First, the lack of information on the patient's type of health insurance in the registry data limited our ability to assess the role of insurance access. Second, mortality information for cases identified by the registry in the early years of the study period was limited, which correlates to the first years of the registry's re-implementation. Incomplete case ascertainment information is also possible if health providers did not report all Cancer Registry cases, a common potential bias in cancer registry-related studies.

In this chapter, age-adjusted incidence and mortality rates trends were described by histologic types, the grade of the tumor, and stage of the disease at diagnosis in Puerto Rico for the 2000 to 2013 period; To our knowledge, no recent publication has described trends in the distribution of new breast cancer cases and mortality by histologic types, tumor grade and stage of the disease in Puerto Rico. It is concerning that women with breast cancer in PR show a statistically significant increase in Type III histological types (Infiltrating ductal and lobular carcinomas). This finding correlates with a similar increase in more aggressive tumor types, Grade 2 (Moderately differentiated) and Grade 3 (Poorly differentiated), and may underlie the observed increases in mortality. The observed rise in cases with localized tumors likely reflects the success of screening efforts in earlier identification of the disease. Notwithstanding, more research is needed to understand better reasons for the increase in mortality associated with Type III and Grade 2 cancers and to understand reasons for the rise in cases and mortality in the Regional to Lymph Nodes stage, in the last part of the period (2009 -

2013). We suggest that this reporting method will become a standard and become an integrated and systematic section in the reporting for future cancer publications in Puerto Rico. However, limited information on deaths from 2000-2005 may have biased the trend analysis in this early period.

The next chapter will provide an applied example of the experience of medical and prescription utilization of a Medicare breast cancer population in Puerto Rico. Care coordination and significant funding were allocated to this segment of the population, which might be an excellent example of best practices on the Island.

Table 3.1 Puerto Rico Malignant Breast Cancer Cases Characteristics; 2000 to 2013

	Malignant					In-Situ	
Histology	Cases	%	Deaths	%		Cases	%
Ductal Carcinoma	14,728	72.8%	2,346	68%		1,588	47.0%
Lobular and Other Ductal CA	2,637	13.0%	365	11%		1,002	29.7%
Mucinous Adenocarcinoma	558	2.8%	40	1%		2	0.1%
Medullary Carcinoma	187	0.9%	19	1%		-	0.0%
Papillary Carcinoma	119	0.6%	5	0%		23	0.7%
Rare Subtypes	268	1.3%	87	3%		356	10.5%
Others	1,731	8.6%	610	18%		405	12.0%
Total	20,228	100.0%	3,472	100%		3,376	100.0%
Tumor Grade	Cases	%	Deaths	%		Cases	%
Well diferrentiated (G1)	2,247	11.1	117	3.4%		546	16.2%
Moderately diferrentiated (G2)	7,612	37.6	1,070	30.8%		964	28.6%
Poorly differentiated (G3)	5,671	28.0	1,210	34.9%		481	14.2%
Undifferentiated (G4)	289	1.4	62	1.8%		237	7.0%
Cell type not determined	4,409	21.8	1,013	29.2%		1,148	34.0%
Total	20,228	100.0	3,472	100.0%		3,376	100.0%
Stage at Diagnosis	Cases	%	Deaths	%			
Localized	10,767	53.2	794	22.9%			
Regional by direct extension	966	4.8	257	7.4%			
Regional to lymph nodes	4,422	21.9	912	26.3%			
Regional (direct extension and lymph nodes)	1,225	6.1	387	11.1%			
Regional, NOS	20	0.1	8	0.2%			
Distant metastasis or systemic disease (leukemia, multiple myeloma)	1,061	5.3	562	16.2%			
Unstaged, Unknown,Unspecified	1,767	8.7	552	15.9%			
Total	20,228	100.0	3,472	100.0%			
Site	Cases	%	Deaths	%		Cases	%
Nipple	230	1.1%	36	1.0%		30	0.9%
Central Portion of the Breast	740	3.7%	108	3.1%		172	5.1%
Upper inner quadrant	1,563	7.7%	176	5.1%		211	6.3%
Lower inner quadrant	876	4.3%	121	3.5%		151	4.5%
Upper outer quadrant	6,199	30.6%	899	25.9%		1,012	30.0%
Lower outer quadrant	1,091	5.4%	145	4.2%		156	4.6%
Axillary tail	154	0.8%	33	1.0%		9	0.3%
Overlapping	2,945	14.6%	381	11.0%		460	13.6%
Breast, NOS	6,430	31.8%	1,573	45.3%		1,175	34.8%
Total	20,228	100.0%	3,472	100.0%		3,376	100.0%
Vital Status	Cases	%					
Dead	5,764	28.5					
Alive	14,464	71.5					
Breat Cancer related Death	Cases	%					
Yes	3,472	17.2					

Table 3.2 Joinpoint Analysis Results; Observed Incidence for Malignant Breast Cancer, PR 2000-2013

			Jointpoint Trend 1		Jointpoint Trend 2		Jointpoint Trend 3		Ave. APC
	Region	**Cases**	**Years**	**APC**	**Years**	**APC**	**Years**	**APC**	**2009-2013**
Histologic Type	All Histologic Types								
	Infiltrating Ductal Carcinomas	14,728	2000-2009	1.2	2009-2013	6.4^			6.4^
	Lobular and other Ductal Carcinomas	2,637	2000-2013	1.9^					1.9^
	Mucinous Adenocarcinomas	558	2000-2013	3.1^					3.1^
	Medullary Carcinoma	187	2000-2013	-9.1^					-9.1^
	Papillary Carcinoma	119	2000-2013	2.7					2.7
	Rare Subtypes	268	2000-2013	1.3					1.3
	Others	1,731	2000-2013	-0.1					-0.1
Tumor Grade	All Grades								
	Well differentiated	2,247	2000-2013	4.8^					4.8^
	Moderately differentiated	7,612	2000-2009	0.24	2009-2013	7.53^			7.5^
	Poorly differentiated	5,671	2000-2013	2.3^					2.3^
	Undifferentiated	289	2000-2013	-4.5					-4.5
	Cell type not determined	4,409	2000-2002	-17.3	2002-2011	0.4	2011-2013	30.14^	14.3
Stage at Diagnosis	All Stages								
	Localized	10,767	2000-2013	3.0					3.0
	Regional to Lymph Nodes	4,422	2000-2009	-0.4	2009-2013	10.3^			10.3^
	Regional by Direct Extension	966	2000-2009	9.4^	2009-2013	-23.9^			-23.9^
	Regional by Direct Extension and Lymph nodes	1,225	2000-2008	7.5^	2008-2013	-13.4^			-13.4^
	Distant	1,061	2000-2013	1.5					1.5
	Unstage, Unknown, Unspecified	1,767	2000-2002	-40.4^	2002-2011	1.0	2011-2013	49.3	22.8^

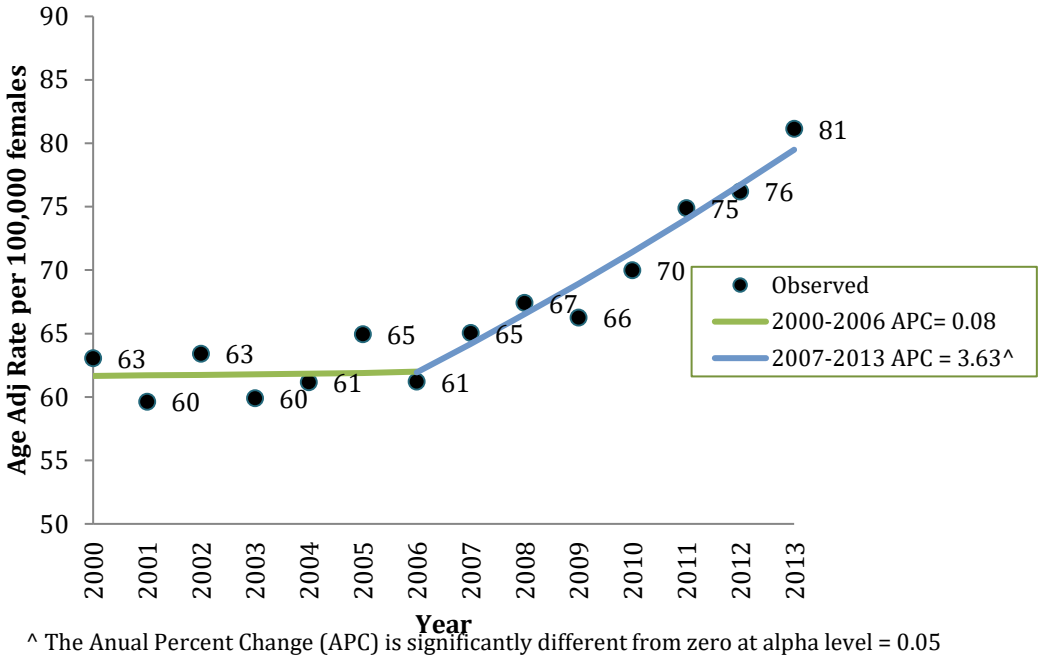
Note: The APC and the AAPC are significantly different from zero at α=0.5

Table 3.3 Percent Distribution of Breast Cancer-related Deaths by Year and Stage at Diagnosis

Stage	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Localized	5	9	21	20	20	22	23	26	25	25	22	27	21	23	26
Regional by Direct Extension (DE)	0	4	6	5	6	7	8	7	7	7	10	7	10	8	7
Regional to Lymph Nodes	5	20	19	31	23	23	35	23	24	25	26	27	25	30	31
Regional (DE and Lymph nodes)	2	5	12	8	7	9	8	13	11	11	15	14	13	10	15
Regional NOS	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
Distant	14	20	15	13	24	17	15	15	14	18	13	16	17	19	14
Unknown	74	41	25	23	20	20	11	16	19	14	13	9	13	9	7
Total	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

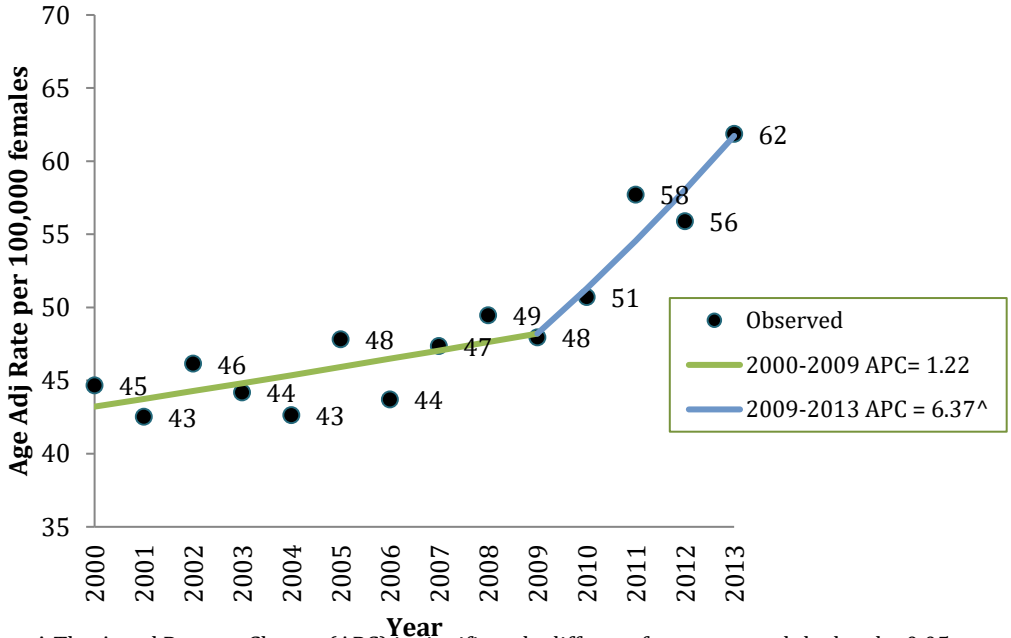
Note: Total deaths for the period 3,472

Figure 3.21 Malignant Breast Cancer Age-Adj Incidence Rates for PR 2000-2013



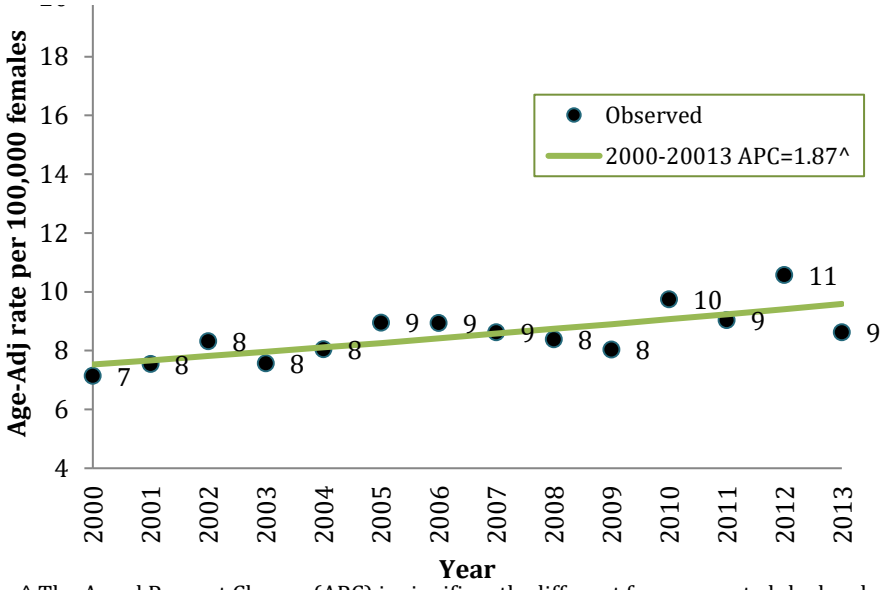
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 1 Joinpoint.

Figure 3.22 Malignant Breast Cancer Age-Adj Rates with Duct Carcinoma



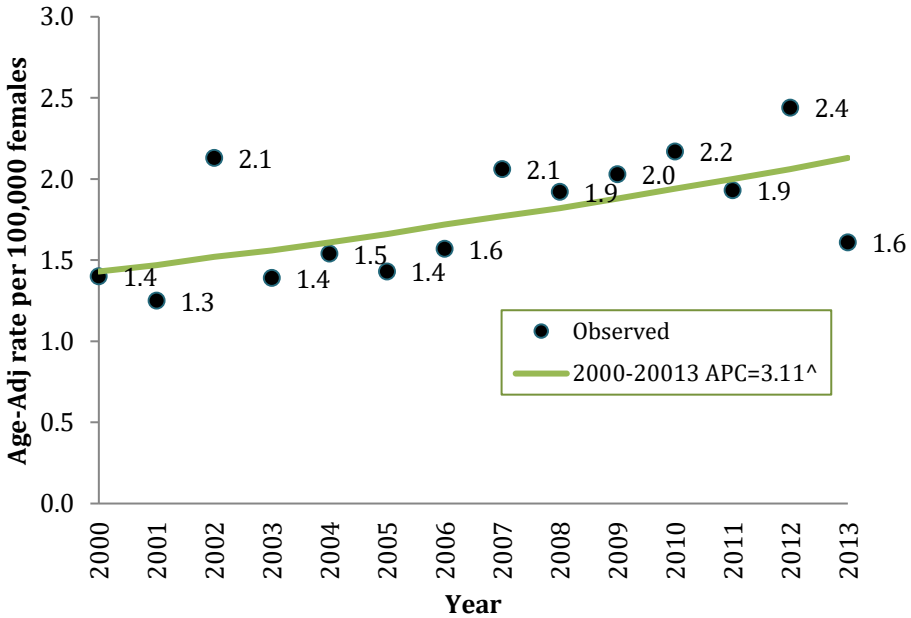
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 1 Joinpoint.

Figure 3.23 Malignant Breast Cancer Age-Adj Rates with Lobolar & Other Ductal Carcinomas



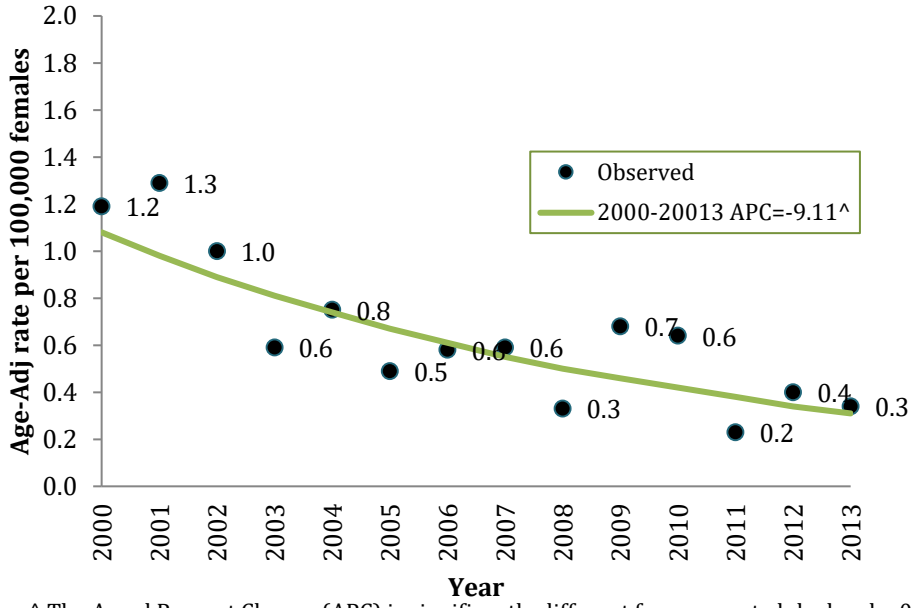
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 3.24 Malignant Breast Cancer Age-Adj Rates with Mucinous Adenoma



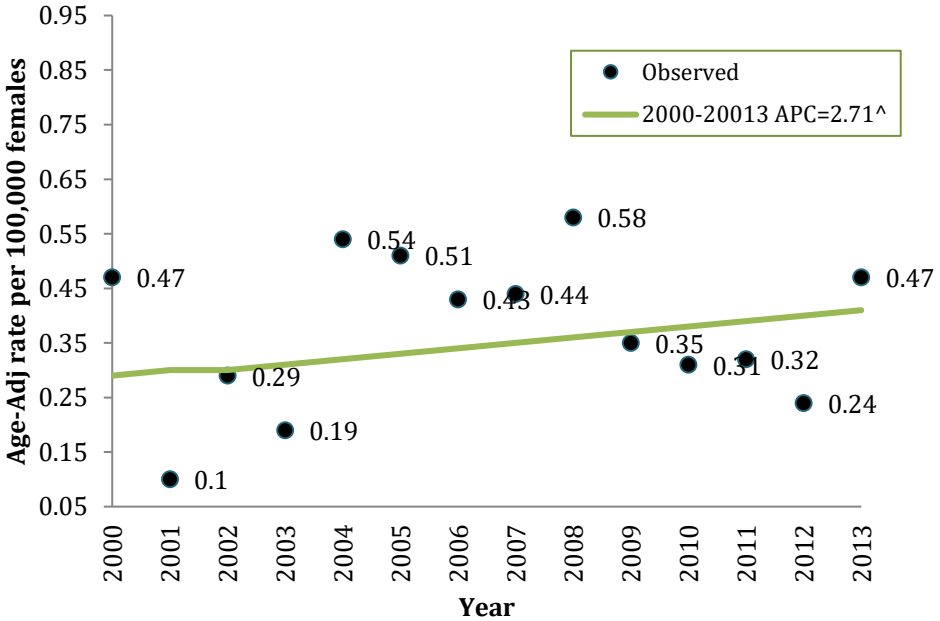
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 3.25 Malignant Breast Cancer Age-Adj Rates with Medullary Carcinoma



