PATIENT AND PROVIDER DETERMINANTS ASSOCIATED WITH THE PRESCRIPTION OF ADJUVANT HORMONAL THERAPIES FOLLOWING A DIAGNOSIS OF BREAST CANCER IN MEDICAID ENROLLED PATIENTS

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ABSTRACT

Approximately one in eight women will be diagnosed with breast cancer, and last year alone over 40,000 women died of cancer of the breast. While new technologies and their applications are increasing the probability of survival for many women, research has suggested that not all women are benefiting equitably from these advances.

Because nearly two-thirds of all breast cancers are estrogen receptor positive, progesterone receptor positive, or both, recent research has focused on developing antiestrogenic adjuvant therapy to prolong life and increase survival. Tamoxifen has long been the gold standard for this type of treatment, however, aromatase inhibitors (AIs) have produced better disease-free survival rates for many patients in recent trials. While more evidence is continually being gathered on the efficacy of these new drugs, little research has been conducted to examine who is actually receiving the most novel forms of these treatments.

The purpose of this study was to examine various patient and provider characteristics associated with being prescribed an AI (v. tamoxifen only therapy) among a cohort of North Carolina (NC) Medicaid enrollees diagnosed with breast cancer. At the patient level, the following were examined: (1) stage of cancer, (2) urban/rural status, (3) year therapy started, (4) age-defined menopausal status, (5)

surgery type, (6) race, (7) tumor size, (8) whether the patient spent more than $10,000 on medical expenses in the year before the study began, and (9) whether the patient visited a hospital, emergency department, nursing home, or home care system in the year prior to study initiation. Provider-level comparisons were made by determining (1) whether the provider was an oncologist or not, and (2) whether the provider practiced in the public or private sector. Data were gathered using the Linked North Carolina Central Cancer Registry-Medicaid Claims database which links NC cancer registry claims with Medicaid data.

A total of 600 patients were analyzed, of which 451 (75.2%) and 149 (24.8%) received tamoxifen only and AI (alone or in combination) therapy, respectively. A logistic regression model was built to determine the odds of an individual ever receiving an AI during the study period. Results showed that patients who lived in urban areas (compared to rural), were postmenopausal (based on age $\geq$ 55), had regional- or distant-staged cancer (opposed to local or unknown), had been hospitalized in the year prior to treatment index, and had breast conserving surgery (BCS) (rather than mastectomy) had 1.97 [1.29, 3.00], 2.26 [1.80, 2.83], 2.74 [1.79, 4.20], 1.87 [1.20, 2.92], 0.64 [0.41, 1.00] times the odds, respectively, of ever receiving an AI compared to tamoxifen only. Additionally, for every one-year increase in the time a patient started hormonal therapy, the odds of receiving AI therapy (compared to tamoxifen only) increased 2.26 [1.80, 2.83] fold.

The differences in antiestrogenic treatment type based on whether the patient visited a hospital in the year prior to the study and in whether the patient lived in urban or rural area may represent disparities in access to advances in care. In the

future, as more information about AI therapy is discovered, access to care must be continually monitored so that an equitable distribution of new treatment options is guaranteed.

Dedicated to my fiancée & my parents

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TABLE OF CONTENTS

Page

Abstract....ii
Dedication....v
Acknowledgments....vi
Vita....vii
List of Tables....x
List of Figures....xi

Chapters

1. Introduction....1

Background to the problem....1
Need for the study....3
Purpose of the study....4

2. Related Literature....6

Breast cancer: a harsh reality and a hopeful future....6
The discover and importance of hormone receptor status....7
Two major options, two different mechanisms....8
Tamoxifen history and perspective....8
AIs: for postmenopausal women, another choice....11
Racial differences and disparities in breast cancer....12
Systems-level differences and disparities in breast cancer....13

3. Methods....15

Research design....15
Data source....15
Study period....16
Study population....16
Data elements....17
Data analysis....18

4. Results....21

5. Discussion……..……..32

Appendix……..……40

List of References……....41

LIST OF TABLES

Table		Page
4.1	Distribution of adjuvant hormonal therapy types (n=600).....	21
4.2	Distribution of adjuvant hormonal therapy types by year of study.....	22
4.3	Demographics and univariate significance for categorical independent variables across antiestrogenic prescription patterns	24
4.4	Odds ratios and confidence intervals for logistic regression modeling of receiving AI (ever) v. tamoxifen (only) therapy	26
4.5	Fractional polynomial model comparisons for continuous variable.....	28

LIST OF FIGURES

Figure Page

4.1 Assessment of confounding in main model 27

4.2 Smoothed plots evaluating the linearity of *year therapy (2000-2004) was started* in the model logit using a lowess smoother (logit scale), a lowess smoother (logistic scale), and a mean smoother, respectively 28

4.3 Area under the ROC curve for final model.....29

4.4 Plot of sensitivity and specificity versus all possible cut-points.....30

4.5 Plot of $\Delta\chi^2$ versus the estimated logistic probability in the final model weighted by $\Delta\beta_{(hat)}$.....31

CHAPTER 1

INTRODUCTION

Background to the Problem

Breast cancer is the most common non-skin cancer among women in the United States and in many other countries.[1] Recent advances in early detection and in new types of therapies and their application, however, have resulted in prolonged survival among women diagnosed with breast cancer.[2-6] Currently, for non-metastatic cancer (stages 0-III) the primary treatment is surgery to remove the tumor.[7] This surgery may be a simple lumpectomy, where the cancerous mass and minimal normal tissue is removed, or a mastectomy in which the entire breast and, in advanced cases, some or all of the surrounding lymph nodes are removed.[8]

While surgery is the primary treatment modality, recent reductions in breast cancer mortality have been largely attributed to the success of novel treatments used in conjunction with surgery.[2, 9, 10] These treatments, referred to as *adjuvant therapy* because of their supplemental nature, typically follow primary (surgical) treatment to help reduce the risk of recurrence.[7, 8] Adjuvant therapy prescribed to women with invasive breast cancer may be either local or systemic. Local adjuvant therapy, known commonly as radiation therapy, uses ionizing radiation (generally X-rays) to target specific areas where cancerous cells may persist. Contrastingly, systemic

adjuvant therapy includes chemotherapy, targeted/biologic therapy, hormonal therapy (tamoxifen or aromatase inhibitors), or any of these in combination.[8]

Each patient is unique, and particular sequences of breast cancer treatment often vary from person-to-person. The typical treatment pathway, however, usually first involves surgery (either lumpectomy or mastectomy), followed secondly by chemotherapy if it is administered, and then by radiation therapy. Again, there are many exceptions to this treatment pathway—many patient-level factors must be carefully examined, taking into account both individual and synergistic anticipated effects and side-effects of various treatment regiments. For example, among women with stage III or stage IV breast cancer, chemotherapy may be given first to shrink large tumors and address cancer in the rest of the body, before surgery.[11] Additionally, some centers or clinical studies give chemotherapy and radiation together, rather than separately in succession.[12, 13] Regardless of variations in the timing and sequence of treatment involving surgical removal, chemotherapy, and radiation therapy, relatively rigid treatment guidelines that minimize the risk of recurrence and extend survival time regarding these options have been developed using data from decades of clinical research.