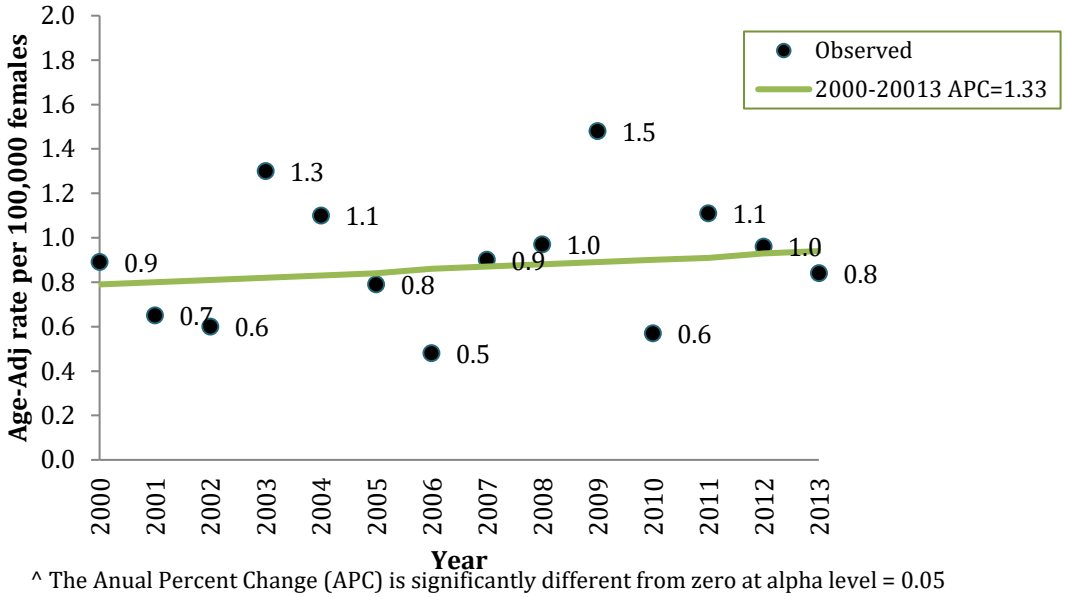
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 3.26 Malignant Breast Cancer Age-Adj Rates with Papillary Carcinoma



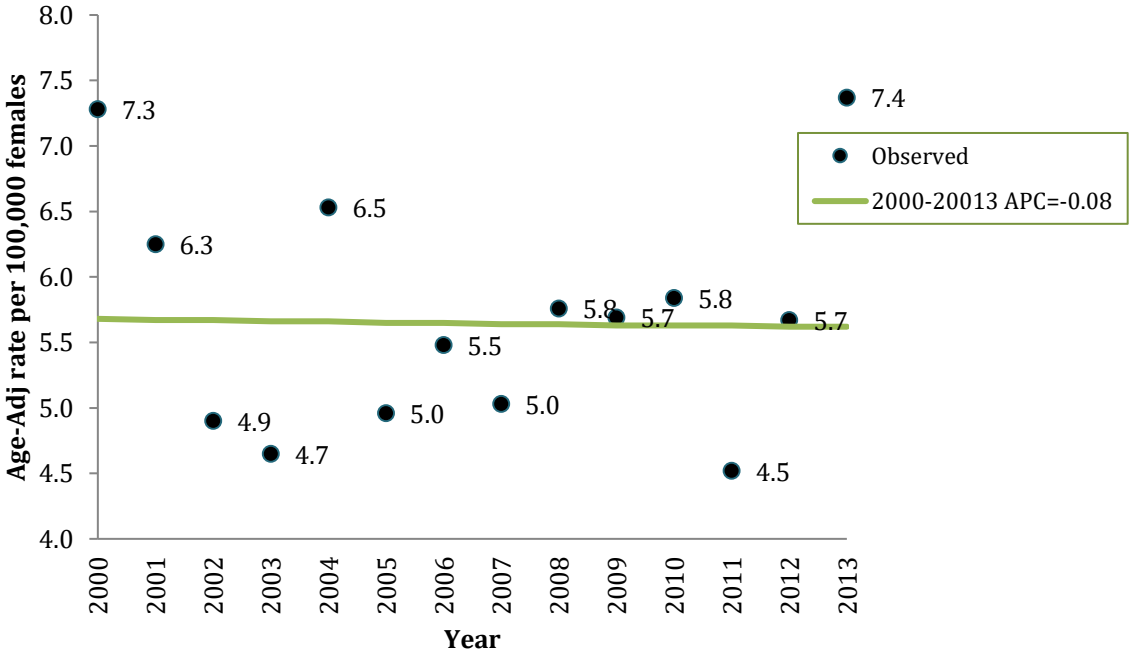
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 3.27 Malignant Breast Cancer Age-Adj Rates with Rares Subtypes



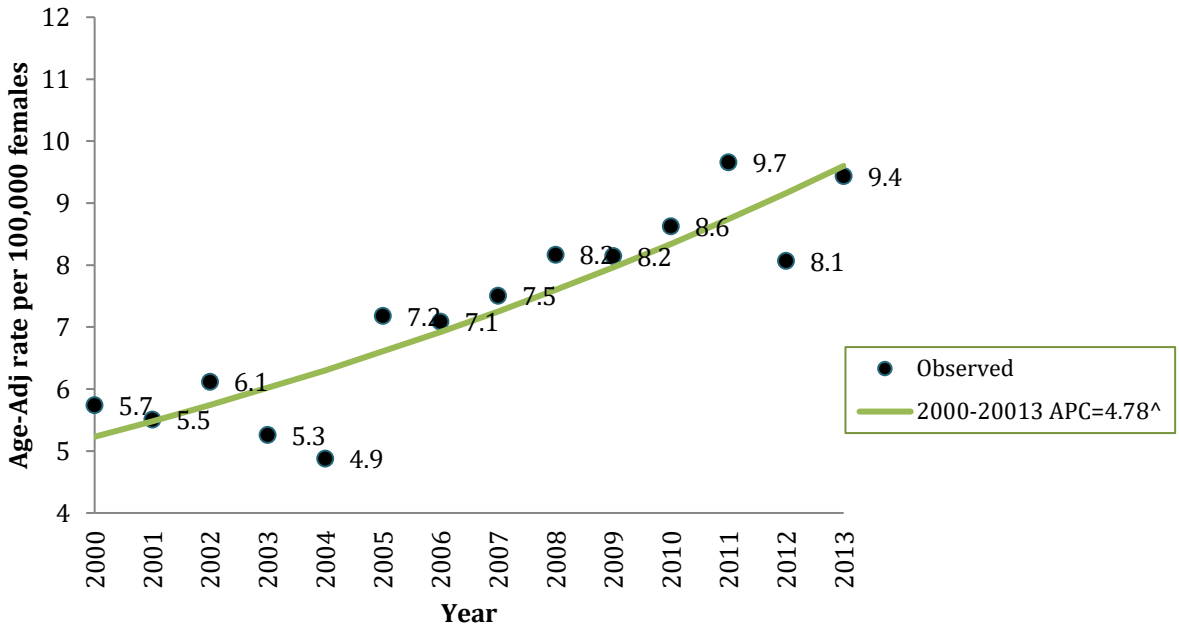
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 3.28 Malignant Breast Cancer Age-Adj Rates with Rare Subtypes



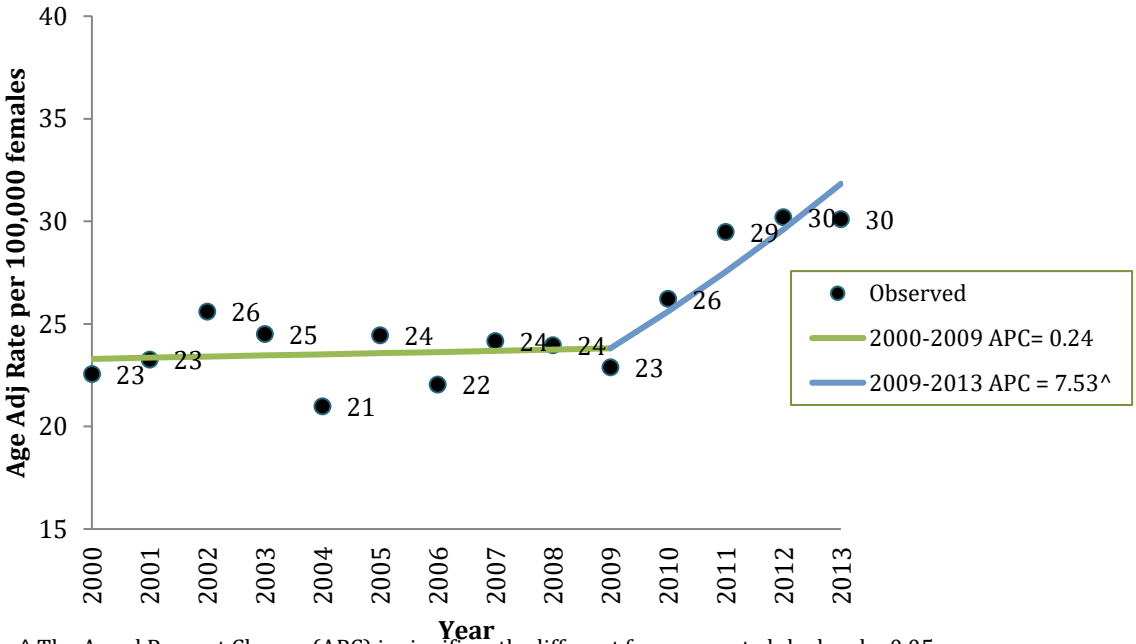
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 3.29 Malignant Breast Cancer Age-Adj Rates with Moderately differentiated



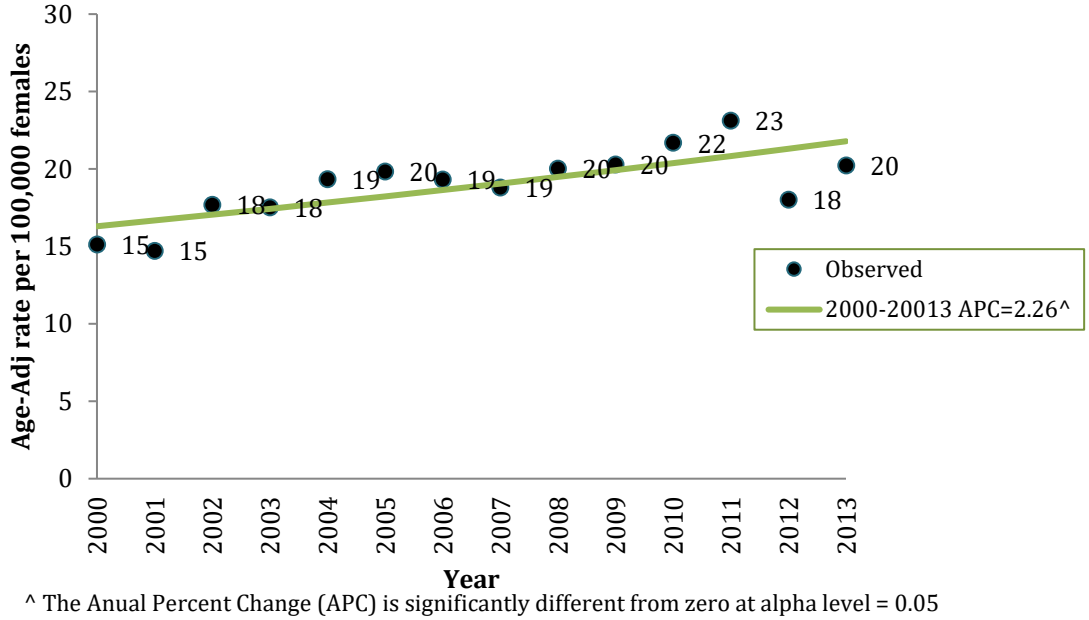
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 3.30 Malignant Breast Cancer Age-Adj Rates with Moderately differentiated



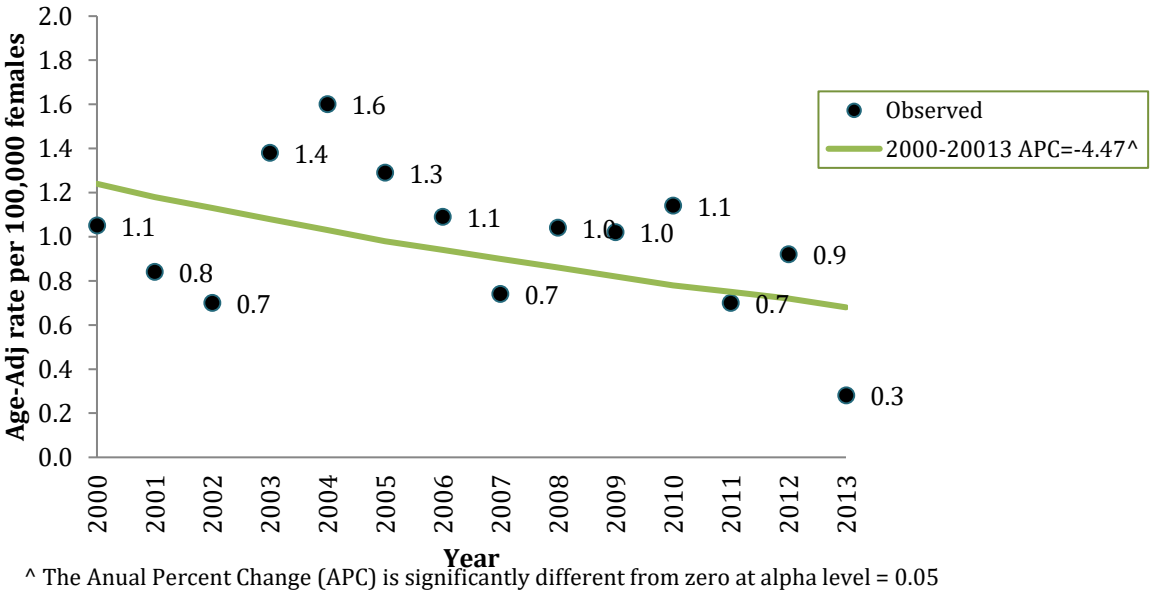
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 1 Joinpoint.

Figure 3.31 Malignant Breast Cancer Age-Adj Rates for Poorly differentiated



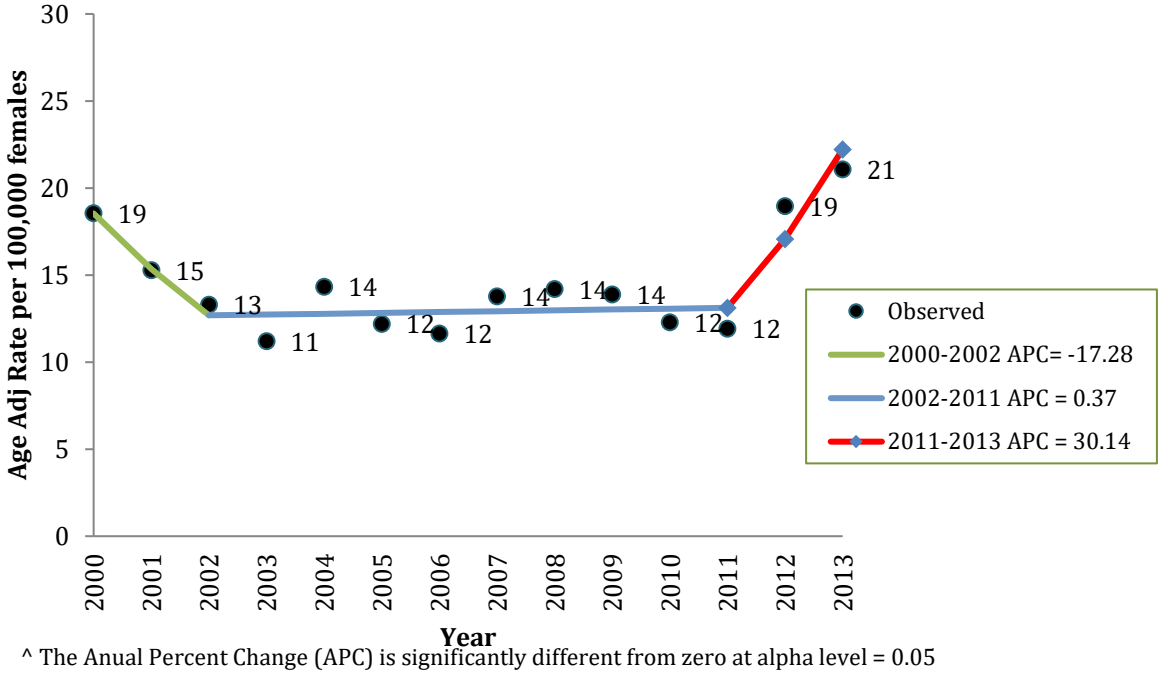
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 3.32 Malignant Breast Cancer Age-Adj Rates for Undifferentiated



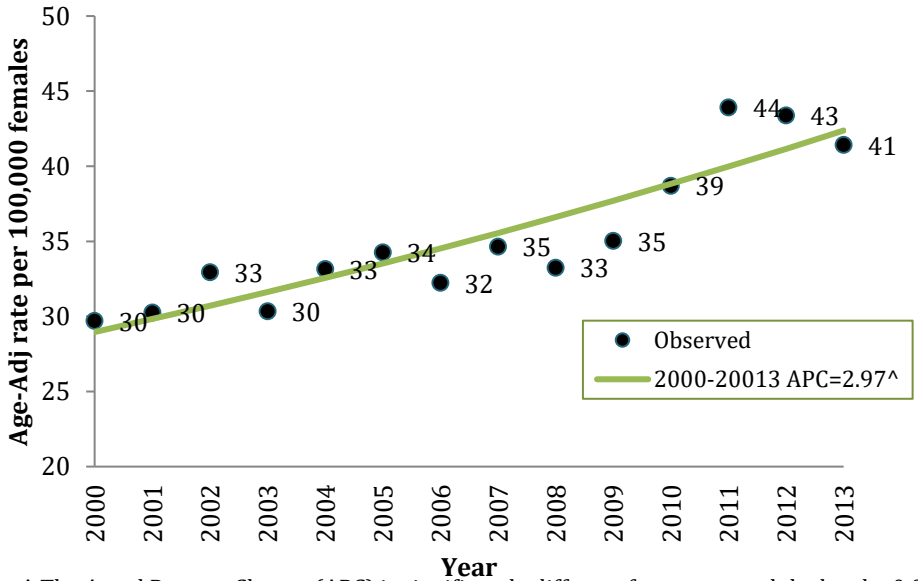
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 3.34 Malignant Breast Cancer Age-Adj Rates for Cell type not determined.



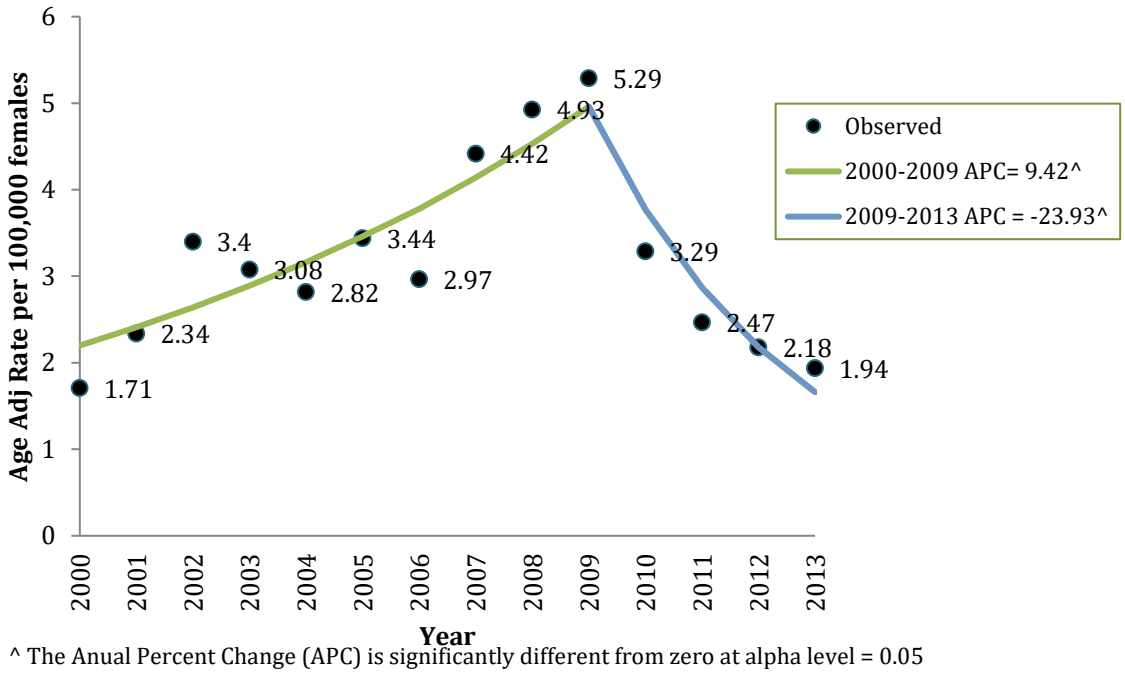
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 1 Joinpoint.

Figure 3.33 Malignant Breast Cancer Age-Adj Rates for Localized Disease Stage



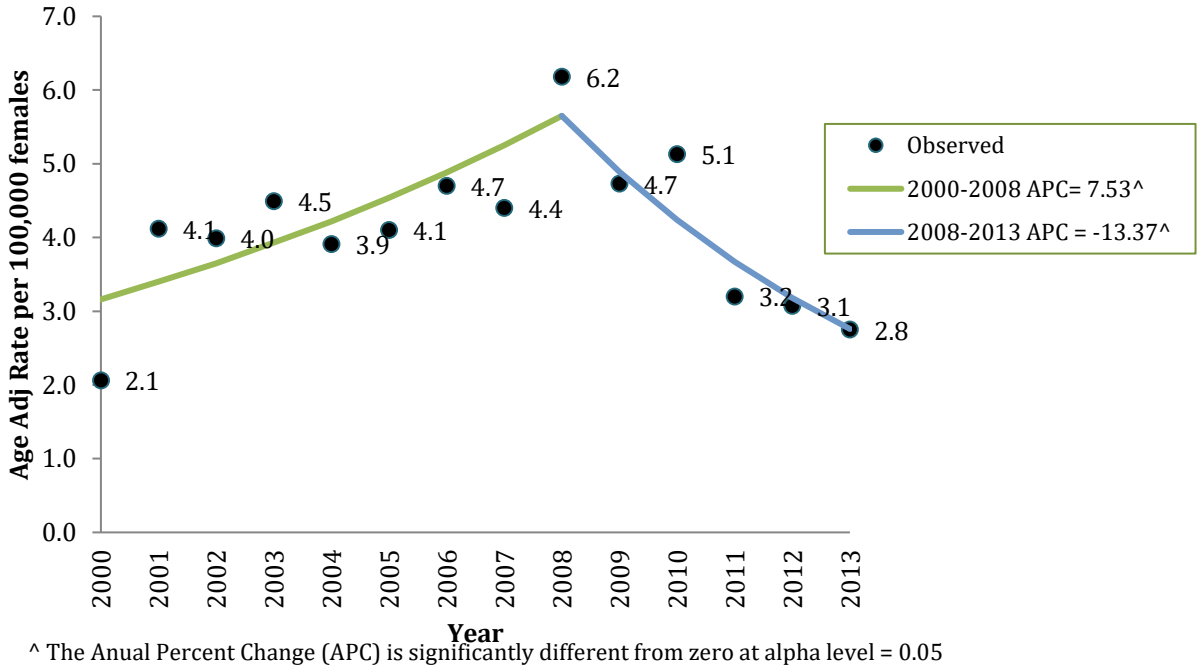
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 3.36 Malignant Breast Cancer Age-Adj Rates with Regional by Direct Extension Stage



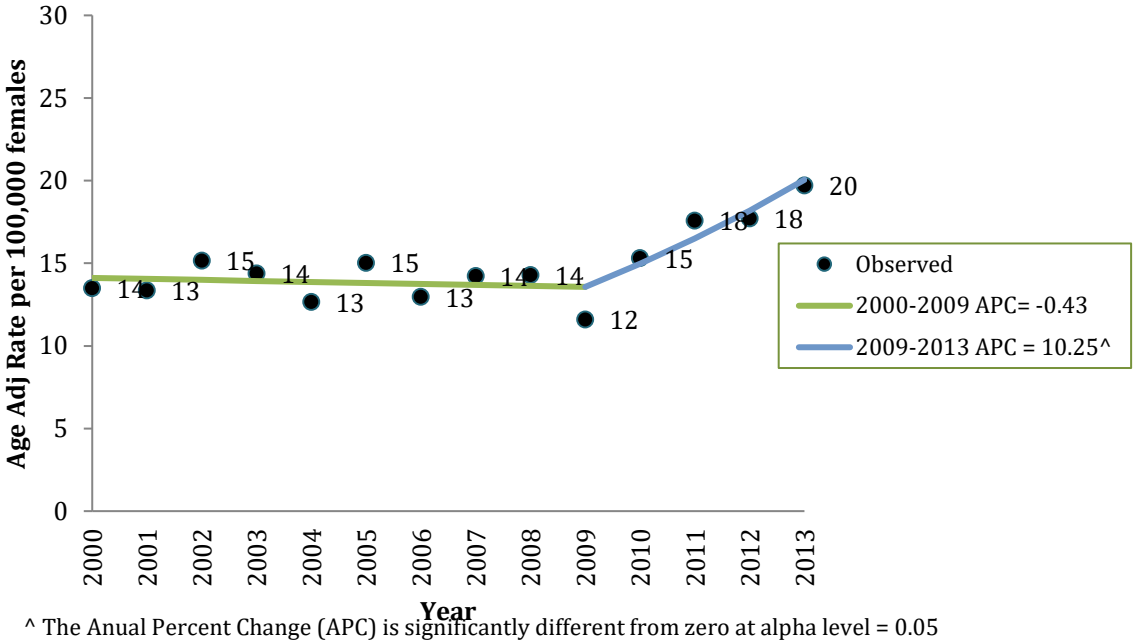
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 1 Joinpoint.

Figure 3.35 Malignant Breast Cancer Age-Adj Rates with Regional by DE and Lymph Node Stage



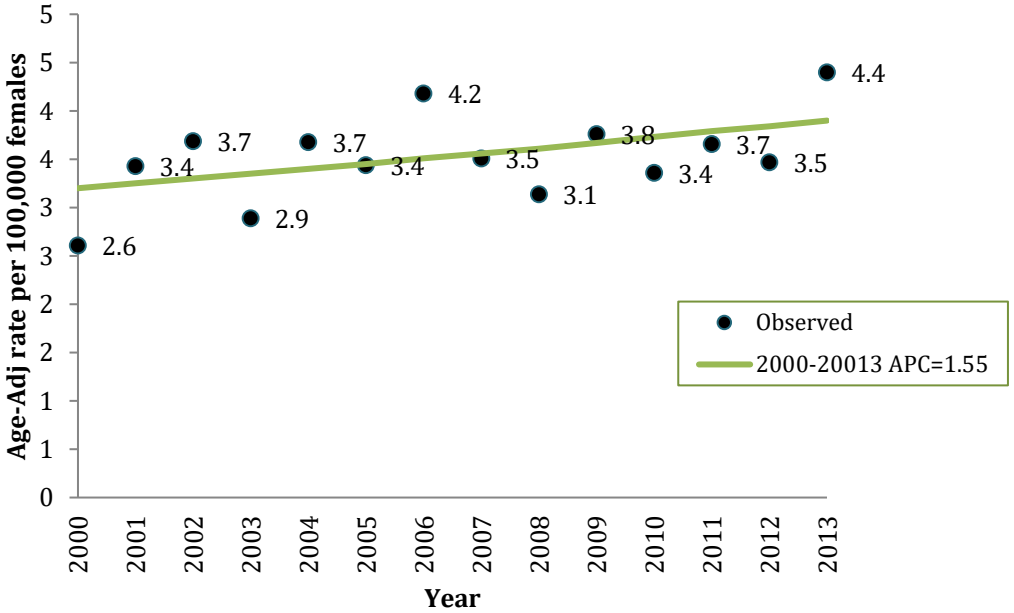
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 1 Joinpoint.

Figure 3.37 Malignant Breast Cancer Age-Adj Rates with Regional to lymph node Staging



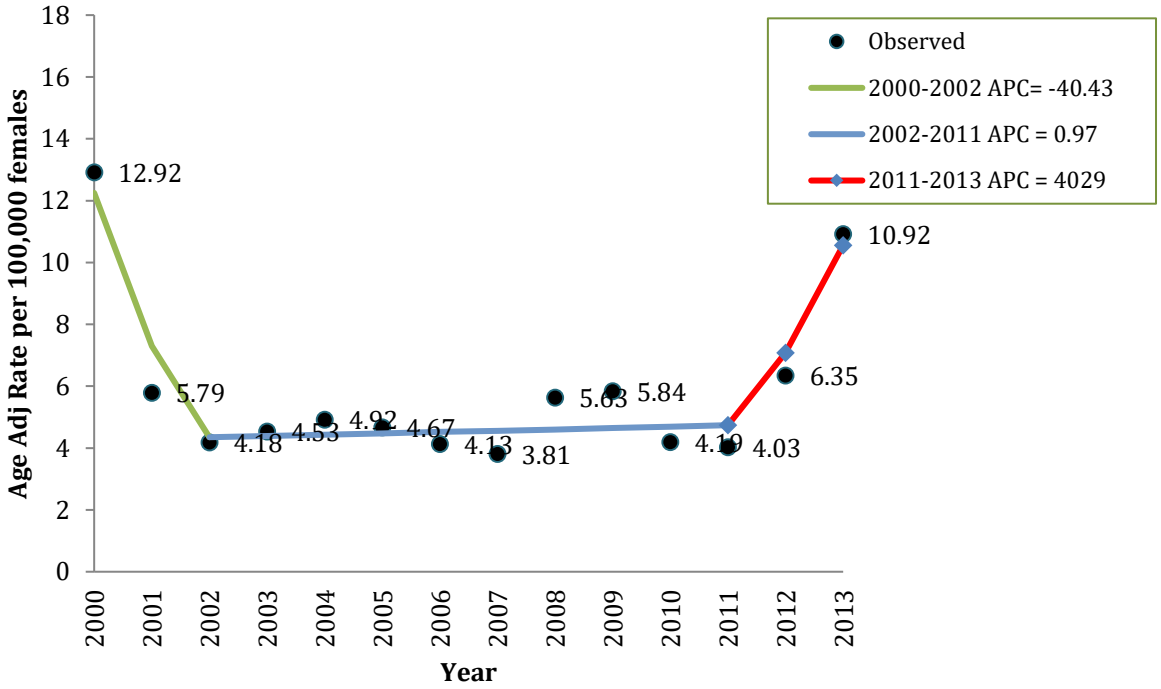
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 1 Joinpoint.

Figure 3.38 Malignant Breast Cancer Age-Adj Rates with Distant Stage



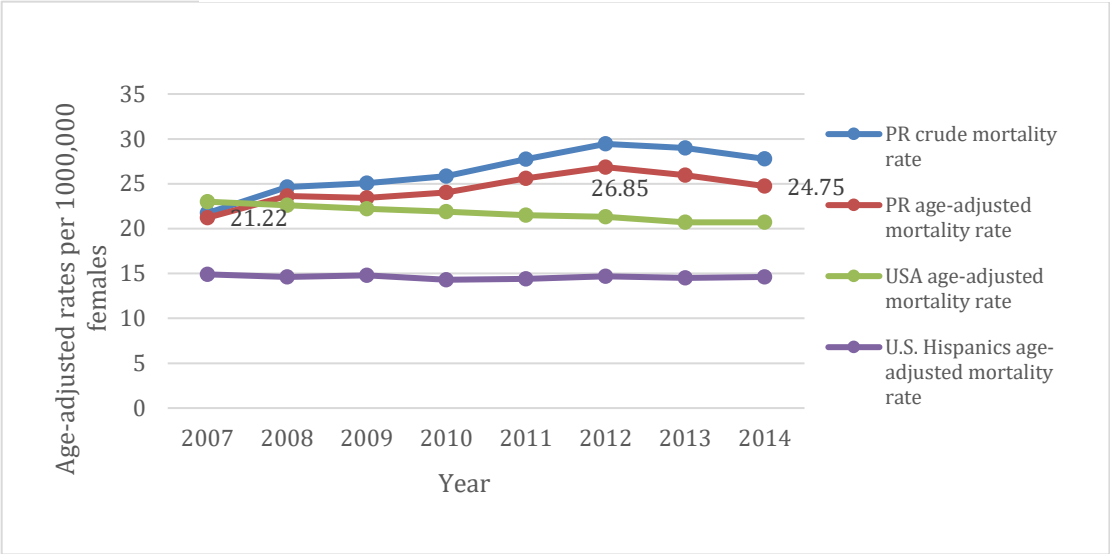
^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 0 Joinpoints.

Figure 3.39 Malignant Breast Cancer Age-Adj Rates with Unknown Stages



^ The Anual Percent Change (APC) is significantly different from zero at alpha level = 0.05
Final Selected Model: 1 Joinpoint.

Figure 3.40 Breast Cancer Mortality Rates for PR and USA



	2007	2008	2009	2010	2011	2012	2013	2014
PR crude mortality rate	21.74	24.62	25.06	25.84	27.72	29.44	28.99	27.79
PR age-adjusted mortality rate	21.22	23.62	23.41	24.04	25.58	26.85	25.95	24.75
USA age-adjusted mortality rate	23	22.6	22.2	21.9	21.5	21.3	20.7	20.7
U.S. Hispanics age-adjusted mortality rate	14.9	14.6	14.8	14.3	14.4	14.7	14.5	14.6

Figure 3.41 Trends for Breast Cancer Age Adjusted Mortality Rates by Histologic Types