Distinct treatment guidelines for adjuvant hormonal therapy, which is most commonly started after other treatments (surgery, chemotherapy, and/or radiation), however, have not been clearly established. Because its targeted effect is to prevent cancer cell promotion in breast tissue by estrogen, hormonal therapy (also known as antiestrogenic therapy) is recommended only for women with hormone receptor positive (HR+) breast cancer which is defined as estrogen receptor positive (ER+) or

progesterone receptor positive (PgR+) breast cancer or both. These specific types of breast carcinoma, however, constitute roughly two-thirds of all breast cancer cases with estimates ranging from 50-75%.[14-16] Recently, because of this high prevalence of ER+ and PgR+ breast cancer, extra emphasis has been placed on exploring the effectiveness of hormonal therapy in both prolonging life after diagnosis and as a curative adjuvant agent.

Two major types of adjuvant hormonal therapy have emerged in current clinical practice—tamoxifen and third generation aromatase inhibitors (AIs)—the former acting as an estrogen antagonist in breast tissue, and the latter acting to prevent the formation of estrogen in non-ovarian tissue. While much research has been devoted to establishing the efficacy of both tamoxifen and different types of aromatase inhibitors; few studies have examined whether various patient and physician characteristics are associated with the type of hormonal adjuvant therapy a patient receives. Stated simply, regarding hormonal adjuvant therapy, we know very little about which physicians are prescribing what, and to whom they are prescribing it.

Need for the Study

Over the last century, advances in breast cancer research regarding these new types of therapies and their application have resulted in prolonged survival and improved quality of life.[2-6] In recent years, discoveries such as the decoding of the human genome have accelerated scientific progress in the area of breast cancer research as well.[17, 18] The irony, however, is that this advancement has occurred at such an expeditious pace that reflection and cautious evaluation of change over the

last century has proved nearly impossible. While change is a global certainty, in our recent past, technology has progressed so rapidly that other aspects of society can scarcely keep up. As a result, despite the scientific progress in breast cancer research of recent times, not all population groups have benefited uniformly from our profound medical advances.[19] Often times, with each new form of technology or new drug created, also created is a gaping divide between the delivery of advanced healthcare services and those who may need it most. This gap, described by Dr. Harold Freeman, medical director of Ralph Lauren Cancer Center and professor of clinical surgery at Columbia University, as a "critical disconnect,"[20] seems to be widening between what cancer researchers discover and what is delivered to American citizens.

While this is a far-reaching problem of the healthcare field, affecting many populations across nearly every type of disease,[21-28] it is particularly evident when examining the dramatic disparities in breast cancer mortality that this "gap" is often filled with poor, underserved, minority, and rural population groups.[19, 29-33] To tease out differences and disparities in health, studies must examine not only if new resources are effective, but also to whom and from whom they are distributed.

Purpose of the Study

Currently, few studies examine the growing demographic of breast cancer survivors and little is known about which specific antiestrogenic treatment or treatments breast cancer patients are being prescribed and whether these differences depend on various patient and/or provider characteristics. Previous research has been effective in developing treatments, determining treatment guidelines for

individual patients, prolonging life, and even allowing recovery. This study looks beyond treatment efficacy, and instead describes patient and physician characteristics that are correlated with prescribed adjuvant hormonal therapy (AI v. tamoxifen) and provides the necessary data to investigate potential health disparities. Furthermore, it serves as a framework for future studies that may explore impending cost and access barriers or aid in the maturation of cancer treatment guidelines. Specifically, the results will be used to determine whether differences/disparities exist in the use of adjuvant hormonal therapy across the Medicaid population in North Carolina at the patient and/or provider level. Because the data were obtained from a Medicaid population, effectively controlling for socioeconomic status (SES), this study will be primarily concerned with non-SES differences and disparities at the patient-level. At the physician level, current study will examine differences and disparities as a result of physician type—specifically, if the prescribing physician is (1) an oncologist or not, and (2) practices in a private or public setting.

CHAPTER 2

RELATED LITERATURE

Breast Cancer: A Harsh Reality and a Hopeful Future

Breast cancer is the most common non-skin cancer among women in the United States and in many other countries.[1] The chance of a woman developing some form of invasive breast cancer is about 1 in 8, and women living in North America have the highest rate of breast cancer in the world. In 2006, over 200,000 women were diagnosed with and over 40,000 women died of cancer of the breast. These deaths make breast cancer the second leading cause of cancer death in women, after only cancer of the lung.[34] As grave as many of these statistics are, another reality of breast cancer is that recent advances in early detection and in new types of therapies and their application have resulted in prolonged survival among women diagnosed with breast cancer.[2-6] Although the breast cancer diagnosis rate has increased, the overall breast cancer death rate has dropped steadily since the early 1990s. As a result, it is estimated that the current population of breast cancer survivors in the United States exceeds 2.3 million.[1, 34, 35] As technology aids both early detection and the development of advanced treatment options, this population is expected to grow, and as it does, information related to health maintenance, specifically data describing what anti-cancer medications physicians are prescribing, and to whom they are

prescribing it will become increasingly important.

The Discovery and Importance of Hormone Receptor Status

Hormone-receptor status is an important factor used to determine the prognosis and treatment of breast cancer. Patients with HR+ disease, defined as ER+ or PgR+ or both, typically respond to hormonal treatments that either block or interfere with the function and production of estrogen or progesterone. This is especially promising news for the majority of patients with breast cancer— approximately 75% and 55% of breast cancers are ER+ and PgR+, respectively.[14, 16]

Primary research evaluating the use of hormonal therapy for breast cancer was not hugely successful. First attempts at effective adjuvant hormonal therapy gauged the response of metastatic carcinoma to ovarian suppression. While only roughly one-out-of-three patients benefited from this therapy,[36] it elucidated the importance of identifying specific receptors so that treatment could be tailored in a more precise manner. Maturing from this early approach, HR+ tumors are now determined specifically through various cell staining techniques and varying degrees of hormone positivity can be determined by a validated scale known as the Allred score.[37, 38] Usually, laboratories report test results simply as either *positive* or *negative* because researchers have been unable to directly link the relative degree of hormone positivity on the Allred score to efficacy of hormone therapy. Yet, evidence that minimally HR+ tumors (based on the Allred score and others like it) have a lower chance of response to hormonal adjuvant therapy is undeniable.[39] Over time, the result has been clear— hormonal therapy is indicated as an important option in the adjuvant treatment setting for breast cancer.[2, 9, 40-44]

Two Major Options, Two Different Mechanisms

The majority of breast cancer cases are stimulated to grow by estrogen.[15] Thus, when estrogen is released and subsequently attaches freely to estrogen receptors in the breast, in patients with HR+ disease, the activated receptor then binds to gene promoters in cancerous cells which promote rapid, uncontrolled cell division and atherogenesis, and inhibit cell death.[45] The result is a prevalent disease that, if left unchecked, is fatal. Consequently, beginning in the 1970s researchers began searching for pharmaceutical mechanisms that could block or suppress estrogen. The current result of this research is the development of two major ways in which hormone-dependent mechanisms responsible for the development and progression of breast cancer can be interrupted. The first is to interfere with the binding of estrogen to ER sites with selective estrogen receptor modulator (SERMs), namely tamoxifen. The second, more novel approach acts directly to reduce the amount of estrogen by interfering with its production, and involves the use of current, third-generation AIs.