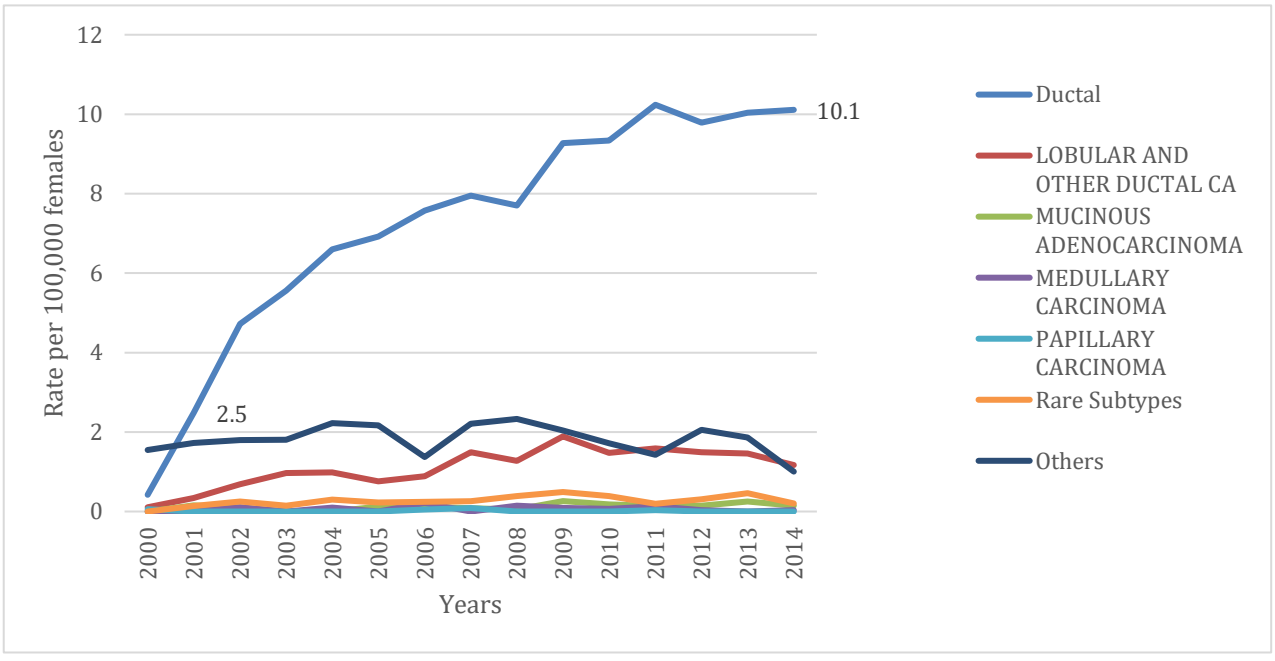


Figure 3.42 Breast Cancer Age-Adjusted Mortality Rates by Grade of the tumor

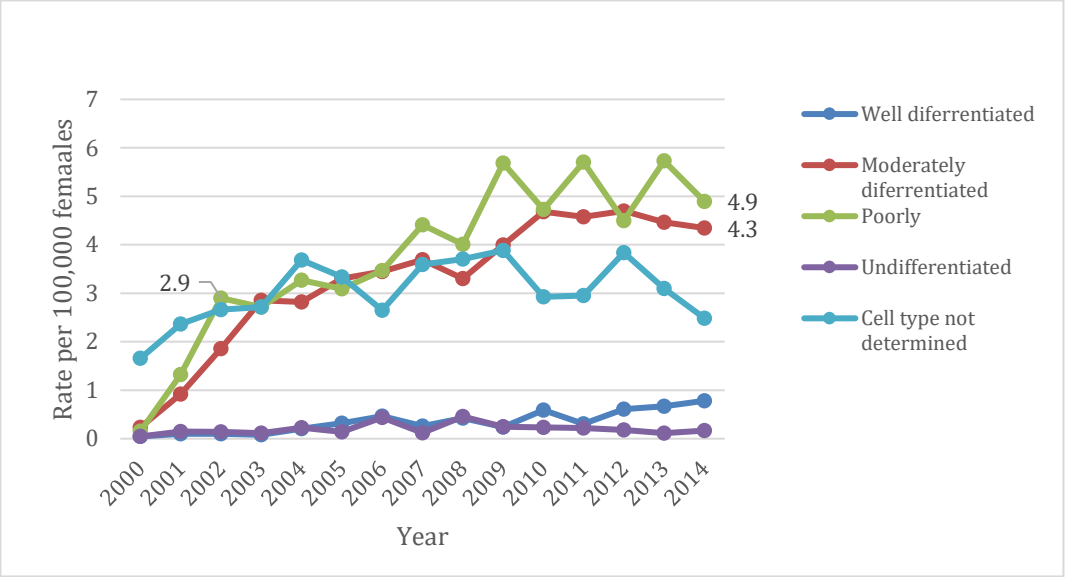
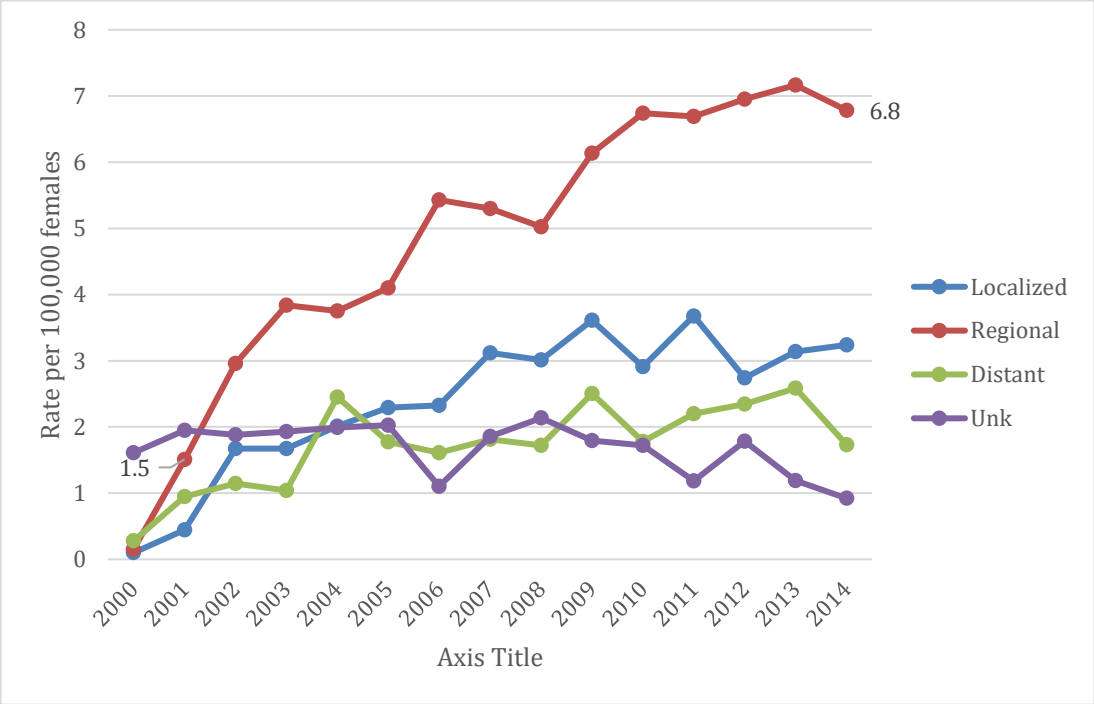


Figure 3.43 Age-Adjusted Mortality Rates by Disease Staging at Diagnosis



References

Breast Cancer Now Organization. https://breastcancernow.org/information-support/facing-breast-cancer/diagnosed-breast-cancer/cancer-grade-size; February 2018.

https://www.breastcancer.org/risk/factors/hrt; Using HRT (Hormone Replacement Therapy).

Joinpoint Trend Analysis Software; https://surveillance.cancer.gov/joinpoint/

Li Christopher, Malone, Kathleen, and Daling Janet. Differences in Breast Cancer, treatment and Survival by Race and Ethnicity.Arch Inter Medicine, Vol 163. January 13, 2003.

Power 2018; Breast Cancer Incidence and Risk Reduction in the Hispanic Population. Cureus. 2018 Feb; 10(2): e2235. doi: 10.7759/cureus.2235

Proyección de población por genero grupo de edad y municipios. Junta de Planificación, Programa de Planificación Económica y Social, Oficina del Censo. https://jp.pr.gov/Econom%C3%ADa/Censo

Puerto Rico 2000, Census 200 Profile. U.S. Department of Commerce Economics and Statistics Administration U.S. CENSUS BUREAU; November 2002, C2KPROF/00-PR.

USA Census Bureau, 2000 Census.

U.S. Census Bureau, 2010 Census of Population and Housing, updated every 10 years. Decennial Census Datasets. Population, Census, April 1, 2010.

CHAPTER IV

A ten-year population treatment profile of breast cancer cases in a Medicare Advantage Independent Practice Association in Puerto Rico

Introduction

Access to health services in Puerto Rico for the medically indigent population changed when the government established a Health Reform initiative in 1994. This initiative gave health insurance companies an essential role in administering health service provision to the medically indigent population. The Health Reform initiative in the Island was implemented by stages starting in 1994 and concluding in 2000. Similarly, in 2006, Puerto Rican (PR) Medicare beneficiaries were now able to enroll in a Medicare Advantage (MA) plan, a type of Medicare health plan (Part C) offered by a private health insurance company that contracts with Medicare to provide Part A, Part B, and Part D benefits. Given the minimal to no co-payments and enhanced benefits in these MA plans, their popularity saw an MA penetration of almost 80% among the eligible Medicare beneficiary population. (Keyser, 2014).

The new Medicare Advantage companies were now locally administering the coordination of screening services and supporting primary care health providers with coordination of care, including cancer screening and cancer treatment modalities for many Medicare patients, who had lacked many of these opportunities before introducing these MA plans. In 2012, a total of 483,978 persons, 75% of the Medicare-eligible population, were enrolled in a MA plan in Puerto Rico (Keyser, 2014). The implementation of the Medicare Advantage program in Puerto Rico resulted in more access for PR Medicare beneficiaries to more health-related preventive screening

services and treatment options. As shown in paper one, breast cancer data analysis shows that the age-adjusted incidence increased in the island, starting in 2006, the year the Program began.

Castellana's Physician Services is an Independent Practice Association (IPA) with approximately 400 primary health care providers serving about 30,000 female patients over the age of 65. This number represents 11% of the Medicare Advantage female population of Puerto Rico. The IPA Castellana exclusively managed Medicare-eligible members in four Geographical Regions on the north and east side of the Island. Thus, findings in this population likely represent the best standard of care in Puerto Rico for the elderly population. Castellana is exclusively contracted with one MA plan called MMM. MMM was the first MA plan to achieve the Centers for Medicare and Medicaid Services (CMS) five-star rating and continues to hold the highest-rated star ranking among all plans on the Island (MMM website, 2020).

This study aims to analyze the distribution of breast cancer cases seen within the Castellana system by year and the related pharmaceutical and medical services utilization during the study period. No study has described, to our knowledge, the pharmaceutical and medical treatment modalities provided to breast cancer patients since the implementation of the Medicare Advance program on the Island. Analyzing these patterns will help evaluate the extent of breast cancer treatment guidelines and help identify areas where there is an opportunity for improvement.

Methods

To describe this breast cancer population, a claims analysis was conducted using linked de-identified patient's files with pharmacy and medical claims information for the period of April 1, 2007, to Oct 20, 2016, paid as of Oct 21, 2016. Files were provided after receiving approval from the Castellana administration and the MMM health plan compliance officer. Data analyses were conducted using the SAS version 9.4, and Epi-Info version 7.2.2.6, the Center for Diseases Control (CDC) Epidemiologic Software System.

To identify breast cancer patients*, three steps requiring data linkage were needed: First*, we identified all patients in the medical claims database with a breast cancer diagnosis. Only medical claims with breast cancer codes based on the WHO International Categorization of Diseases (ICD-9) codes within any of the first four diagnostics field positions in the claim (Table 4.1) were included. This inclusion criterion was applied to the 2,538,701 lines of medical claims. Laboratory and radiological claims were not considered because such claims could be the result of a screening effort. However, as not all breast cancer patients might have a medical claim with breast cancer ICD-9 codes, a second step was then undertaken to ensure that a better identification of breast cancer patients occurred. Using the pharmacy claims files, Patients were selected if using antineoplastic drugs indicated for breast cancer by the Federal Drug Administration. Identified cases were merged with the first group, and duplicate patients were deleted. A third step was done to obtain all their pharmacy drug-related utilization for the study period with all breast cancer patients identified. We filtered a total of 1,159,253 lines of pharmacy utilization claims files to locate only those pharmacy claims from individuals identified to be breast cancer patients. This step was

done to gather all pharmacy utilization from the pharmacy claims dataset. Finally, all their medical claims utilization files were built to study the treatment profiles.

Data Management

Merged dataset sets were analyzed using the CDC Epi-Info and SAS statistical software. Descriptive statistics were generated for the study population. For the geographical plotting analysis, the latitude and longitude coordinates for each municipality were used to plot each case residing in a given municipality using the EPI-Info maps software module.

Results

A total of 5,112 unique female breast cancer patients were identified from the medical claims file. Eighty-five (85) cases out of these 5,112 claims were not identified in the demographic file. As a result, 5,027 cases had both medical claims and demographic related information. However, to maximize the provided information, 5,112 represented the analytical sample. We evaluated the percentage of patients who remained continuously active in the Health plan during the study period receiving services by the Health plan and were under the clinical guidance of a Primary Care Physician (PCP) in the Castellana Group. A total of 1,009 (20.5%) cases were active in the IPA since April 2004. By June 1, 2016, 2,902 (57%) of the breast cancer patients were still active and receiving services coordinated by the IPA's primary care physicians (Figure 4.1). To be non-active, a member (patient) might have decided to change to a different PCP, not under the Castellana Group, or the patient may have died.

Of the 5,027 Castellana's breast cancer cases, 85% were over 65 years of age while close to 14% of the cases between 45 and 64 years of age. The median age for

the cases was 73 years, the minimum reported age was 35, and the maximum was 106 years of age.

The identified patients' geographical residence was clustered; cases were concentrated from the middle to the east part of the Island, where the Castellana's provider network renders services (Table 4.2 and Figure 4.1). This is consistent with the allocation of the geographical locations of the Castella Primary Care Physicians' offices. Figure 4.2 provides the distribution of cases over time, stratified by location. Of the cases, 64% were also State-funded, or as called by the Government, were "Platinos", which signifies that they were under the 200%-poverty federal income level. During the study period, close to 30% of the breast cancer patients received at least one breast cancer specialty drug, derived from the pharmacy claims files, to treat their condition (Table 4.2).

Prescription Utilization Summary among Breast Cancer Patients

A total of 880,884 prescriptions were identified and paid out of the pharmacy claims file from the 5,112 breast cancer patients. The number of medications (any prescription) per case increased from 2.7 prescriptions per case in January 2008 to 3.5 prescriptions per case in October 2016 (Figure 4.3),

The Hormonal and Related Agents (HRA) Drug Category, 13,215 breast cancer Specialty Drugs prescriptions, were identified as dispensed in pharmacies across the Island from the largest categorical group. Of these, 98% were administered orally, and 13,033 (98.62%) were within the Antineoplastic - HRA drug classification category (Table 4.3). The Identified used drugs and drug categories within this study population are listed (Table 4.4). Among the subclasses of the anti-neoplastic HRAs, aromatase

Inhibitors accounted for 73.7% of the total prescriptions for the study period followed by antiestrogens with 24.9 of the prescriptions (Table 4.5). The use of Aromatase Inhibitors increased from 60% in the year 2008 to 74% in 2016.

In contrast, the use of Antiestrogen decreased from 40% in the year 2006 to 14% in the year 2018. (Figure 4.4). To further analyze the use of Aromatase Inhibitors versus the use of Antiestrogens, the prescriptions per breast case were analyzed. The number of prescriptions for Aromatase Inhibitors per breast cancer case significantly increased from .10 prescriptions per case in 2008 to almost one prescription per case (.77) in 2016. The number of prescriptions per case for Antiestrogens remains stable during the period with .06 prescriptions for the year 2008 compared to .11 prescriptions per case in 2016 (Figure 4.7).

To evaluate the Breast Cancer patient's drug utilization by intravenous administration, all injectables were identified from the Medical Utilization Datafile. A total of 1,884,744 claims from injectables services were identified from the breast cancer case medical data file with a median of 3.8 injectable services per case in 2010, increasing to a median of six injectable services per breast cancer case in June 2016 (Figure 4.6).

Specifically, for breast cancer related injectable drugs, a total of 231,660 claims (3%) were identified from the breast cancer specialty drugs list (Table 4.6). Most of the claims (78%) indicate that breast cancer cases undergoing specialty drug treatment were treated at the medical provider doctor’s office (oncologists). Paclitaxel is the most frequently used drug for treatment.

Medical Service Categories

Out of the 2,538,701 service claims, a total of 188,227 were identified with a breast cancer code as the principal diagnosis in the service claim. Services increased consistently across the study period and were coded to service categories based on the American Medical Association's Coding Standard. The number of services per case increased across the study period from 64.8 services per case per year in 2007 to 110.5 services per case per the year in 2015 (Table 4.7).

The main categories of services rendered for the Breast Cancer patients were Office/other outpatient services (16%), Injectable drugs (13%), Radiation and Oncology (12%), and Chemotherapy (10%). Those services were mainly rendered in the office setting (56%), in Independent Laboratories (22%), and the On Campus-Outpatient Hospital setting 15%. (Table 4.8 & 4.10). For breast cancer as a primary diagnosis, all services categories increased except for the service category of Radiation Oncology, which presented a major drop in 2013 (Table 4.9 & 4.11).

Surgical Procedures

A total of 985 out of 5,112 breast cancer patients had mastectomy procedures during the studio period. This accounts for 20% of the population (Figure 4.8). The procedure (19301) of "Mastectomy, partial" (e.g., lumpectomy, tylectomy, quadrantectomy, segmentectomy) increased from 39.5% of cases in 2007 to 57.28% in 2016. In contrast, the procedure (19302) "Mastectomy, partial with axillary lymphadenectomy" (e.g., lumpectomy, tylectomy, quadrantectomy, segmentectomy); decreased from 31.08% in 2010 to 11.65% in the year 2016. (Figure 4.9).

Discussion

This study's objective was to describe the demographic characteristics of a Medicare Advantage breast cancer population in Puerto Rico and analyze the utilization of pharmaceutical and medical services for breast cancer treatment during the study period. An analysis of the trends and types of treatment using claims paid data from a private health plan will help evaluate if there was more and better adoption of treatment guidelines during this period, identifying areas of opportunity for improvement.

The analysis demonstrated an increase in the utilization of services in pharmacy claims and medical service claims. By the end of the study period, more patient services were available to the breast cancer population of the Medicare Independent Practice Association (IPA) of Primary Care Physicians. Prescriptions per case and injectables per case both increased. The percent receiving aromatase inhibitors also increased during the study period. In contrast, the use of antiestrogens decreased. A lack of estrogen receptor and progesterone receptor testing may be one of the reasons for this decrease. Our prior study of the Puerto Rico Central Cancer Registry identified the registry's lack of information on receptor data. These facts raise the question of whether providers are not ordering these tests or whether the health plan is not approving them, given the lack of evidence for the corresponding therapy. This question requires further research.

Among the medical utilization services, we observed increases in the medical provider office setting category. Primary care physicians and oncologists evaluated more breast cancer cases, and care and coordination of services were increased by the IPA and the health insurance company during the study period. The percent of independent laboratory utilization also increased during the study period, showing more access to the system. In contrast, the use of Outpatient Hospital services decreased, which may be a

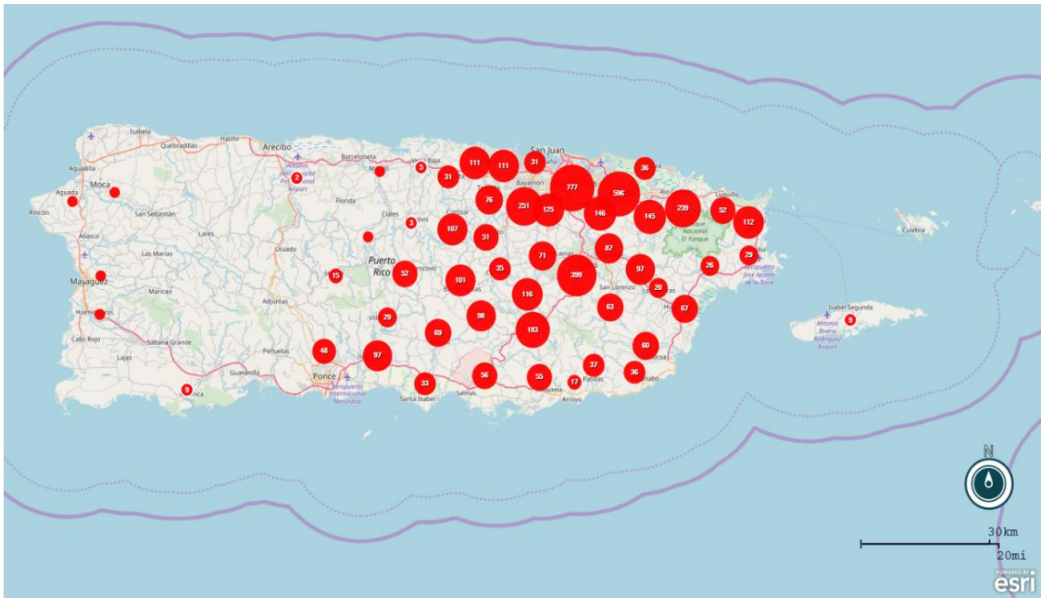
direct effect of more patients visiting the providers at their office instead of using a hospital setting for preventive ambulatory services. One of the specific breast cancer treatment modalities evaluated in this study was mastectomy utilization among this population. The overall percentages of partial mastectomies increased during the period, suggesting better adoption of treatment guidelines in this population (National Comprehensive Cancer Network, 2020).

The main strength of this study was to perform a complementary analysis of breast cancer incidence and mortality data evaluating the course of diagnosis and treatment using an electronic claims-based dataset. This method helps to describe the time of diagnosis and treatment using billed services and diagnostics codes billed by service providers to a private health plan. The use of health insurance data allows us to study prevention screening efforts, diagnosis, surgical procedures, and prescribed drug therapies used for treatment during the disease. It also provides information on the type of service providers who participated in the diagnosis and treatment stages. This information is not available in the State Cancer Registries. Reliable data is derived from health plans given that they are subject to audits by multiple federal and local entities of their validity to safeguard the fiscal sources of the patients and the government. Some of these entities are: Center of Medicaid and Medicare, the Department of Health of Puerto Rico, “Oficina del Comisionado de Seguros de Puerto Rico,” NCQA certified auditors and private auditing companies. Nonetheless, this data has some limitations such as variability due to the multiple coders, possible errors when billing, and lack of information on the results of procedures and laboratory services, as the only information available is whether or not the procedure or service was done. The analysis of this type

of data requires programming and coding expertise not necessarily available at the Cancer registries, which might be an economic and procedural challenge for small Registries to achieve.

In summary, these data suggest that breast cancer patients' treatment improved among Medicare female beneficiaries across the study period, consistent with the findings of Chapter II and Chapter III. Analysis of data from the Cancer Registry demonstrated an increase in breast cancer incidence after 2006, which corresponds to the timing of the implementation of the Medicare Advantage program on the Island. Several questions remain to be answered, such as integrating this analysis with elements of clinical characteristics of the tumor and staging the cases. A possible recommendation that can be derived from this study is to increase awareness of the importance of evaluating the preventive services and treatment received by a breast cancer patient based on the tumor's clinical characteristics and staging of the condition as seen by the medical provider. A detailed evaluation of treatment episodes can be suggested as a next step complementing the claims-based information with the electronic medical record information for breast cancer patients in Puerto Rico.

Figure 4.44 Castellana's Breast cancer patients by Geographical Region



(5,027 cases)

Note: Generated with Epi-Info.

Figure 4.45 Enrollment Activity for Castellena's Breast Cancer patients by Region

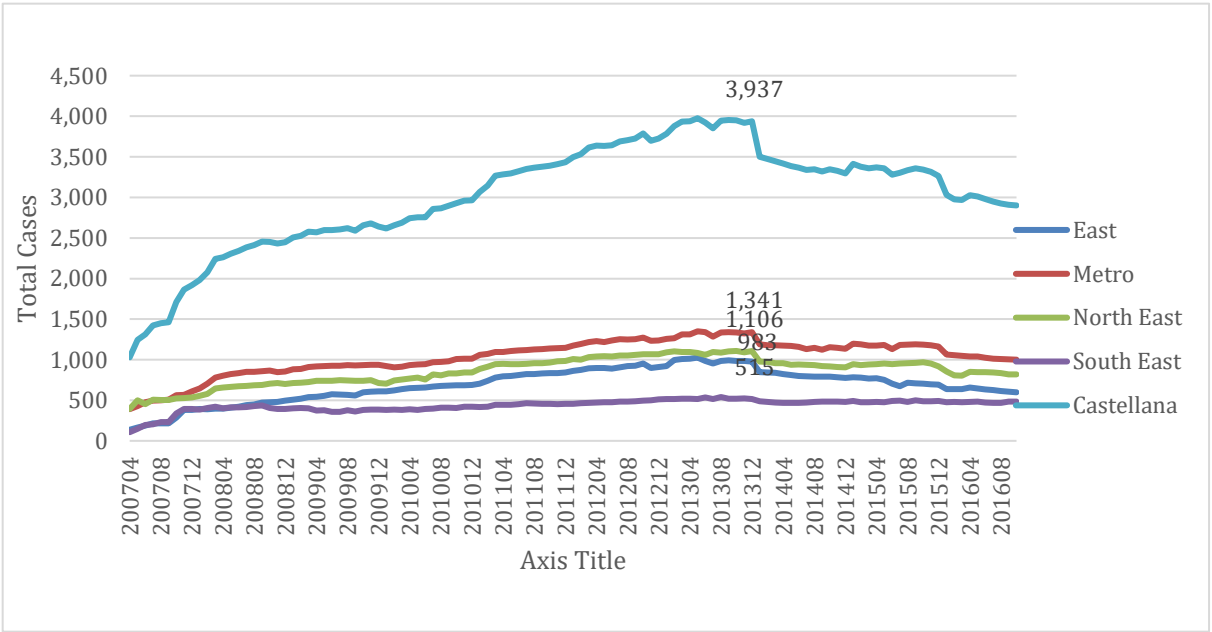


Figure 46 Prescriptions per Breast Cancer Case

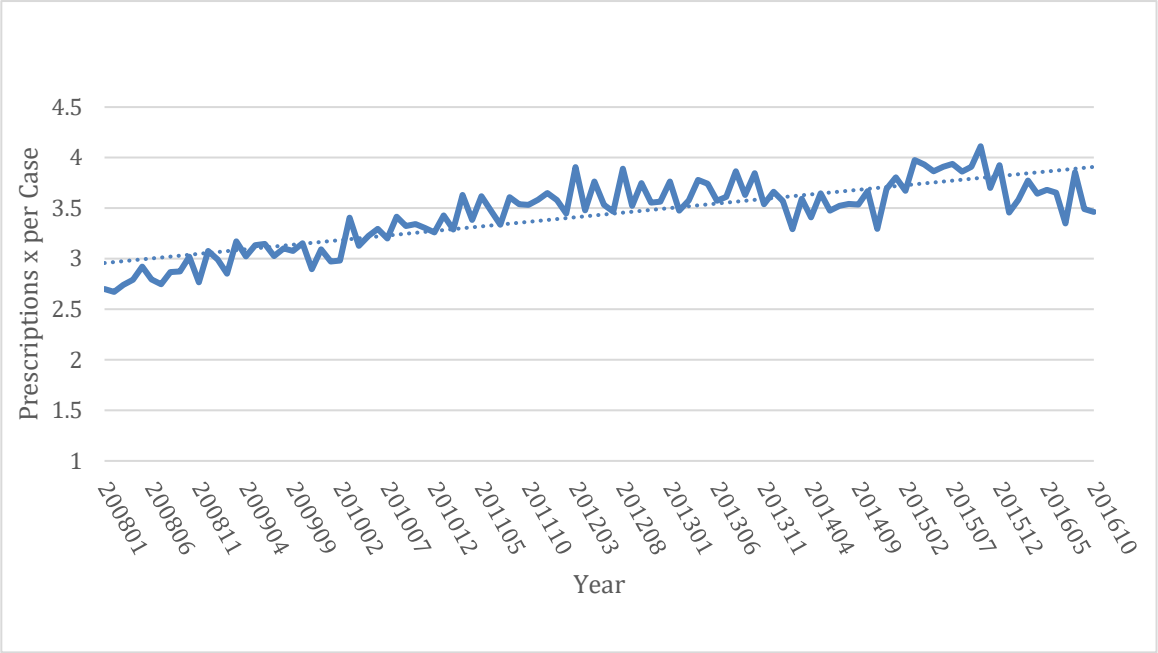


Figure 47 Percent of Breast Cancer Cases by year and Drugs sub class category

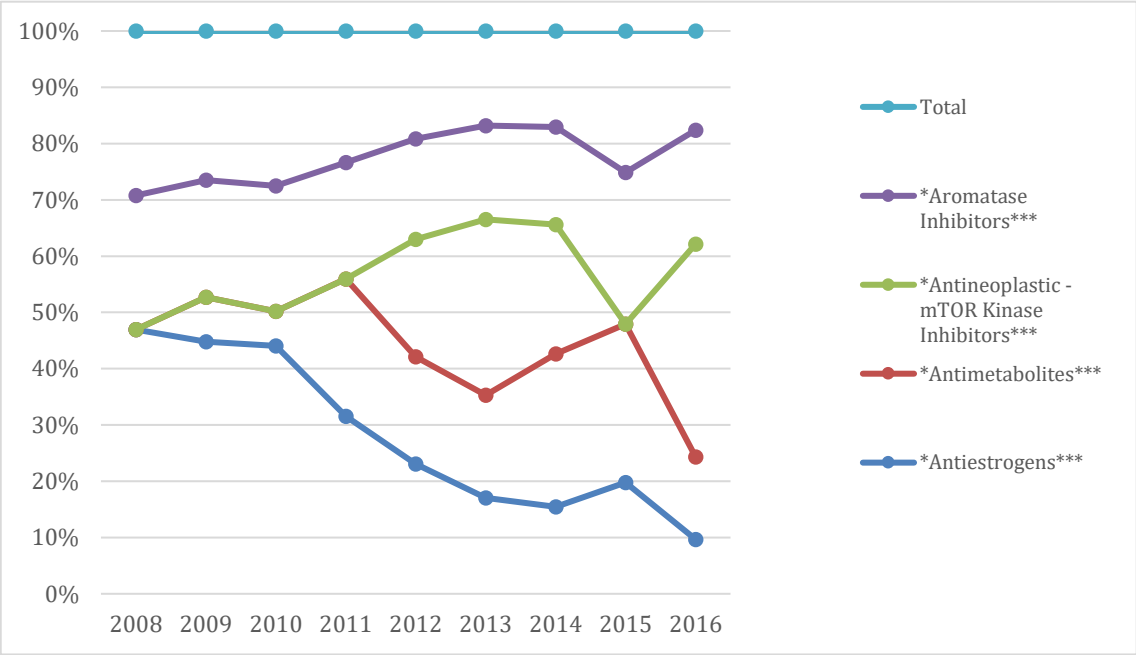


Figure 48 Breast Cancer Prescriptions per Breast Cancer Case a Year by Drug Category

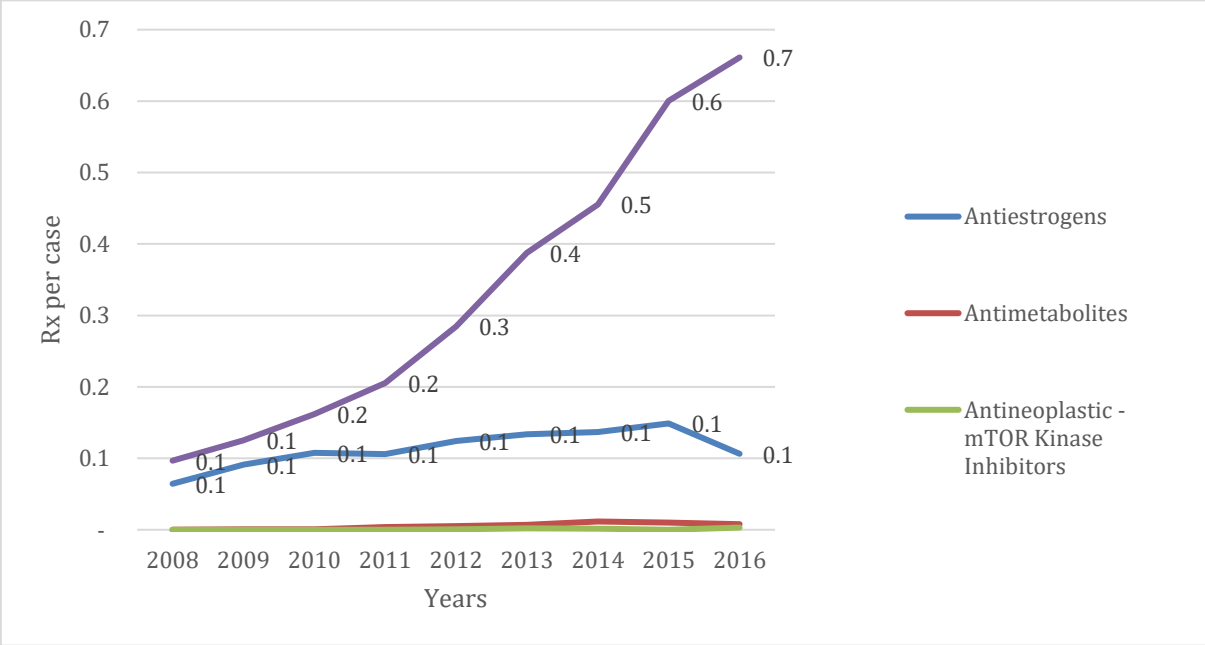


Figure 49 Overall Injectables Prescriptions per Breast Cancer Cases

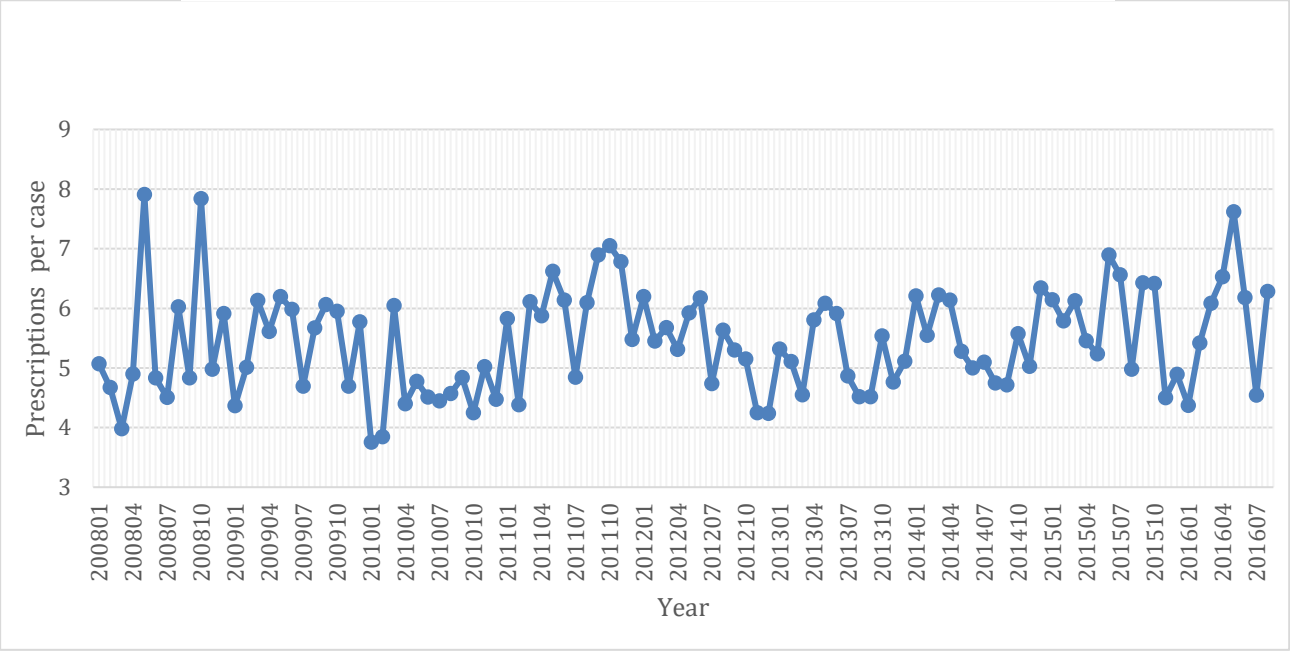


Figure 50 Medical Claims Services per Breast Cancer case during the study period

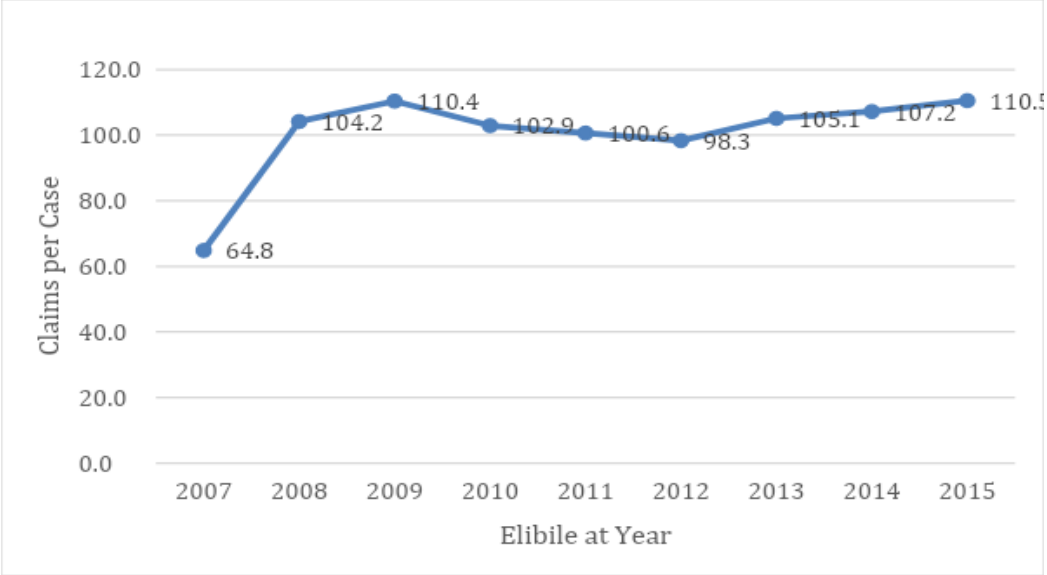


Figure 51 Percent Distribution of Mastectomies during 2008-2016

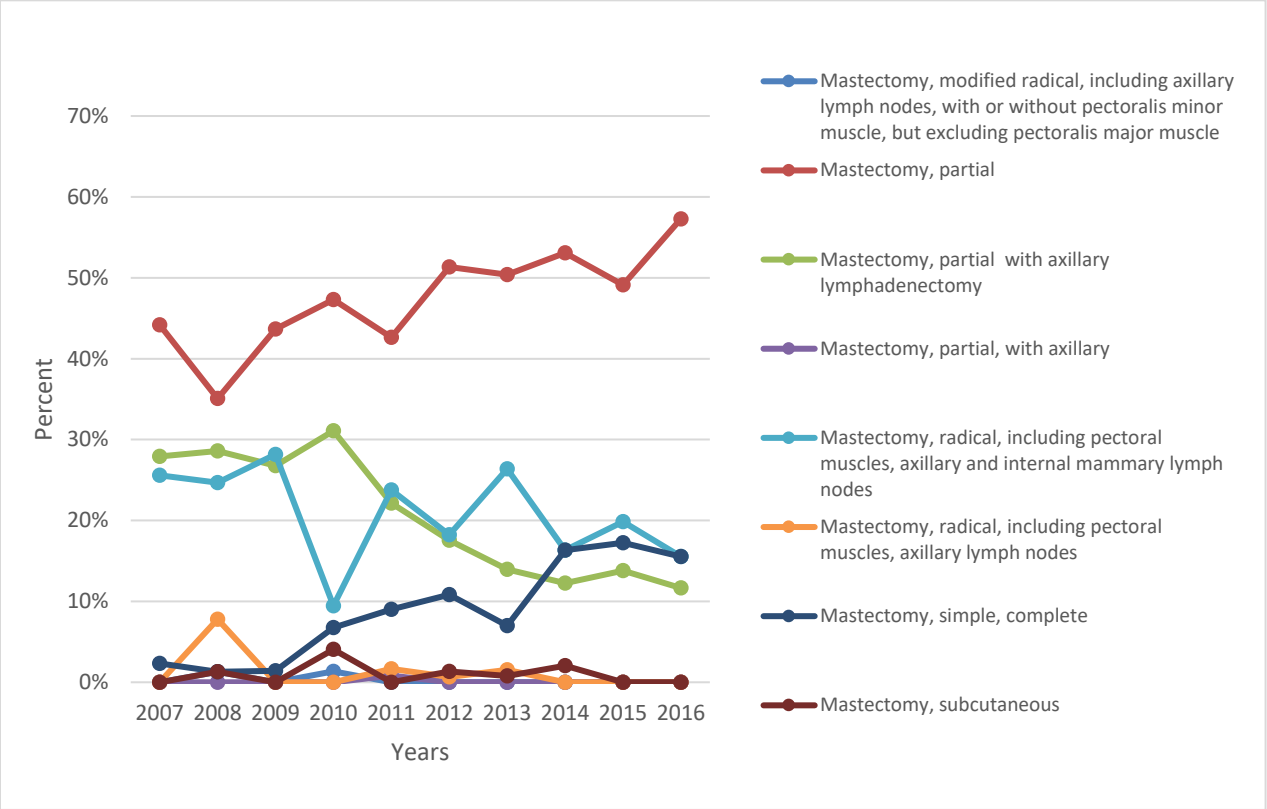


Table 4.1; Diagnostics codes used to identify Breast Cancer Cases from Medical Claims