Tamoxifen History and Perspective

Tamoxifen was initially identified in the 1960s as part of a program designed to develop a contraceptive.[46-48] The phrase "control of hormone-dependent tumors" was added to the patent on tamoxifen by ICI Pharmaceuticals Division (now AstraZeneca) only as an afterthought to its primary goal, the "management of the sexual cycle." In 1972 and on the verge of termination, the program evaluating tamoxifen published results listing tamoxifen for use as a specific application for the treatment of breast cancer.[48, 49] Prompted by these results, tamoxifen was approved for clinical use in the United Kingdom one year later. Evidence at that time showed

that tamoxifen inhibited the binding of estrogen to breast and mammary estrogen receptor sites both *in vivo* and *in vitro*.[50-53]

During this time, however, tamoxifen was still not widely accepted. Upon its inception as a breast cancer treatment, tamoxifen was used mainly as a palliative application for advanced disease.[54] Furthermore, although it was later proved incorrect,[2] the Nolvadex Adjuvant Trial Organization (NATO) trial of adjuvant tamoxifen found no evidence supporting the idea that a patient with a HR+ disease was more likely to benefit from tamoxifen than a HR- patient. This false finding prevented rapid popularization of tamoxifen, and because of the speculation it raised, the U.S. approved tamoxifen only for the treatment of advanced breast cancer in post-menopausal women in December, 1977. Throughout the 1980s, tamoxifen continued to show little promise because trials did not focus on women only with HR+ disease.[55] In 1998, however, a meta-analysis conducted at Oxford University (England) showed that tamoxifen was a life-saving early breast cancer intervention for both pre- and postmenopausal women with HR+ disease.[2]

Since that time, the SERM tamoxifen has been the gold standard for treatment of HR+ disease.[56] Results from the Early Breast Cancer Trialists' Collaborative Group's (EBCTCG) showed that tamoxifen, prescribed for five years, reduced breast cancer mortality by 26% and reduced disease recurrence by 47% in women with ER+ breast carcinoma even when controlling for age, menopausal status, chemotherapy usage, or tumor size.[2] Additionally, by blocking estrogen, tamoxifen therapy may be beneficial in improving lipid profiles and in preventing bone demineralization in postmenopausal women.[57]

Tamoxifen therapy, however, is not without flaw or controversy. Although mortality related to breast carcinoma is reduced in those using tamoxifen, its partial estrogen agonist effects in tissues outside of the breast are associated with double the risk of thromboembolic disease and a 2.5-fold increased risk of endometrial carcinoma.[58, 59] Furthermore, although most patients are initially responsive to tamoxifen therapy, acquired tamoxifen resistance is a common problem and may occur as early as 12-18 months after the initiation of therapy.[59, 60] Additional studies have suggested that tamoxifen, because it binds directly to estrogen receptors, may even promote cancer cell growth in patients who have developed resistance to tamoxifen therapy.[60, 61] Moreover, tamoxifen is not a guaranteed cure. In fact, between 10-20% of patients with ER+ cancer of the breast who are treated with tamoxifen will develop and die of recurrent metastatic disease within 5 years of their initial diagnosis.[62, 63] Another study showed that about a third of women diagnosed with ER+ breast cancer will ultimately relapse despite adjuvant tamoxifen, regardless of chemotherapy use.[64]

These facts summarize the current reality of tamoxifen therapy—while tamoxifen has improved both prognosis and survival for many breast cancer patients—for other patients, tamoxifen alone has either produced too many harsh side effects or worked ineffectively. As a result, researchers have been forced to explore additional avenues of hormone therapy, ultimately searching for an antitumor agent that has fewer unwanted side-effects and that has pharmacodynamics that do not heavily promote resistance over time. The current alternative answer seems has come in the form of aromatase inhibitors (AIs).

AIs: For Postmenopausal Women, Another Choice

For premenopausal women, there still is not much of a choice. In these women, estrogen is produced by the ovaries and transported via the bloodstream directly to the breast. Therefore, the only way to stop its cancer causing effect—aside from ovarian ablation—is to block the estrogen receptor itself, hence tamoxifen. For postmenopausal women, however, other mechanisms of averting estrogen are possible because in these women most estrogen is produced outside of the ovaries, namely through androgen hormones stored in adipose tissue and the adrenal glands. Unlike tamoxifen, instead of blocking estrogen by binding in its place to estrogen receptors, AIs prevent the synthesis of estrogen in nonovarian tissue by suppressing aromatase enzyme activity.[45] This particular mechanism of action is promising for postmenopausal women because it works to prevent the source of estrogen production rather than its uptake—working, perhaps, more directly and with less chance for resistance. Additionally, while AIs have their own unique unwanted side-effects,[65, 66] many researchers and physicians alike believe that alternating tamoxifen with AIs may help offset side-effects for both medications.[9, 15, 41, 45]

The most common adverse side-effects for AIs reported to date are hot flashes, vaginal dryness, loss of sexual desire, fatigue, arthralgias, joint stiffness, and loss of bone mineral density with subsequent increased risk of fracture.[67] Over the past decade, a series of clinical trials with varying study designs have demonstrated superior efficacy of various AIs when compared to tamoxifen in a range of treatment situations.[9, 41-44] The American Society of Clinical Oncology guidelines now

recommend that an AI be included in a woman's adjuvant regimen if she has ER+ and/or PgR+ disease.[15]

Currently, three generations of AIs have been developed. Each new generation of drugs is associated with a higher specificity for the aromatase enzyme and fewer side effects than its predecessor. The third generation of AIs consists of three separate medications grouped into two classes. The first class consists of non-steroidal AIs that bind reversibly to the aromatase enzyme and include anastrozole and letrozole. The steroidal AI, exemestane, binds to aromatase irreversibly. All are highly effective in inhibiting the aromatase enzyme with letrozole, anastrozole, exemestane having 99%, 97%, and 98% inhibition, respectively, of the aromatase enzyme.[45]

Racial Differences & Disparities in Breast Cancer

While countless studies have shown the benefits of adjuvant hormonal therapy in treating breast cancer over the last decade, there is still little certainty on how well these findings are being translated to the entire population. Differences and disparities based on race must be closely paid attention to as the use of hormonal therapy expands. Irrespective of other factors such as age, socioeconomic status (SES), and geographic location, race has long been an independent risk factor in breast cancer.