ICD9 Code	Diagnostic Code Description
174	Malignant neoplasm of female breast
174.0	Malignant neoplasm of nipple and areola of female breast
174.1	Malignant neoplasm of the central portion of female breast
174.2	Malignant neoplasm of the upper-inner quadrant of female breast
174.3	Malignant neoplasm of the lower-inner quadrant of female breast
174.4	Malignant neoplasm of upper-outer quadrant of female breast
174.5	Malignant neoplasm of the lower-outer quadrant of female breast
174.6	Malignant neoplasm of axillary tail of female breast
174.8	Malignant neoplasm of other specified sites of female breast
174.9	Malignant neoplasm of breast (female), unspecified
V86.0	Estrogen receptor-positive status [ER+]
V86.1	Estrogen receptor-negative status [ER-]

Table 4.2; Socio-Demographic Characteristics of the Castellana Medicare Advantage IPA

	Age Category		**Frequency**	**Percent**
Patients Age	18 - 44		46	0.92%
	45 - 64		694	13.81%
	65 - 75		2168	43.13%
	76- 84		1452	28.88%
	85+		667	13.27%
			Frequency	Percent
Geographical Region	Central		934	18.58%
	East		819	16.29%
	North		12	0.24%
	Northeast		1,364	27.13%
	North-Metro		660	13.13%
	Northwest		2	0.04%
	San Juan		777	15.46%
	Southeast		400	7.96%
	Southwest		57	1.13%
	West		2	0.04%
			Frequency	Percent
State-funded Medicaid	Yes		3,233	64.32
	No		1,794	35.68
			Frequency	Percent
Specialty Drug ever used	Yes		1,536	30.55
	No		3,491	69.45

Table 4.3; Percent distribution of Orally Prescribed Drugs to Castellan Medicare Advantage Breast Cancer Patients

Drug subclass	Frequency	Percent
Aromatase Inhibitors	9,744	73.7%
Antiestrogens	3,289	24.9%
Antimetabolites	158	1.2%
Antineoplastic - mTOR Kinase Inhibitors	24	0.2%

Table 4.4; Break down of Prescribed Drugs to Castellana Medicare Breast Cancer Cases by Drug Class, Subclass, and Drug Names

Drug class	Drug subclass	Brand
Alkylating Agents	Nitrogen Mustards	Cyclophosphamide
Antimetabolites	Antimetabolites	Methotrexate
Antineoplastic - Hormonal and Related Agents	Antiestrogens Aromatase Inhibitors Estrogen Receptor Antagonist LHRH Analogs	Tamoxifen Anastrozole Aromasin Exemestane Femara Letrozole Faslodex Zoladex
Antineoplastic Enzyme Inhibitors	Antineoplastic - mTOR Kinase Inhibitors Poly (ADP-ribose) Polymerase (PARP) Inhibitors	Afinitor Lynparza
Mitotic Inhibitors	Mitotic Inhibitors	Docetaxel Paclitaxel Vinblastine

Table 4.5 Percent Distribution for Breast cancer drugs and Drugs Subclass among the Castellana's Breast Cancer Patients

DRUG SUBCLASS	Afinitor	Anastrozole	Aromasin	Exemestane	Femara	Letrozole	Methotrexate	Tamoxifen	Total
Antiestrogens	0	0	0	0	0	0	0	3,289	3,289
Row%	0%	0%	0%	0%	0%	0%	0%	100%	100%
Antimetabolites	0	0	0	0	0	0	158	0	158
Row%	0%	0%	0%	0%	0%	0%	100%	0%	100%
Antineoplastic - mTOR Kinase Inhibitors	24	0	0	0	0	0	0	0	24
Row%	100%	0%	0%	0%	0%	0%	0%	0%	100%
Aromatase Inhibitors	0	5,461	642	1,727	618	1,296	-	-	9,744
Row%	0%	56.04%	6.59%	17.72%	6.34%	13.30%	0%	0%	100%
TOTAL	24	5,461	642	1,727	618	1,296	158	3,289	13,215
Row%	0.20%	41.30%	4.90%	13.01%	4.70%	9.80%	1.2%	24.9%	100%
Col%	100%	100%	100%	100%	100%	100%	100%	100%	100%

Table 4.6; Injectable Utilization for the Castellana's Breast Cancer Patients

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total	%
Office Location	**1940**	**1770**	**1196**	**3948**	**5987**	**4197**	**4814**	**6346**	**3906**	**4013**	**38117**	**78%**
Cyclophosphamide, 100 mg	12	30	12	30	732	450	696	612	360	648	3582	
Goserelin acetate implant, per 3.6 mg			4	16	16	24	8	48	20	32	168	
Injection, docetaxel, 1 mg				1100	1875	950	1450	2100	950	975	9400	
Injection, paclitaxel protein-bound particles, 1 mg		23	7		19	7	23	20	7	6	112	
Injection, paclitaxel, 1 mg									2398	2244	4642	
Injection, paclitaxel, 30 mg	1869	1617	1113	2730	3276	2646	2457	3423	21		19152	
Injection, vinblastine sulfate, 1 mg	8	10						2			20	
Methotrexate sodium, 5 mg							84	42	105	21	252	
Methotrexate sodium, 50 mg	51	90	60	72	69	120	96	99	45	87	789	
Home		**87**	**651**	**663**	**1936**	**2393**	**1196**	**526**	**275**		**7727**	**16%**
Cyclophosphamide, 100 mg					522	546	270	60	18		1416	
Goserelin acetate implant, per 3.6 mg					4						4	
Injection, docetaxel, 1 mg				450	1125	1100	550	100	75		3400	
Injection, paclitaxel protein-bound particles, 1 mg					6	12	16	1	2		37	
Injection, paclitaxel, 1 mg									176		176	
Injection, paclitaxel, 30 mg		63	651	210	189	735	357	357			2562	
Injection, vinblastine sulfate, 1 mg								8	4		12	
Methotrexate sodium, 5 mg		21			63						84	
Methotrexate sodium, 50 mg		3		3	27		3				36	
Inpatient						**42**	**3**	**25**	**50**		**120**	**0%**
Injection, docetaxel, 1 mg								25	50		75	
Injection, paclitaxel, 30 mg						42					42	
Methotrexate sodium, 50 mg							3				3	
Outpatient hospital	**84**	**231**	**126**	**214**	**229**	**371**	**215**	**441**	**604**	**659**	**3174**	**6%**
Cyclophosphamide, 100 mg					54	72	78	78	42	114	438	
Injection, docetaxel, 1 mg				25	175	275	125	300	150	150	1200	
Injection, paclitaxel protein-bound particles, 1 mg									29	21	50	
Injection, paclitaxel, 1 mg									374	374	748	
Injection, paclitaxel, 30 mg	84	231	126	189		21		63			714	
Methotrexate sodium, 50 mg						3	12		9		24	
Grand Total	2024	2088	1973	4825	8152	7003	6228	7338	4835	4672	49138	**100%**

Table 4.7; Summary of Medical Claims services, Breast Cancer Cases and Claims per Case

	2007	2008	2009	2010	2011	2012	2013	2014	2015
All medical claims	98,473	214,763	240,492	244,689	271,919	298,286	336,336	304,309	317,317
Breast Cancer Cases	1,519	2,062	2,179	2,378	2,702	3,034	3,200	2,839	2,871
Claims per case	64.8	104.2	110.4	102.9	100.6	98.3	105.1	107.2	110.5

Table 4.8; Percent Distribution of Service Category of Breast Cancer Cases

Top Service Class	Services	%
Office/other outpatient services	29,004	15.7%
Drugs Administered Other Than Oral Method, Chemotherapy Drugs	24,794	13.4%
Radiation oncology	22,779	12.3%
(Hydration, therapeutic, prophylactic, diagnostic injections and infusions, and chemotherapy and other highly complex drug or highly complex biologic agent administration)	18,346	9.9%
Hematology and coagulation	12,390	6.7%
Diagnostic/screening processes or results	11,707	6.3%
Organ or disease-oriented panels	9,486	5.1%
Nuclear medicine	2,829	1.5%
Others	56,892	30%

Table 4.9; Distribution of Services by Medical Service Categories by Year of Service of Breast Cancer Cases

Place of Service	2007	2008	2009	2010	2011	2012	2013	2014	2015
Office/Other outpatient services	3.7	7.5	8.7	10.4	12.7	14.5	17.6	14.3	10.6
Drugs Administered other than Oral Methods, Chemotherapy	5.2	10.5	6.5	8.0	14.5	13.6	14.9	15.8	11.1
Radiation Oncology	4.4	13.2	12.2	9.3	12.8	18.7	13.7	10.8	4.9
Nuclear Medicine	3.4	10.0	10.7	12.5	12.4	14.5	14.5	12.7	9.7
Chemotherapy	2.9	4.8	7.0	9.3	13.3	15.2	17.5	18.0	12.0
Hematology and coagulation	4.0	8.7	8.3	8.8	13.2	14.7	17.3	14.2	10.8

Table 4.10; Distribution of Medical Claims Services by Place of Service

Place of Service	Services	%
Office	105,094	56
Independent Laboratory	40,427	21
On Campus-Outpatient Hospital	28,477	15
Home	6,173	3
Inpatient Hospital	4,047	2
Ambulance -Land	3,181	2
Ambulatory Surgical Center	449	0
Emergency Room - Hospital	158	0
Custodial Care Facility	70	0
Mobile Unit	68	0
Skilled Nursing Facility	3	0
Urgent Care Facility	1	0
Unknown	79	0

Table 4.11; Percent distribution of Medical Services by Place of Service and Year of Service

Place of Service	2007	2008	2009	2010	2011	2012	2013	2014	2015
Office	58%	54%	53%	57%	54%	55%	54%	59%	59%
Independent Laboratory	17%	19%	22%	20%	21%	22%	24%	23%	22%
On Campus-Outpatient Hospital	20%	17%	19%	15%	16%	15%	14%	13%	13%
Home	2%	5%	3%	4%	5%	4%	3%	2%	2%
Inpatient Hospital	2%	4%	2%	2%	2%	2%	2%	2%	1%
Ambulance	0%	2%	1%	3%	2%	2%	2%	1%	1%
Others	0%	0%	0%	1%	0%	0%	0%	0%	0%
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%

References

American Medical Association. Current Procedural Terminology Codes (CPT 2020)

Epi-Info CDC Software 7.2.2.6. Centers for Diseases Control and Prevention.

Henry Keyser Foundation, 2014. https://www.kff.org/medicare/issue-brief/a-dozen-facts-about-medicare-advantage-in-2020/

MMM Website. MMM único plan que logra 4.5 Estrellas y mantiene el más alto estándar en cuidado coordinado en Puerto Rico, Nov, 2020. https://www.mmm-pr.com/noticias/detalle?id=58&slug=mmm-nico-plan-que-logra-4-5-estrellas-y-mantiene-el-ms-alto-estndar-en-cuidado-coordinado-en-puerto-rico

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncologic Breast Cancer. https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

NCQA Website. (https://www.ncqa.org/news/ncqa-releases-2019-health-insurance-plan-ratings/#:~:text=CMS%205%2Dstar%20rated%20Medicare,Medicare%20and%20171%20Medicaid%20plans.)

SAS 9.4 Software; Student version. Analytics Software and Solution, Inc.

World Health Organization's Ninth Revision, International Classification of Diseases (ICD-9 codes)

CHAPTER V

Conclusions

This dissertation was undertaken to contribute to the understanding of how breast cancer is experienced in Puerto Rico. During the period of 1987 to the year 2012, an increasing number of new cases and a relatively steady mortality rate have been observed on the Island. Although a possible decline in mortality may have begun to emerge in 2011, this increase in incidence with little change in mortality has occurred despite efforts by the government and private sectors to increase access to health services for the population and reduce the burden of disease in the Island.

The second chapter of this thesis described the age-adjusted incidence and mortality rates of malignant breast cancer among Puerto Rican women by the Health Reform service regions to achieve this goal. The Health Reform of 1994-2001 was a government-led strategy to increase access to services to the medically indigent population to reduce health disparities between the public and private healthcare sectors.

To expand on the understating of the disease, the third chapter of this thesis addressed these rates in more detail stratifying by clinicians' clinical characteristics to allocate treatment to patients. The elements included tumor grade, histological type, and staging of the disease at diagnosis. The fourth chapter reviewed the services received by more than 5,000 women with breast cancer from a large and important Medicare Advantage practice in Puerto Rico, the first such analysis of such a database in Puerto Rico.

The main findings in chapter II were that all Health Reform service regions experienced increases in the malignant breast cancer incidence rates from 2000 to 2013. The increase was statistically significant in seven out of the ten regions and more extensive in the Southeast, East, North, and Central Regions. The second important factor observed in this study was that the incidence rates showed a significant sharp increase that began in 2007. In the year 2007, the Medicare Advantage Program became available on the island. The Medicare Advantage Program is federally funded and administered by private health insurance companies on the Island. This sharp increase in incidence rates might have been the result of the allocation of more funds for the elderly population that joined the new Medicare Advantage Program as elderly women were now able to receive more and faster referrals to screening, diagnosis, and treatment services previously limited to a segment of the population.

All this activity resulted in more visibility of cases and identification of the disease at earlier stages, which was expected to translate into earlier treatment resulting in a decrease in mortality. Improvements in health services access allowed Puerto Rican females to receive earlier breast cancer screening, earlier diagnostic testing, and access to treatment, which might account for the decrease in breast cancer mortality after 2011. Regions with increases in incidence, such as the Southeast and Southwest regions showed slower growth in mortality. These data suggest that government Health Reform and the Medicare Advantage Program have increased breast cancer services access. Better and faster documentation of new cases in the health service regions translates to earlier treatment, reducing early mortality in more aggressive types of tumors, especially among patients in advanced stages of the disease unaware of their

diagnosis. The observed increases in the Southeast, East, and Central Region suggest that the historical gap in services has been abridged by the new resources made available by the state and federal programs now administered by the private health insurance companies in those geographical areas.

Not having the information on the type of health insurance from the cancer registry data limited the analysis options for the insurance funding source. Given that this study utilized the State Cancer Registry data, incomplete case ascertainment is a possible source of bias as all cases might not be reported to the health providers' registry. An alternative to mitigate this situation would be to complement surveillance efforts with new cases reported to health insurance companies, which would complement information on cases reported to medical providers' Cancer Registry. This might also help to better document the registry's insurance types, which would enhance the analytical options for future studies. This information is essential for local health and state administrators who could use this data to better coordinate prevention efforts in the government and private health industry.

The third chapter evaluated the incidence and mortality rates between 2000 and 2013 by stage of the disease at diagnosis, histology tumor type, and tumor grades of malignant breast cancers. To our knowledge, no recent publication has described trends in the distribution of breast cancer cases by clinical characteristics of the disease in Puerto Rico. This chapter's main finding was that the trend analysis showed a sharp and significant increase in the incidence among Type III tumors (Invasive, moderately metastasizing) for the period. This increase was higher for infiltrating ductal cell carcinomas, followed to a lesser degree by lobular carcinomas for the study period.

Almost 80% of the mortality was attributable to Type III tumors, with nearly 70% attributable specifically to infiltrating duct cell carcinomas. However, the only type that presented an increase in the period's mortality rates was the infiltrating ductal cell carcinomas. Among Type II histologic tumors (Invasive, circumscribed margins, rare metastasis), Mucinous tumors presented a small but significant increase during the period. The remaining types showed either non-significant reductions or stable patterns during the period.

Moderately differentiated tumors were first stable, between 2000 and 2009 and presented a sharp and statistically significant increase through the year 2014. Malignant breast cases with well-differentiated and poorly differentiated tumors increased steadily across the whole period. In contrast, the incidence of breast cancer with undifferentiated tumors decreased. More aggressive tumors were more frequently associated with mortality, with 35% of the breast cancer deaths from “poorly differentiated” (Grade 3) tumors. Less aggressive, “moderately differentiated” (Grade 2) tumors represented 31% of the deaths. Given the increases in incidence and mortality rates for poorly differentiated tumors (Grade 3), more attention needs to be allocated to patients with aggressive tumors, with targeted chemotherapy in the early stages of the disease, to help destroy any cancer cells that may have spread as a result of the cancer being faster growing. Regarding the disease stage, cases with a regional to lymph node stage were initially stable from 2000 to 2009 but followed with a sharp and statistically significant increase starting from 2009 to 2014. Localized tumors like tumors with well and poorly differentiated grades showed a constant rise in incidence rates for the whole period. Incidence among well-differentiated tumors and tumors with regional to lymph

nodes stage increased after 2009, which has been correlated with the increase in the use of combined estrogen and progestin hormone replacement therapy in older women, which has been documented to increase breast cancer risk. However, this correlation has not been investigated in Puerto Rican women.

Adjusted incidence and mortality rates were described; however, limited information on deaths from 2000-2005 skewed the trend analysis in the early part of the period, which might bias the mortality rates. With this study methodology, we expect that describing breast cancer incidence and mortality rates by histological types, grade, and staging will become an integrated and systematic section in the reporting for future cancer publications in Puerto Rico.

The fourth chapter's objective was to describe the socio-demographic characteristics of a Medicare Advantage breast cancer population in Puerto Rico and analyze the utilization of pharmaceutical and medical services for breast cancer treatment during the study period. An analysis of the trends and types of treatment helped evaluate if the adoption of treatment guidelines improved during this period and identified areas of opportunity to improve care.

The analysis demonstrated an increase in service utilization based on a review of the pharmacy claims and medical service claims. By the end of the study period, more patient services were available to the breast cancer population of the Medicare Independent Practice Association (IPA) of Primary Care Physicians. Prescriptions per case and injectables per case both increased. The percent receiving aromatase inhibitors also increased during the study period. In contrast, the use of antiestrogens decreased. A lack of estrogen receptor and progesterone receptor testing may be one of the reasons

for this decrease. Our prior study of the Puerto Rico Central Cancer Registry identified the registry's lack of information on receptor data. These facts raise the question of whether providers are not ordering these tests or whether the health plan is not approving them, given the lack of evidence for the therapy.

Among the medical utilization services, we observed increases in treatment in the medical provider office setting. Primary care physicians and oncologists attended more breast cancer cases, and care and coordination of services were increased by the IPA and the study period's health insurance company. The percentage of utilization among independent laboratories also increased, suggesting more access within the system. In contrast, the Outpatient Hospital services' use decreased, which may be a direct effect of more patients visiting providers at their office instead of using a hospital setting for preventive ambulatory services. One of the specific breast cancer treatment modalities evaluated in this study was mastectomy utilization among this population. The overall percentages of partial mastectomies increased during the period, suggesting better adoption of treatment guidelines.