Even though breast cancer incidence is lower in black women than in white women, black women have higher breast cancer mortality rates, are more likely to be diagnosed at an advanced stage of disease, and have worse stage-for-stage survival than white women.[68-70] Based on data from breast cancer patients diagnosed after

1995 and followed until 2003, the American Cancer Society reported the survival rate for black women was only 77% compared to a 90% survival rate for white women, and that this difference was significant.[1, 71] Furthermore, breast cancer death rates have declined faster in white women compared to African American women in past two decades.[35, 71] These findings have been reported again and again in current literature, and have even been found in databases where all patients, regardless of race, had equal access to care.[72]

It is important then that, as medical treatment progresses, both researchers and clinicians alike pay very close attention to whether new treatments widen or narrow the racial gap in breast cancer mortality. Adjuvant hormonal therapy is currently a novel treatment frontier, and studies have already found a significant racial difference in rates of adjuvant hormonal therapy usage.[73] Previous differences in race have been attributed to the fact that non-white women typically had lower levels of knowledge, more inaccurate beliefs, and more barriers to screening compared with white women,[74] yet it may certainly be compounded by the fact that non-white women may not be receiving new treatments. The current study will examine if this may be the case.

Systems-Level Differences & Disparities in Breast Cancer

The healthcare system may create its own differences and/or disparities in breast cancer simply by the way it is arranged. ''Between-physician'' differences may be viewed as a consequence of systems-level factors such as the geographical distribution of different types of physicians coupled with residential segregation by SES and race/ethnicity.[75-77] Physicians treating patients of different racial/ethnic or

SES backgrounds may differ in their training in physician–patient communication and preventive care. There is evidence that physicians who treat black patients are less likely to be board-certified and more likely to see themselves as unable to provide high-quality health care.[78] Also, physicians serving in low income, minority communities are more likely to be graduates of foreign medical schools and less likely to be board certified.[79-82] Another study found that inner-city physicians were not as knowledgeable about national guidelines for preventive care as physicians in general.[83]

Disparities in the quality of training and knowledge of prevention and treatment are likely to result in less frequent discussion of cancer screening and treatment options among physicians treating patients of racial/ethnic minority and/or low-SES. Treatment for breast cancer may also differ by practice settings, with large physician groups more likely to have access to specialists and new treatments than small groups and solo practices. Thus, the type of and practice location of a provider are important distinctions that must be made when trying to tease out various racial/ethnic differences and/or disparities.

CHAPTER 3

METHODS

Research Design

This study was based on a retrospective design which examined the relationship between selected patient and physician characteristics and whether an aromatase inhibitor was ever prescribed to a patient as hormonal adjuvant therapy (v. tamoxifen only) over a given time period. In this study, patients were North Carolina (NC) Medicaid enrollees identified in the Linked North Carolina Central Cancer Registry-Medicaid Claims data (CCR-Claims linked database). This dataset was developed and validated by Dr. Roger Anderson and his colleagues at Wake Forest University, NC.[84] These data were previously de-identified and an Ohio State University institutional review board (IRB) exemption was granted after approval from the NC Department of Health and Human Services (see Appendix).

Data Source

The CCR-Claims linked database was created by linking Medicaid claims and demographic information with the central cancer registry's information on all cancer cases diagnosed among North Carolina residents. Detailed claims for both NC Medicaid and Medicare and for the dually insured are also included in the linked dataset.

To link data from the two entities, Anderson et al. used patients' social security numbers and first three letters of their first names to combine the two records.[84]

Study Period

This study examined the CCR-Claims linked database population that was prescribed antiestrogenic monotherapy (only one drug) from January 1, 2000 to December 31, 2004.

Study Population

Cases of primary breast cancer were identified from the CCR-Claims linked database files using the *International Classification for Disease Code-9th revision* (ICD-9). From these 4,393 patients, anyone with at least one claim of any antiestrogenic prescription medication (tamoxifen, anastrozole, exemestane, letrozole) was identified using *National Drug Code* (NDC). This led to a subset of 2,316 patients. The current study did not examine why patients were not prescribed antiestrogenic therapy because background clinical information for individual patients was limited. Thus, the current study had inadequate ability to determine hormonal therapy eligibility.

A final set of inclusion criteria were used: (1) newly started on AI or tamoxifen therapy (i.e. no claim for an index prescription in a one-year pretreatment period), (2) hormone-receptor positive tumors, (3) invasive breast cancer (stage I-IV), (4) started on adjuvant hormonal monotherapy during study period, (5) continuous enrollment in Medicaid both twelve months before and twelve months after the date of first prescription, (6) female, age 18 or older, and (7) self-reported race of white or African American. After this final set of inclusion criteria, the total number of

patients was 609. This data manipulation was previously performed by Dr. Rajesh Balkrishnan, (Ohio State University, Columbus, OH) to develop an ideal study cohort for examining adjuvant hormonal therapy prescription differences across various patient and physician demographics.

Because a primary outcome of interest was to examine differences in antiestrogenic prescription patterns between non-Hispanic whites and African Americans, three patients with a self-reported ethnicity of "Hispanic" were not included. An additional six patients were not included in the analysis because information relating to zip code of residence was absent. This left a final study sample of 600 patients.

Data Elements

Patient demographic variables were obtained from Medicaid records. The variables *race* and *ethnicity* are self-reported in the Medicaid dataset. For current study, *race* was dichotomous (white v. African American) and racial classifications of American Indian or Alaska natives, and Asian Americans or Pacific Islanders were excluded as part of the initial exclusion criteria because of insufficient sample size among each racial group. *Ethnicity* was defined as Hispanic / non-Hispanic, but was not included in the analysis because only three patients identified themselves as "Hispanic." Age was also obtained from Medicaid records; only women 18 or older were included. Age was used as a proxy for determining menopausal status (pre v. post) using the American Association of Blood Banks cutoff of fifty-five years. Geographical status (urban vs. rural) was determined by using the US Census Bureau

and US Department of Health and Human Services designations of urban and rural, and were based on self-reported county of residence.

Additionally, Medicaid claims records were used to determine background characteristics of both patients and providers and include: type of provider seen (oncologist vs. non-oncologist); practice setting (public vs. private); year hormonal therapy was started; type of surgery received (breast conserving surgery (BCS) vs. mastectomy); whether the patient was high cost (claims $\geq$ $10,000 in year prior to study initiation); and whether or not the patient was hospitalized, received home care, visited the emergency department, and/or was in nursing home care prior to receiving antiestrogenic treatment. Additionally, information on the specific oral adjuvant hormonal therapy that patients were prescribed was obtained using National Drug Code (NDC) code for that prescription provided in the Medicaid claims record.

Information on cancer stage and tumor size was available in the CCR-Claims data from the NC cancer registry files. The NC Cancer registry uses the Surveillance Epidemiology and End Results (SEER) summary stage system for categorizing and staging breast cancers. Stage was dichotomized as localized (confined to the primary site, i.e. no lymph nodes involved) versus regional (spread to regional lymph nodes or directly beyond primary site), distant (metastasized), or unstaged. Tumor size was reported in centimeters (cm) and represented dichotomously ($\leq$1cm v. >1cm, unknown).

Data Analysis

This study analyzed whether patient or physician characteristics predict which patients receive any type of AI (v. tamoxifen only) as antiestrogenic hormonal

therapy among a group of female patients diagnosed with breast carcinoma (stage I-IV) that were 18 or older and prescribed at least one type of adjuvant hormonal therapy. Descriptive analyses were used to assess differences in the background characteristics across the two major types of adjuvant hormonal therapy under study (tamoxifen and AIs). Continuous variables were assessed using means, and two-sample t-tests were used to determine statistically appreciable differences. Percentages were used to describe categorical variables and statistical association was assessed using the chi-square test.

Logistic regression analysis was performed to model combined effects. Initial univariate analyses were performed on biologically and socially meaningful variables (described previously), and variables were added into the model based on level of statistical significance. The Likelihood Ratio (LR) test was used to determine improved statistical fit using a p-value < 0.05 as significant model improvement and p-value <0.10 as marginal improvement worthy of secondary consideration. The formula for the LR test using log likelihood (LL) is: [2 X LL of larger model] – [2 X LL of smaller model]

$\sim \chi^2$ with degrees of freedom equal to the number of variables difference between the two models. Additionally, each justifiable interaction term was tested for statistical significance, and confounding was assessed as a variable that changed the OR of a variable already in the model by $\geq$ 10-15%.[85] Any significant interaction terms or appreciable confounders remained in the final model.

Once the model was complete, the assumptions underlying logistic regression analysis were verified. The assumptions were defined as: (1) the outcome variable

follows a binomial distribution, (2) the values of the outcome were statistically independent, and (3) the mean $E(y|x) = P(x)$ was given by the function $P(x) = [e^{\beta_0 + \beta_x}] / [1 + e^{\beta_0 + \beta_x}]$.[86] Accepting linearity of the logit for continuous variables was assessed as well. The variable representing the *year in which hormonal therapy was started* was the only variable modeled continuously. This assumption was verified using fractional polynomials and smoothed plots.[86]

Goodness-of-Fit of the model was assessed to determine how well the model accurately predicted observed values. The Hosmer-Lemeshow (HL) χ^2 value was used to evaluate goodness-of-fit. A p-value >0.05 indicates good model fit. Model discrimination was evaluated using a Receiver Operating Characteristic (ROC) curve. Outcomes of the test range from zero to one, and acceptable, excellent, and outstanding discrimination were determined to be 0.70, 0.80, and 0.90, respectively.[86] Diagnostic tests were performed to ensure no covariate patterns served as outliers. All analyses were conducted using STATA software version 9.2 (StataCorp LP, Texas Station, Texas).

CHAPTER 4

RESULTS

A total of 600 patients were included for final analysis after all exclusion criteria. Just over three-fourths of the women were prescribed tamoxifen only therapy over the study period (Table 4.1).

Type of Therapy	**Number of Patients (%)**
Tam (only)	451 (75.17)
AI (ever)	149 (24.83)

Table 4.1 Distribution of adjuvant hormonal therapy types (n=600)

The percentage of women ever prescribed AIs, however, increased in an approximately linear fashion (LR χ^2 $p < 0.01$) over the four years of the study (Table 4.2). On average, patients receiving tamoxifen only therapy began treatment in June of 2001, while patients who ever received AI therapy began treatment in February of 2002. More importantly, this difference (~7 months) was significant ($t = -7.29$, $p<0.01$).

	Number of Patients(%) by Year				
Therapy	*2000*	*2001*	*2002*	*2003*	*2004*
Tam (only)	51 (100)	188 (88.26)	144 (64.86)	49 (55.68)	19 (73.08)
AI (ever)	0 (0)	25 (11.74)	78 (35.14)	39 (44.32)	7 (26.92)

Table 4.2 Distribution of adjuvant hormonal therapy types by year of study

Initial univariate comparisons revealed that the percentage of women with localized breast cancer (opposed to regional, distant, or unstaged) was significantly higher ($p<0.001$) among patients who received tamoxifen only (55.2%) compared to those who received AI therapy (34.2%). Additionally, the percentage of patients who lived in rural counties was higher ($p=0.013$) for women who received tamoxifen only (47.2%) than for those who received AIs (35.6%). Moreover, the percentage of women with a tumor size less than 1cm was significantly smaller ($p=0.033$) among women who received AI therapy (12.8%) than those who received tamoxifen only (20.0%). Menopausal status was marginally significant at the univariate level ($p=0.081$), and the percentage of postmenopausal (age$\geq$55) women that received AI therapy (83.9%) was higher than that of those who received tamoxifen only (77.2%).

While the percentages of antiestrogenic prescription patterns varied across other patient and provider categories, these differences were not significant at the univariate level. A patient's race, the type of surgery a patient received (BCS v. mastectomy), whether the patient spent over $10,000 in healthcare costs in the year

before the study, and whether the patient entered the hospital, the emergency department, a nursing home, or home care in the year before the study began were not initially significant at the univariate level with all p-values > 0.10. Provider characteristics were insignificant at the univariate level as well; the provider's practice setting (public v. private, p=0.431), and whether the provider was an oncologist or not (p=0.251) were not associated with the type of prescribed antiestrogenic treatment. Table 4.3 summarizes these findings.