In summary, these data suggest that breast cancer patients' treatment improved among female Medicare beneficiaries across the study period, consistent with the findings of chapter II and chapter III. Analysis of data from the Cancer Registry demonstrated an increase in breast cancer incidence after 2006, which corresponds to the implementation of the Medicare Advantage program on the Island. There are still questions to be answered, such as integrating this analysis with elements of clinical characteristics of the tumor and staging the cases to evaluate if the services prevented complications and mortality for the patient. A possible recommendation that can be derived from this study

is to increase the awareness of the importance of evaluating the preventive services and treatment received by a breast cancer patient based on the clinical characteristics of the tumor and staging of the condition as seen by the medical provider. A detailed evaluation of the episodes of treatment can be suggested as a next step complementing the claims-based information with the electronic medical record information for breast cancer patients in Puerto Rico

Taken as a whole, this dissertation does provide for the first time an evaluation of the malignant breast cancer incidence and mortality rates by an applied service element (Health Reform health services regions), which help understand its effects on the Island. Increases in services for the female medical indigent population with breast cancer were observed during the study period. Expanding the typical trend incidence and mortality trend analysis in breast cancer to include key clinical prognosis elements such as histological type, the grade of the tumor, and the disease stage provides additional information to the scientific community to better understand the disease profile in Puerto Rico. Finally, integrating an analysis of breast cancer surveillance with examinations of change patterns in treatment regimens using a medical claims database further enhances understanding of the incidence and mortality profile.

We expect that this methodology will be adopted and replicated periodically by the Puerto Rico Cancer Registry. Our recommendations include more information on additional biomarkers and health insurance types for breast cancer patients within the Cancer Registry information. Also, to Cancer Registry data analysis, breast cancer research in the Island must be complemented with studies of breast cancer utilization information coming from the claims-based systems of the private health insurance

companies. These data will augment the Registry's surveillance efforts with electronic data on newly identified patients and their procedures and outcomes identified while screened or receiving treatment. These services are billed to the health insurance companies daily by medical providers all over the Island. This integrated approach might enhance the information's completeness and analytical discussion in the public health arena of cancer among researchers and public health officers.

APPENDICES

REGISTRO CENTRAL DE CÁNCER DE PUERTO RICO

Puerto Rico Central Cancer Registry
PMB #315 PO BOX 70344 San Juan, PR 00936-8344

STATUS
○ Completed ○ In progress
For PRCCR Use Only

APPLICATION TO ACCESS PRCCR DATA

This form must be completed and submitted with each proposal to use data from the Puerto Rico Central Cancer Registry (PRCCR). This is to assure that appropriate procedures are implemented for the use of PRCCR data.

Type of Proposal Submitted	
◉ New	○ Amended

The Puerto Rico Central Cancer Registry recognizes four categories, levels, or types of data that can be released for cancer surveillance and research purposes. Please choose the category/level that best fits your research request.

○ **Level I** Reports of **aggregate data** stratified by non-confidential data fields (i.e. case counts by sex, municipality, etc.).

○ **Level II** **Data files containing individual, record-level data with no personal identifiers.** The files will not contain name, street address, phone number, social security number, date of birth, any reporting facility, or physicians involved in the patient's care. The files may contain county of residence.

◉ **Level III** Data files containing individual, record-level data with personal identifiers, to be used for purposes of **record linkage**, either electronic or manual, but not direct patient contact. Once the record linkage is complete, the personal identifiers will be removed from the data set.

○ **Level IV** Files containing individual, record-level data with personal identifiers, to be used for research purposes involving **direct patient or family contact.**

REGISTRO CENTRAL DE CÁNCER DE PUERTO RICO

LEVEL III CHECKLIST

The data set to be linked includes personal identifiers, however, once the record linkage is completed, the personal identifiers will be removed from the linked data set before it is sent to the requesting party. Therefore, in order initiate the release of a Level III data set from the PRCCR, there are three items that must be included for the request to be considered.

1. **Completed Level III Application Form**
2. **Signed Assurance Form**
3. **Signed Certification of Confidentiality for Researchers**
4. **Copy of approved expedited review by an appropriate Institutional Review Board (IRB)**

As part of the application, the Puerto Rico Central Cancer Registry requests a brief description of the research project as well as a brief description of the Principal Investigator's credentials, education and research interests to be included in the Puerto Rico Central Cancer Registry's Annual Report. By signing the application, you are giving the Puerto Rico Central Cancer Registry permission to use this information in the report. The Registry does reserve the right to edit the submitted descriptions for formatting purposes.

Please enclose the requested documents and mail, fax, or email to:

Naydi Pérez Ríos, MS
Epidemiologist/ Analysis and Research Unit Coordinator
Puerto Rico Central Cancer Registry
University of Puerto Rico Comprehensive Cancer Center
E-mail: nprios@rcpr.org
Fax: (787) 522-3283

Contact Naydi Pérez Ríos at (787) 772-8300 x.1112 with any questions regarding the application process.

REGISTRO CENTRAL DE CÁNCER DE PUERTO RICO

APPLICATION FORM FOR LEVEL III DATA

ORGANIZATION OR INDIVIDUAL REQUESTING ACCESS		
Date of request	**Name of person requesting data**	**Title, Degree, and Rank**
10/12/14	Cristóbal Cintrón-Vargas	Msc., DrPH Candidat

Organization	**Address**
University of Michigan	Villas de la Playa, 273 Joyuda St. Vega Ba

Telephone number	**Fax number**	**E-mail address**
939-630-6463		ccintron@umich.edu

Other person who should be contacted if more information is needed		
Name	**Address (if different from above)**	
Sioban Harlow, PhD.	SPH, University of Michigan, Ann Arbor, M	
E-mail address	**Telephone number**	**Date data are needed**
harlow@umich.edu	1-734-763-5173	10/31/2014

Is this study externally funded?	**Name of the funding organization**	**IRB expiration date**
○ Yes ◉ No		06/25/2016

THE RESEARCH PROJECT	
Provide the purpose and intend of requested data.	**Individual data requested**
The purpose of this research is to complete the requirements of a doctoral dissertation in epidemiology from the School of Public Health at the University of Michigan.	Name and Last names Patient Sex, Age at Diagnosis, Cancer type,
	Cancer sites being studied
	Breast Cancer

Variables requested

- ☑ Age
- ☑ Sex
- ☑ Diagnostic date
- ☑ Grade
- ☑ Histology
- ☑ Diagnostic confirmation
- ☑ Vital status
- ☑ Cause of death
- ☑ Date of last contact
- ☑ Stage
- ☑ Other: Patient Sex, Age at Diagnosis, Date at death, Grade, tumor size and Township of Residence.

Provide a brief description of the Principal Investigator

Cristobal Cintron-Vargas is a doctoral student from the School of Public Health with interest in Cancer Research and a Former Department of Health Epidemiologist from the Maternal and Child Health Division.

REGISTRO CENTRAL DE CÁNCER DE PUERTO RICO

III. ASSURANCES

If data from the Puerto Rico Central Cancer Registry (PRCCR) are used in any publication (or presentation), the following statement must be included:

Data used in this publication (or presentation) were provided by the Puerto Rico Central Cancer Registry.

The citation for the reference list is:

Puerto Rico Central Cancer Registry. Comprehensive Center Cancer of the University of Puerto Rico. Incidence Case File (Date Release: Month, Year).

Also each publication must include the following disclaimer:

The collection of cancer-incidence data was supported, in part, by the National Program of Cancer Registries (NPCR) of the Centers of Disease Control and Prevention (CDC) by the Puerto Rico Central Cancer Registry as part of the statewide cancer reporting program mandated by the Puerto Rico State Law No. 28 of March 20, 1951, and Law No. 113 of July 30, 2010 (Law of the Puerto Rico Central Cancer Registry. The ideas and opinions expressed herein are those of the author(s) and endorsement by the PR is not intended nor should be inferred.

A copy of any publication or presentation that outlines using data from the Puerto Rico Central Cancer Registry should be mailed to the Registry at:

Naydi Pérez Ríos, MS
Epidemiologist/ Analysis and Research Unit Coordinator
Puerto Rico Central Cancer Registry
University of Puerto Rico Comprehensive Cancer Center
E-mail: nprios@rcpr.org
Fax: (787) 522-3283

Authorship for Publications with data of the PRCCR

Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.
If the Research and Analysis Staff of Puerto Rico Central Cancer Registry fulfills the previous description they meet the authorship criteria and must be part of the authors of the publication.

Name of Person Requesting Data: Cristobal Cintron-Vargas

Signature of Person Requesting Data: _____

Date: 10/12/2014

REGISTRO CENTRAL DE CÁNCER DE PUERTO RICO

IV CERTIFICATION OF CONFIDENTIALITY FOR RESEARCHERS

I Cristobal Cintron-Vargas **certify the following:**

1. That I have been notified and am very conscious that all the information about cancer patients provided by the Puerto Rico Central Cancer Registry (PRCCR) is **strictly confidential.**

2. That I will not use or allow that others use the information given by the PRCCR for any other purpose other than the one specified in the ***Provide the purpose and intend of requested data*** field from **APPLICATION FORM FOR LEVEL II DATA,** described previously.

3. That I will not present/publish information in which an individual could be identified. I will not publish any information about a particular individual including any information generated from a case by means of the list of cases given by the PRCCR. In addition, I will avoid the publication of tables that contain cell that are less than six (6) cases.

4. That I will not attempt to know the identity of any person whose information about his/her disease of cancer is obtained of the supplied records, except when the permission has been granted in written to me by PRCCR.

5. That if the identity of a person reveals itself inadvertently, I:
   a. will not give use of the disclosed information
   b. will have to notify the incident to the PRCCR
   c. will not inform the revealed identity to any other person

6. That I will not reveal the information (partially or completely) nor will I allow that other people to reveal it to any one, unless that person has the written approval from the PRCCR. (Note: The information that has been delivered is for the exclusive use of the person(s) or entity that made the request. The person or entity that receives it has the obligation to keep it secured and protected. The disclosure of this information to a third party, without additional authorization from the Puerto Rico Central Cancer Registry, is prohibited).

7. That I will not answer questions about cancer patients by telephone.

8. That I will not link or allow that any other person links the information of the PRCCR with individual files of any other data base, except with the special permission of the PRCCR.

9. When the information system is accessed in a common used computer or in the local area net (LAN) of the PRCCR, I will share neither my user's name nor password with any other person. Neither, I will allow that other persons use my computer account after having entered to the system with my user name and password.

10. I will not copy, distribute, do reverse engineering, obtain wages for the sale or the use, nor will I incorporate the electronic programs provided by the PRCCR in any other computerized system.

11. As soon as the investigation is completed, I will return or destroy (as agreed) all the information that will be no longer needed for the objective specified in our request.

12. The source of information will have to be mentioned in **every work published.**
    (Note: The appropriate citation must be associated with the data file used.)

Signature of Person Requesting Data: _____

Date: 10/12/2014

PMB 315 PO BOX 70344 SAN JUAN, PR 00936-8344
Tel. (787) 772-8300 EXT. 1100 Fax: (787) 552-3283

REGISTRO CENTRAL DE CÁNCER DE PUERTO RICO

19 de MARZO de 2014

CERTIFICACIÓN DE CONFIDENCIALIDAD PARA INVESTIGADORES

CERTIFICO:

1. Que he sido notificado y estoy muy consciente de que toda la información sobre pacientes de cáncer que se encuentra en las oficinas del Registro Central de Cáncer es **estrictamente confidencial.**
2. No utilizaré o permitiré que otros utilicen los datos suministrados por el Registro Central de Cáncer para ningún otro propósito que no sea el de realizar investigaciones científicas (informes estadísticos y análisis).
3. No presentaré/publicaré datos con los que pueda ser identificado un individuo. No publicaré ninguna información sobre un individuo en particular incluyendo cualquier información generada de un caso en general mediante la lista de casos suministrada por el Registro Central de Cáncer de Puerto Rico. En adición, deberé evitar la publicación de casos de celdas pequeñas.
4. No intentaré conocer la identidad de cualquier persona cuya información sobre su enfermedad de cáncer se obtenga de los expedientes suministrados, excepto cuando lo haya solicitado y me sea concedido el permiso.
5. Si la identidad de una persona se descubre inadvertidamente, deberé cumplir con lo siguiente:
   a. no daré uso de lo descubierto
   b. deberé notificar el incidente al Registro Central de Cáncer
   c. no informaré la identidad descubierta a ninguna otra persona
6. No revelaré los datos (parcial o completamente) ni permitiré que otros los revelen a ninguna otra persona excepto que la misma cuente con la aprobación, por escrito, del Registro Central de Cáncer.
7. No me pondré en contacto con las personas registradas (o familiares de las personas) cuya identificación la facilite el Registro Central de Cáncer confidencialmente (por ejemplo una investigación basada en entrevistas) excepto si primero se ha obtenido en cada caso, autorización del médico que lo trata.
8. No contestaré preguntas sobre pacientes de cáncer por teléfono.
9. No me enlazaré o permitiré que otros enlacen los datos del Registro Central de Cáncer con archivos individuales de cualquier otra base de datos, excepto con permiso especial del Registro Central de Cáncer.
10. Al accesar los datos del sistema en una computadora de uso común o en la red de área local (LAN) del Registro Central de Cáncer, no compartiré mi nombre de usuario ni contraseña con ninguna otra persona. Tampoco permitiré que otras personas utilicen mi cuenta de computadora después de haber entrado al sistema con mi nombre de usuario y contraseña.
11. NO deberé copiar, distribuir, realizar ingeniería inversa, obtener ganancias por la venta o su uso, ni incorporar en ningún otro sistema computarizado, los programas electrónicos provistos por el Registro Central de Cáncer.
12. Al terminar la investigación, devolveré o destruiré (según lo acordado) todos los datos que no necesite más para el objetivo especificado en la petición.
13. La fuente de información deberá ser citada en <u>todo trabajo publicado</u>. La cita apropiada debe estar asociada con el archivo de datos utilizado.

Cristobal Cintrón
Nombre

Cristobal Cintrón
Firma

V. Las de la Playa
Tiguat 833 Vega Baja
939 630-6463
Dirección y teléfono

cris.cintron@gmail.com
E-mail

PRCCR 12 – Doc. Confidencialidad Investigadores
Rev 11/2011

MSO of Puerto Rico, Inc.

MMM | PMC Medicare Choice

October 16, 2013

University Of Michigan
Department of Epidemiology
School of Public Health

RE: Age Adjusted Breast Cancer Incidence and Mortality Rates and a Comprehensive Breast Cancer Treatment Modalities Evaluation in the Castellana's Independent Primary Association Groups in Puerto Rico

Dear Dr. Sioban Harlow:

The following letter is to notify our endorsement to allow Cristobal Cintron Vargas, to conduct a Descriptive study of Castellana's Breast Cancer patient's incidence and mortality complementing our claims data with information with the State Cancer Registry information.

The Doctoral Dissertation objectives presented to us were:

1. To assess trends for age-adjusted Breast Cancer mortality and incidence rates in Castellana's members and stratified by geographical regions and Platino Status.
2. To assess whether characteristics of the disease at the time of diagnosis as recorded in the State Cancer Registry or Medical Records suggests:
    a) Late Stage at the time of diagnosis
    b) Higher Prevalence of aggressive histological types
    c) Tumors with higher grading scores
3. To assess frequency of hormones receptor assays and compare the Staging, Grading and Histological types of patients with ER receptor assays with those and who had no data from the MMM, Health Care Inc.

We will provide related necessary information and protocols required by the University of Michigan IRB's Committees.

Cordially,

Raul F. Montalvo-Orsini, MD, MBA
President,
MSO of Puerto Rico, Inc.

cc. Priscilla González,
Castellana Vice President

The information contained herein is privileged and confidential and is for the exclusive use of the recipient. If you receive it by mistake, you are not authorized to use, distribute or copy it. Please notify the sender immediately at 787-200-1689 to make arrangements for return of the documents.

www.mso.pr PO BOX 71114 SAN JUAN PR 00936-8014

HIPAA BUSINESS ASSOCIATE AGREEMENT

This **Business Associate Agreement** (this "Agreement") is made and entered into this **1st** day of **September**, 2016 (the "Effective Date"), by and between **MMM HOLDINGS, LLC**, a Puerto Rico LLC Company having its principal place of business at 350 Chardon Avenue, Suite 500 San Juan PR 00918 ("Covered Entity") and **Cristobal Cintrón Vargas** having its principal place of business at Villas de la Playa Joyuda ST. 273, Vega Baja, Puerto Rico 00963. ("Business Associate").

WITNESSETH

WHEREAS, Business Associate and Covered Entity are executing a Business Associate Agreement herewith ("BAA"), whereby Business Associate agrees to perform PHI identification for educational purposes. In connection with the BAA, Covered Entity may disclose to Business Associate certain information subject to the Health Insurance Portability and Accountability Act of 1996, Pub. L. No. 104-191, and its implementing regulations at 45 C.F.R. Parts 160, 162, and 164, as amended by the Health Information Technology for Economic and Clinical Health (HITECH) Act of the American Recovery and Reinvestment Act of 2009, Pub. L. No. 111-5 (collectively, "HIPAA"). Covered Entity and Business Associate hereby agree to the terms and conditions of this Agreement in compliance with HIPAA.

WHEREAS, Business Associate acknowledges its responsibility to comply with the requirements of HIPAA which are applicable to business associates and all applicable regulations issued by the U.S. Department of Health and Human Services ("HHS") to implement the HIPAA requirements.

NOW, THEREFORE, In consideration of the foregoing, and the mutual promises contained herein and other valuable consideration, the legal sufficiency of which is hereby acknowledged, the parties hereby agree as follows:

1. **Definitions**

   1.1. Unless otherwise specified, all terms used but not otherwise defined in this Agreement shall have the same meaning for those terms as set forth under HIPAA.

2. **Business Associate Obligations**

   2.1. **Permitted Uses and Disclosures**. Business Associate shall not, and shall ensure that its directors, officers, employees, contractors and agents do not, use or disclose Protected Health Information ("PHI") created, received, maintained or transmitted for the Covered Entity in any manner that would violate HIPAA. Business Associate agrees that it will not use or disclose PHI other than as permitted or required by this Agreement or as required by law. Except as otherwise limited in this Agreement, Business Associate may use or disclose PHI to perform functions, activities, or services for, or on behalf of, the Covered Entity as specified in the BAA, provided that such use or disclosure would not violate the HIPAA Privacy Rule if done by Covered Entity or the minimum necessary policies and procedures of the Covered Entity.

   2.2. **Use/Disclosure for Administrative Activities.** Notwithstanding Section 2.1, Business Associate may use and/or disclose PHI for management and administrative activities of Business Associate or to comply with the legal responsibilities of Business Associate; provided, however, that with respect to any such disclosure: (i) the disclosure is required by

law; or (ii) Business Associate obtains reasonable assurances from the third party that receives the PHI that the third party will treat the PHI confidentially and will only use or further disclose the PHI in a manner consistent with the purposes that the PHI was provided by Business Associate, and promptly report any breach of the confidentiality of the PHI to Business Associate. Business Associate may also for use and/or disclose PHI for data aggregation services, if data aggregation services are to be provided by Business Associate for the health care operations of Covered Entity pursuant to the BAA or any agreements between the Parties evidencing their business relationship.