Predictor Variable	Description	TAM (only) n (%)	AI (ever) n (%)	Total n (%)	p-value univariate
Cancer stage	Unstaged	15 (3.3)	8 (5.4)	23 (3.8)	<0.001[a]
	Distant	5 (1.1)	14 (9.4)	19 (3.2)	
	Regional	182 (40.4)	76 (51.0)	258 (43.0)	
	Local	249 (55.2)	51 (34.2)	300 (50.0)	---
Patient county of residence	Urban	238 (52.8)	96 (64.4)	334 (55.7)	0.013
	Rural	213 (47.2)	53 (35.6)	266 (44.3)	---
Tumor size	Unknown	42 (9.3)	17 (11.4)	59 (9.8)	0.033[b]
	≥1cm	319 (70.7)	113 (75.8)	432 (72.0)	
	<1cm	90 (20.0)	19 (12.8)	109 (18.2)	---
Menopausal status	Post (age≥55)	348 (77.2)	125 (83.9)	473 (78.8)	0.081
	Pre (age<55)	103 (22.8)	24 (16.1)	127 (21.2)	---
Type of surgery	Mastectomy	297 (65.9)	94 (63.1)	391 (65.2)	0.539
	BCS	154 (35.2)	55 (36.9)	209 (34.8)	---
Hospitalized *in year prior to study*	Yes	245 (54.3)	91 (61.1)	336 (56.0)	0.150
	No	206 (45.7)	58 (38.9)	264 (44.0)	---
Race	Black	194 (43.0)	73 (49.0)	267 (44.5)	0.203
	White (non-Hisp)	257 (57.0)	76 (51.0)	333 (55.5)	---
High cost patient *≥$10,000 in year prior to study*	Yes	98 (21.7)	42 (28.2)	140 (23.3)	0.106
	No	353 (78.3)	107 (71.8)	460 (76.7)	---
Home health care *in year prior to study*	Yes	108 (24.0)	43 (28.9)	151 (25.2)	0.231
	No	343 (76.1)	106 (71.1)	449 (74.8)	---
Nursing home visit *in year prior to study*	Yes	53 (11.8)	18 (12.1)	71 (11.8)	0.914
	No	398 (88.2)	131 (87.9)	529 (88.2)	---
ED visit *in year prior to study*	Yes	67 (14.9)	26 (17.5)	93 (15.5)	0.448
	No	384 (85.1)	123 (82.5)	507 (84.5)	---
Type of provider	Oncologist	56 (12.4)	24 (16.1)	80 (13.3)	0.251
	Non-oncologist	395 (87.6)	125 (83.9)	520 (86.7)	---
Provider practice setting	Private	3 (0.7)	2 (1.3)	5 (0.8)	0.431
	Public	448 (99.3)	147 (98.7)	595 (99.2)	---

[a] p-value the result of dichotomous comparison: local v. regional, distant, or unstaged

[b] p-value the result of dichotomous comparison: <1cm v. ≥1cm or unknown

Table 4.3 Demographics and univariate significance of categorical independent variables across antiestrogenic prescription patterns

Model building was performed using variables analyzed at the univariate level and forward analysis. Results of the final multivariate logistic regression model revealed that patients who lived in urban areas (compared to rural), were postmenopausal (based on age $\geq$ 55), had regional, distant or unstaged cancer (opposed to local), had been hospitalized in the year prior to treatment index, and had BCS (rather than mastectomy) had 1.97 [1.29, 3.00], 2.26 [1.80, 2.83], 2.74 [1.79, 4.20], 1.87 [1.20, 2.92], 0.64 [0.41, 1.00] times the odds, respectively, of ever receiving an AI compared to tamoxifen only, controlling for each variable and the year the patient initiated hormonal therapy. Additionally, for every one-year increase in the time a patient started hormonal therapy, the odds of receiving AI therapy (compared to tamoxifen only) increased 2.26 [1.80, 2.83] fold.

While a higher percentage of African Americans (compared to non-Hispanic whites) received aromatase inhibitors, the difference was not significant. Additionally, there was no significant difference in prescribed hormonal therapy (AI v. tamoxifen only) based on whether a patient's provider was an oncologist or not, whether a patient spent more than $10,000 on medical expenditures in the year prior to the study beginning, or whether the patient visited a nursing home or had home healthcare or went to the emergency department (ED) in the year prior to study initiation. These logistic regression modeling results are summarized in Table 4.4.

Predictor Variable[a]	Description	Odds Ratio	Std. Error	p-value	95%CI
Year hormonal therapy started	Continuous *(2000-2004)*	2.26	0.26	<0.001	[1.80, 2.83]
Menopausal status	Post (age≥55)	2.20	0.61	0.004	[1.28, 3.78]
	Pre (age<55)	---	---	---	---
Type of surgery	Mastectomy	0.64	0.15	0.054	[0.41, 1.00]
	BCS	---	---	---	---
Cancer stage	Regional, Distant, Unstaged	2.74	0.6	<0.001	[1.79, 4.20]
Local		---	---	---	---
Patient county of residence	Urban	1.97	0.42	0.002	[1.29, 3.00]
	Rural	---	---	---	---
Hospitalized *in year prior to study*	Yes	1.87	0.42	0.006	[1.20, 2.92]
	No	---	---	---	---
Tumor size	≥1cm, unknown	1.29	0.29	0.265	[0.83, 2.01]
	<1cm	---	---	---	---
Race	Black	1.27	0.26	0.251	[0.84, 1.91]
	White (non-Hispanic)	---	---	---	---
High cost patient *≥$10,000 in year prior to study*	Yes	1.30	0.32	0.294	[0.80, 2.11]
	No	---	---	---	---
Home health care *in year prior to study*	Yes	1.26	0.30	0.820	[0.50, 1.73]
	No	---	---	---	---
Nursing home visit *in year prior to study*	Yes	0.93	0.30	0.820	[0.50, 1.73]
	No	---	---	---	---
ED visit *in year prior to study*	Yes	0.84	0.22	0.499	[0.50, 1.40]
	No	---	---	---	---
Type of provider	Oncologist	1.28	0.36	0.379	[0.74, 2.26]
	Non-oncologist	---	---	---	---
Provider practice setting	Private	1.65	1.56	0.596	[0.26, 10.51]
	Public	---	---	---	---

[a] Variables above line represent the final model after forward selection, variables below line represent insignificant variables added univariately into the final model via forward selection

Table 4.4 Odds ratios and confidence intervals for logistic regression modeling of receiving AI (ever) v. tamoxifen (only) therapy

Furthermore, none of the variables that were insignificant in the final model (below line in Table 4.4) were appreciable confounders using the 10-15% change-in-OR standard (Figure 4.1).[85] Additionally, no plausible interaction terms from the final model were significant at the $p<0.05$ level (*cancer stage* X *urban status*; *cancer stage* X *hospitalizations in year prior*; *cancer stage* X *surgery type*; *type of surgery X urban status*; *menopausal status* X *surgery type*).

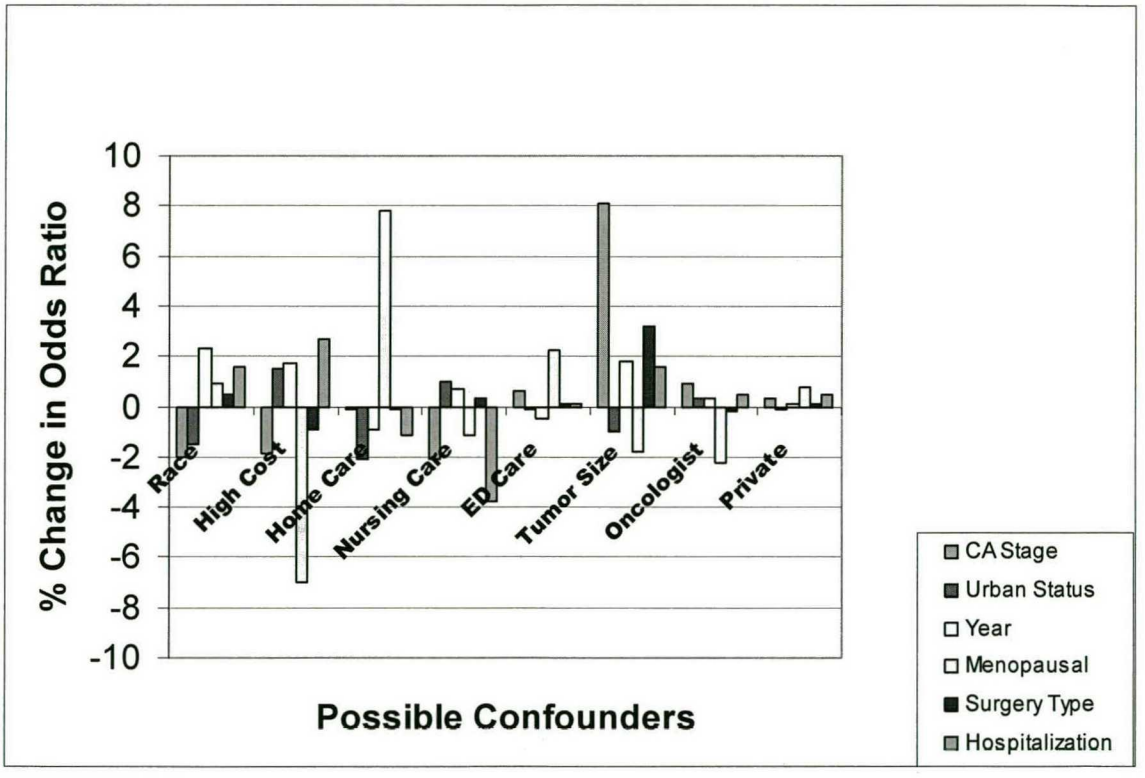

Figure 4.1 Assessment of confounding in main model

Only one variable, *the year a patient started adjuvant hormonal monotherapy*, was modeled continuously. The method of fractional polynomials suggested that the linear model was best (Table 4.5). Smoothed plots suggested that linear modeling

was acceptable as well (Figure 4.2). Additionally, collapsing the variable categorically proved difficult because *year=2000* had a zero cell—making it more meaningful to model continuously.

Model Characteristics	df	Deviance	Gain	p-value	Power(s)
Not in model	0	637.085	--	--	
Linear	1	580.782	0.000	0.000	1
m = 1	2	580.727	0.056	0.813	-2
m = 2	4	580.729	0.053	1.000	-2 -2

Table 4.5 Fractional polynomial model comparisons for continuous variable

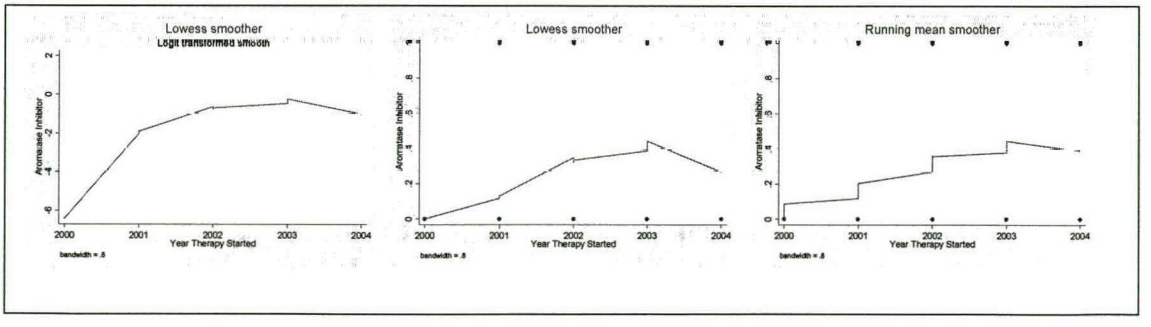

Figure 4.2 Smoothed plots evaluating the linearity of *year therapy (2000-2004) was started* in the model logit using a lowess smoother (logit scale), a lowess smoother (logistic scale), and a mean smoother, respectively

The Hosmer-Lemeshow goodness-of-fit statistic for the model was 11.60 with a corresponding p-value of 0.170 when compared to a chi-square distribution with eight degrees of freedom—indicating a robust fit.[86] Model discrimination was determined to be between "acceptable" and "excellent" with the area under the ROC curve computed as 0.7554 (Figure 4.3).[86] This implies simply that over three-fourths of the women who were ever prescribed an AI, actually had a higher probability of having ever been prescribed them as predicted in the final model.

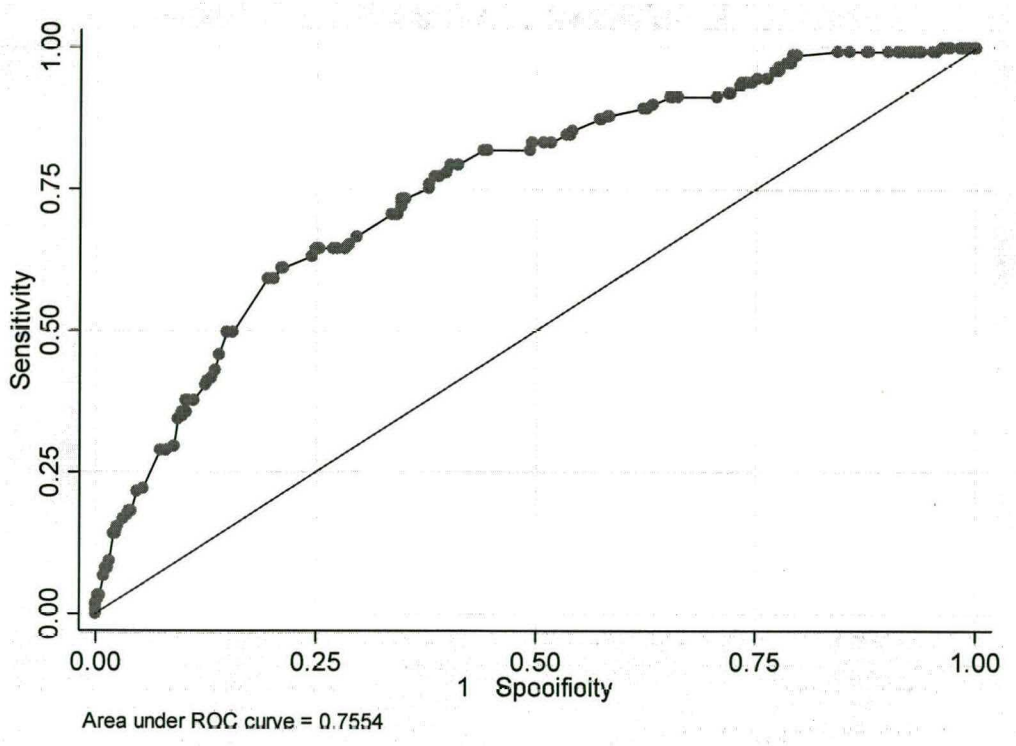

Figure 4.3 Area under the ROC curve for final model

The sensitivity and specificity of the curve were maximized at a cut-point of approximately 0.30 (Figure 4.4), however, the model can be tailored to have either higher specificity or sensitivity depending on the goals of research.