2.3. **Disclosure Required by Law.** If Business Associate believes it has a legal obligation to disclose any PHI, it will notify Covered Entity as soon as reasonably practical after it learns of such obligation, and in any event at least ten (10) business days prior to the proposed release, as to the legal requirement pursuant to which Business Associate believes the PHI must be released. If Covered Entity objects to the release of such PHI, Business Associate will allow Covered Entity to exercise any legal rights or remedies Covered Entity might have to object to the release of the PHI. Business Associate agrees to provide such assistance to Covered Entity, at Covered Entity's expense, as Covered Entity may reasonably request.

2.4. **Subcontractors of Business Associate**.

2.4.1. Business Associate agrees to enter into written contracts with any agent or independent contractor that creates, receives, maintains or transmits PHI on behalf of the Business Associate (collectively, "Subcontractors"). Such contracts shall obligate Subcontractor to abide by the same conditions and terms as are required of Business Associate under this Agreement, and shall require Subcontractor to notify Covered Entity of Incident(s), as defined by Section 3, in the same manner and timeframe as provided in Section 3.

2.4.2. Business Associate shall provide to Covered Entity copies of such written contracts entered into between Business Associate and its Subcontractor within twenty (20) days of execution, which shall include the name and contact information of such Subcontractor. Business Associate agrees to take reasonable steps to ensure that its Subcontractors' actions or omissions do not cause it to breach the terms of this Agreement.

2.5. **Restriction**. Business Associate agrees to comply with any requests for restrictions on certain disclosures of PHI to which Covered Entity has agreed in accordance with 45 C.F.R. § 164.522 and of which Business Associate has been notified by Covered Entity, including but not limited disclosures to a health plan if the PHI pertains solely to a health care item or service for which the individual or person other than the health plan on behalf of the individual, has paid the Covered Entity in full.

2.6. **Performance of Covered Entity's Obligations.** To the extent Business Associate has agreed to carry out one or more of Covered Entity's obligations under 45 C.F.R. Part 164, Subpart E, Business Associate shall comply with the requirements of Subpart E that apply to Covered Entity in the performance of such obligations.

2.7. **Minimum Necessary**. Business Associate shall comply with the minimum necessary requirements for use and disclosure of PHI set forth at 45 C.F.R. § 164.502(b).

2.8. **Access and Amendment**. Business Associate shall notify the Covered Entity within five (5) days of receipt of a request received by Business Associate for access to, or amendment of, PHI. The Covered Entity shall be responsible for responding, or objecting, to such requests.

2.8.1. **Access**. Upon request, Business Associate agrees to furnish Covered Entity with copies of the PHI maintained by Business Associate in a Designated Record Set in the time and manner designated by Covered Entity to enable Covered Entity to respond to an individual request for access to PHI under 45 C.F.R. § 164.524. If the PHI that is the subject of a request for access is maintained electronically and if the Individual requests an electronic copy of such information, Business Associate shall provide Covered Entity with access to the PHI in the electronic form and format requested by the Individual, if it is readily producible in such form and format; or, if not, in a readable electronic form and format as agreed to by Covered Entity and the Individual.

2.8.2. **Amendment**. Upon request and instruction from Covered Entity, Business Associate shall amend PHI in a Designated Record Set that is maintained by, or otherwise within the possession of, Business Associate in accordance with 45 C.F.R. § 164.526. Any request by Covered Entity to amend such information shall be completed by Business Associate within fifteen (15) business days of Covered Entity's request.

2.9. **Accounting**. Business Associate agrees to document disclosures of PHI as would be required for Covered Entity to respond to a request by an Individual for an accounting of disclosures of PHI in accordance with 45 C.F.R. § 164.528 and, if required by and upon the effective date of, Section 13405(c) of the HITECH Act and related regulatory guidance; and provide to Covered Entity or an Individual upon Covered Entity's request, information collected in accordance with this Section, within ten (10) days of receipt of written request by Covered Entity. In the event an individual delivers the initial request for an accounting directly to Business Associate, Business Associate shall within ten (10) days forward such request to Covered Entity. The Parties agree and acknowledge that it is Covered Entity's responsibility to respond to all accounting requests.

2.10. **Remuneration and Marketing.** No communication shall be made for purposes of fundraising, sale and/or marketing, as defined by HIPAA, with PHI created, received, maintained or transmitted for the Covered Entity without prior written authorization by Covered Entity.

2.11. **Security Obligations and Safeguards.**

2.11.1. **Security Rule Obligations.** Business Associate shall utilize appropriate physical, administrative and technical safeguards and comply with 45 C.F.R. Part 164, Subpart C with respect to electronic PHI, to prevent use or disclosure of PHI other than as provided for by this Agreement.

2.11.2. **Encryption.** PHI stored, maintained, transmitted or retained for or on behalf of Covered Entity shall be rendered unusable, unreadable, or indecipherable to unauthorized individuals through the use of a technology or methodology specified by the Secretary of the U.S. Department of Health and Human Services ("HHS") pursuant to 45 C.F.R. Section 164.402.

2.12. **Access by Secretary of Health & Human Services.** Business Associate agrees to allow the Secretary of HHS access to its books, records and internal practices with respect to the disclosure of PHI for the purposes of determining the Covered Entity or Business Associate's compliance with HIPAA.

3. **Reporting Obligations**

3.1. Business Associate agrees to notify Covered Entity of any (i) Security Incident; (ii) use, access or disclosure of PHI which is inconsistent with the terms of this Agreement; and/or (iii) suspected breach of unsecured PHI (collectively, an "Incident"), within five (5) days of discovery.

3.1.1. The Parties agree that this Section 3 satisfies any notice requirements by Business Associate of the ongoing existence and occurrence of attempted but Unsuccessful Security Incidents (as defined below) for which no additional notice to Covered Entity shall be required. For purposes of this Agreement, "Unsuccessful Security Incidents" include activity such as pings and other broadcast attacks on Business Associate's firewall, port scans, unsuccessful log-on attempts, denials of service and any combination of the above, so long as no such incident results in unauthorized access, use or disclosure of PHI.

3.2. Business Associate agrees to implement response and record-keeping systems to facilitate compliance with the notification requirements of this Section.

3.3. In the event of any such Incident, Business Associate shall provide to Covered Entity, in writing, such details concerning the Incident as Covered Entity may request, and shall cooperate with Covered Entity, its regulators and law enforcement to assist in regaining possession of such unsecured PHI and prevent its further unauthorized use or disclosure, and take reasonable remedial actions as may be required by Covered Entity to prevent further Incidents.

3.4. If Covered Entity determines that it may need to provide notice pursuant to 45 C.F.R. Part 164 Subpart D, as a result of an Incident that is attributable to Business Associate or Subcontractor, Business Associate shall bear all reasonable direct and indirect costs associated with such determination including, without limitation, the costs associated with providing notification, providing fraud monitoring or other services to affected Individuals and any forensic analysis required to determine the scope of the Incident.

3.5. Business Associate shall establish policies and procedures for mitigating and to mitigate, to the greatest extent practicable, any harmful effect that is known to Business Associate from any Incident or violation of this Agreement, HIPAA or other applicable laws or regulations.

3.6. Business Associate agrees to update, as soon as possible, the notice provided to Covered Entity under this Section to include the following information Covered Entity is required to include in its notice to the Individual pursuant to 45 C.F.R. § 164.404(c). Business Associate shall submit updated information to Covered Entity immediately at the time the information becomes available to Business Associate.

3.6.1. The identification of each individual whose Unsecured PHI has been, or is reasonably believed by Business Associate to have been, accessed, acquired, used or disclosed during the Incident;

3.6.2. A brief description of what happened, including the date of the Incident and the date of discovery of the Incident, if known;

3.6.3. A description of the types of unsecured PHI that were involved in the Incident (such as whether the full name, social security number, date of birth, home address, account number, diagnosis, disability code, or other types of information were involved);

3.6.4. Any steps the Individual should take to protect themselves from potential harm resulting from the Incident;

3.6.5. A brief description of what is being done to investigate the Incident, mitigate the harm and protect against future Incidents; and

3.6.6. Contact procedures for Individuals to ask questions or learn additional information which shall include a toll-free number, an e-mail address, Web site, or postal address, if Covered Entity specifically requests Business Associate to establish contact procedures.

4. Term and Termination

4.1. **Term**. This Agreement shall be effective as of the Effective Date and shall terminate upon termination of the BAA or this Agreement, whichever is sooner.

4.2. **Termination Upon Material Breach**. Covered Entity may, in its sole discretion, terminate the Services Agreement and this Agreement, upon determining that Business Associate violated a material term of this Agreement. If the Covered Entity makes such a determination, it shall inform Business Associate in writing that the Covered Entity is exercising its right to terminate under this Section and such termination shall take effect immediately.

4.3. **Reasonable Steps to Cure Material Breach**. At the Covered Entity's sole option, the Covered Entity may, upon written notice to Business Associate, allow Business Associate an opportunity to take prompt and reasonable steps to cure a violation of any material term of this Agreement to the complete satisfaction of the Covered Entity within ten (10) days of the date of written notice to Business Associate. Business Associate shall submit written documentation acceptable to the Covered Entity of the steps taken by Business Associate to cure any material violation. If Business Associate fails to cure a material breach within the specified time period, then the Covered Entity shall be entitled to terminate this Agreement.

4.4. **Return or Destruction of PHI upon Termination**. Within thirty (30) days of termination of this Agreement, Business Associate will return to Covered Entity all PHI created, received, maintained or transmitted by Business Associate from or on behalf of the Covered Entity; and ensure that all Subcontractors return PHI created, received, maintained or transmitted by Subcontractor from or on behalf of Business Associate for purposes related to the Services Agreement. If Business Associate cannot obtain the PHI from any Subcontractor, Business Associate will so notify Covered Entity and will require that such Subcontractor directly return PHI to Covered Entity. Alternatively, Covered Entity may request that Business Associate destroy all such PHI, and ensure that Subcontractors take similar action. Business Associate shall provide written documentation of such destruction. Business Associate will be responsible for ensuring Subcontractor returns or destroys such PHI in accordance with this Section.

4.5. **Alternative Measures**. If Business Associate believes that returning or destroying PHI in accordance with Section 4.4 is infeasible, Business Associate will provide written notice to Covered Entity within five (5) business days of the effective date of termination of this Agreement. Such notice will set forth the circumstances that Business Associate believes make the return or destruction of PHI infeasible and the alternative measures that Business Associate recommends for assuring the continued confidentiality and security of the PHI. Covered Entity will notify Business Associate of whether it agrees that the return or destruction of PHI is infeasible. If Covered Entity does not agree that the return or destruction

of PHI is infeasible, Covered Entity will provide written notice of its decision, and Business Associate will proceed with the return or destruction of the PHI pursuant to the terms of this Section within fifteen (15) days of the date of Covered Entity's notice. Business Associate shall ensure that all Subcontractors follow a similar process with regard to alternate measures to return or destruction.

4.6. **Retention of PHI After Termination.** To the extent any PHI is retained after termination of this Agreement, regardless of reason, Business Associate agrees, and shall ensure that any Subcontractor agrees, to:

4.6.1. Limit the use or disclosure of the retained PHI to the purposes for which such PHI was retained;

4.6.2. Return or destroy the retained PHI when it is no longer needed for the purpose(s) for which such PHI was retained; and

4.6.3. Extend all protections, limitations, obligations and restrictions of this Agreement (or, in the case of a Subcontractor, of the written Agreement pursuant to Section 2.4) to PHI retained after termination of this Agreement, including without limitation the provisions of Sections 2.11, 3, and 7 (and their corresponding provisions in Subcontractor's agreement). All such protections, limitations, obligations and restrictions shall survive termination of this Agreement and the Services Agreement.

5. **Modification and Amendment**. This Agreement contains the entire understanding of the parties regarding the obligations of Business Associate under HIPAA and will be modified only by a written document signed by each party except as otherwise provided in this Section. The parties acknowledge and agree that HIPAA may be amended and additional guidance and/or regulations may be issued after the date of the execution of this Agreement and may affect the parties' obligations under this Agreement ("Future Directives"). The parties agree to abide by such Future Directives as these Future Directives may affect the obligations of the parties. If Future Directives affect the obligations of the parties, then Covered Entity shall notify Business Associate of Future Directives in writing within thirty (30) days before Future Directives are effective. The notification of Business Associate by Covered Entity of Future Directives shall be considered amendments to this Agreement binding on both parties.

6. **Relationship of the Parties**. The Parties hereto acknowledge that Business Associate shall be and have the status of independent contractor in the performance of its obligations under the terms of this Agreement as to Covered Entity. Nothing in this Agreement shall be deemed or construed to create a joint venture or partnership between Covered Entity and Business Associate.

7. **Indemnification and Insurance.**

7.1. Business Associate agrees to defend, indemnify and hold Covered Entity and its affiliates and each of their partners, officers, managers, representatives, employees and agents (each an "Indemnitee") harmless from and against any and all claims, losses, damages, judgments, liabilities, costs, fees and expenses (including reasonable attorney's fees and expenses) of any kind or nature that any Indemnitee incurs or that are asserted against any Indemnitee arising in any way directly or indirectly from (i) Business Associate's negligence or breach of its obligations under this Agreement or HIPAA, (ii) a Subcontractor's breach of its obligations under HIPAA; or (iii) Business Associate's or Subcontractor's provision of services under this Agreement, including but not limited to any violations of any federal, state and/or local laws or

regulations arising from or related to Business Associate's or Subcontractor's services, acts or omissions related to this Agreement.

7.2. Unless greater coverage is required under any other agreement between Covered Entity and Business Associate for the provision of services related to this Agreement, Business Associate shall maintain the following insurance covering itself and each Subcontractor, if any, through whom Business Associate provides services: (i) a policy of commercial general liability and property damage insurance, and electronic data processing insurance, with limits of liability not less than two million dollars ($2,000,000) per occurrence and two million dollars ($2,000,000) annual aggregate; and (ii) such other insurance or self-insurance as shall be necessary to insure it against any claim or claims for damages arising under this Agreement or from violating Business Associate's own obligations under HIPAA, including but not limited to, claims or the imposition of administrative penalties and fines on Business Associate or its subcontractors or agents, if any, arising from the loss, theft, or unauthorized use or disclosure of PHI. Such insurance coverage shall apply to all site(s) of Business Associate and to all services provided by Business Associate or any subcontractors or agents under this Agreement.

8. **Exception to Limitations and Exclusions.** Business Associate's obligations under this Agreement and any breach by Business Associate or a Subcontractor of the obligations in this Agreement shall not be subject to any limitations on damages that may be specified in the Services Agreement or any agreement, invoice, statement of work or similar document setting forth the services Business Associate is providing to Covered Entity.

9. **Injunctive Relief.** Business Associate expressly acknowledges and agrees that the breach, or threatened breach, by it of any provision of this Agreement may cause Covered Entity to be irreparably harmed and that Covered Entity may not have an adequate remedy at law. Therefore, Business Associate agrees that upon such breach, or threatened breach, Covered Entity will be entitled to injunctive relief to prevent Business Associate from commencing or continuing any action constituting such breach without having to post a bond or other security and without having to prove the inadequacy of any other available remedies. Nothing in this paragraph will be deemed to limit or abridge any other remedy available to Covered Entity at law or in equity.

10. **Assistance in Litigation or Administrative Proceedings.** Business Associate shall make itself and any Subcontractor(s) available to Covered Entity to testify as witnesses, or otherwise, in the event of litigation, administrative proceedings or investigations being commenced against Covered Entity, its directors, officers, or employees based upon a claimed violation of this Agreement, HIPAA, or other laws relating to security and privacy.

11. **Right of Inspection**. Within ten (10) business days of a written request by Covered Entity, Business Associate and its Subcontractors, if any, shall allow Covered Entity to conduct a reasonable inspection of the facilities, systems, books, records, agreements, policies and procedures relating to the use or disclosure of PHI pursuant to this Agreement for the purpose of determining whether Business Associate has complied with this Agreement; provided, however, that (i) Business Associate and Covered Entity mutually agree in advance upon the scope, location and timing of such an inspection; and (ii) Covered Entity shall protect the confidentiality of all confidential and proprietary information of Business Associate to which Covered Entity has access during the course of such inspection.

12. Miscellaneous

12.1. **Ownership Rights.** Business Associate agrees and acknowledges that Business Associate has no ownership rights related to the PHI subject to this Agreement.

12.2. **Conflicts.** The terms and conditions of this Agreement will override and control over any conflicting term or condition of other agreements between the parties; provided, in the event that the Services Agreement contains provisions relating to the use or disclosure of PHI which are more restrictive than the provisions of this Agreement, the more restrictive provisions will control. All non-conflicting terms and conditions of such agreements shall remain in full force and effect.

12.3. **Compliance and Severability.** The parties hereto shall comply with applicable laws and regulations governing their relationship, including, without limitation, HIPAA, and any other federal or state laws or regulations governing the privacy, confidentiality or security of patient health information. If a provision of this Agreement is held invalid under any applicable law, such invalidity will not affect any other provision of this Agreement that can be given effect without the invalid provision. Further, all terms and conditions of this Agreement will be deemed enforceable to the fullest extent permissible under applicable law, and, when necessary, the court is requested to reform any and all terms or conditions to give them such effect. Business Associate shall comply with applicable state and federal statutes and regulations as of the date by which business associates are required to comply with applicable statutes and regulations. Any ambiguity in this Agreement shall be resolved to permit Covered Entity to comply with HIPAA and other federal or state laws or regulations governing the privacy, confidentiality or security of patient health information.

12.4. **Waiver.** The waiver by Business Associate or Covered Entity of a breach of this Agreement will not operate as a waiver of any subsequent breach. No delay in acting with regard to any breach of this Agreement will be construed to be a waiver of the breach.

12.5. **Assignment.** This Agreement will not be assigned by either party without prior written consent of the other party. This Agreement will be for the benefit of, and binding upon, the parties hereto and their respective successors and permitted assigns.

12.6. **Governing Law,** The interpretation and enforcement of this Agreement will be governed by the laws of the State of the location of the Covered Entity.

12.7. **No Third Party Beneficiary Rights.** Nothing express or implied in this Agreement is intended or shall be interpreted to create or confer any rights, remedies, obligations or liabilities whatsoever in any third party.

12.8. **Headings.** The section headings contained in this Agreement are for reference purposes only and will not affect the meaning of this Agreement.

12.9. **Counterparts.** This Agreement may be executed in counterparts, each of which will be deemed to be an original, but all of which together will constitute one and the same instrument. Transmission of images of signed signature pages by electronic means (including PDF or facsimile) shall have the same effect as the delivery of manually signed documents.

12.10. **Notice.** Except as otherwise provided in this Agreement, any notice permitted or required by this Agreement will be considered made on the date personally delivered in writing or

mailed by certified mail, postage prepaid, to the other party at the address set forth on the signature page or as either party may designate in writing:

IN WITNESS WHEREOF, the parties hereto have executed this Agreement which is effective as of the date first above written.

COVERED ENTITY:

By:

Name: Orlando González Rivera

Title: President

Date: 9/14/2016

BUSINESS ASSOCIATE:

By:

Name: Cristobal Cintrón Vargas

Title: Doctoral Student

Date: 9/15/2016