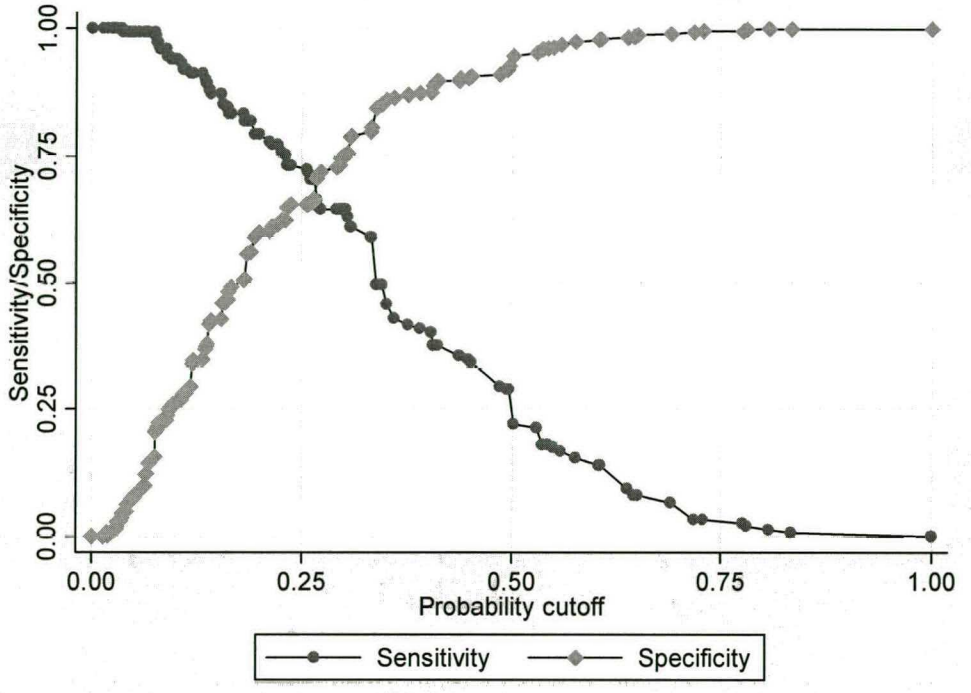

Figure 4.4 Plot of sensitivity and specificity versus all possible cut-points

To examine individual covariate patterns within the model, logistic regression diagnostic tests were performed. The estimated logistic probability was compared to the Hosmer-Lemeshow $\Delta\chi^2$ and Pregibon's $\Delta\beta_{(hat)}$. Only two points had a reasonable effect on the fit of the model, however, their small level of influence did not significantly alter the risk factor coefficients, making it unnecessary to remove any

covariate patterns (Figure 4.5). Overall, the results indicate that no covariate patterns were extreme outliers, and confirmed good fit of the model.

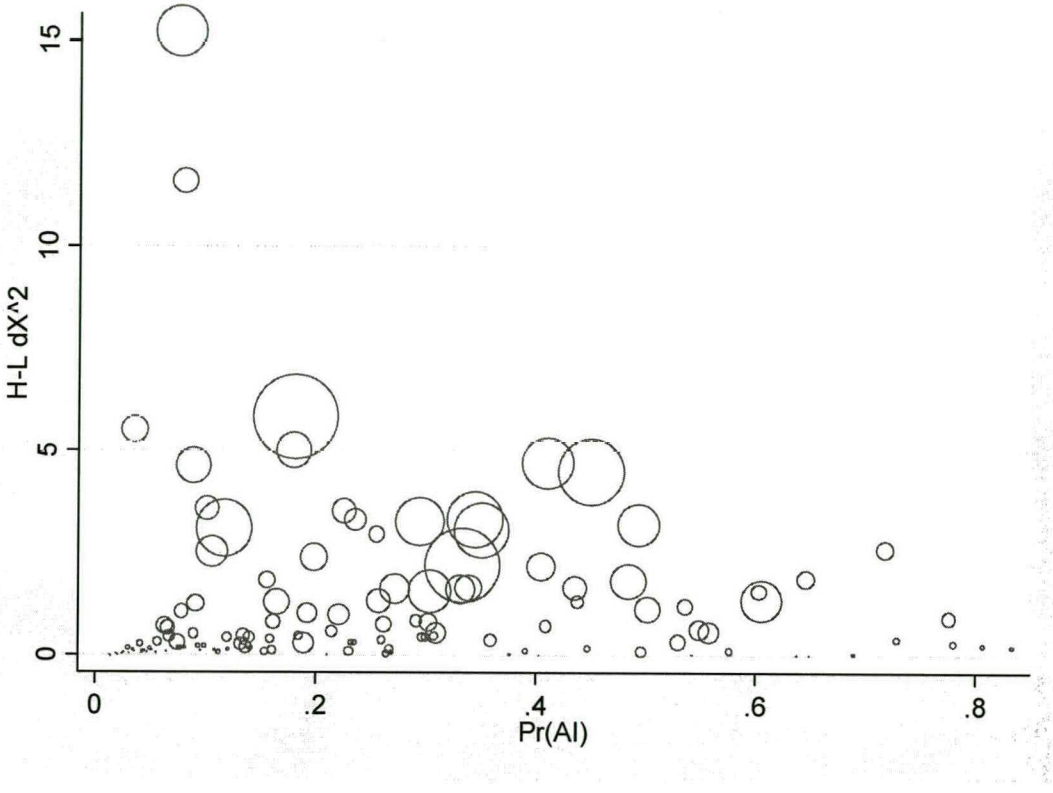

Figure 4.5 Plot of $\Delta\chi^2$ versus the estimated logistic probability in the final model weighted by $\Delta\beta_{(hat)}$

CHAPTER 5

DISCUSSION

Much research has been conducted to develop, test, and understand the use and effects of new breast cancer treatment and prevention, and the United States has made truly remarkable steps towards finding a cure and offering hope. In spite of these tremendous gains, however, much of this scientific advancement often gets lost in translation. Thus, not everyone benefits equally from novel scientific research, and often times certain groups of individuals tend to be disproportionately affected by gaps in translational research. The purpose of this study was to gain a better understanding about both patient and physician characteristics that determine whether or not an individual is prescribed the newest generation of AIs (versus those that receive tamoxifen therapy alone) and whether these differences represent disparities.

This study identified six major findings regarding the likelihood an individual will receive some type of AI as adjuvant hormonal therapy in contrast to receiving only tamoxifen. First, during the study period (2000-2004) the odds of a patient ever receiving AI therapy increased linearly. Intuitively, this is mainly a reflection of the growing acceptability and popularity of AIs during the study period. While anastrozole, letrozole, and exemestane were first approved by the US Food and Drug Administration (FDA) *before* the study period in 1996, 1998, and 1999, respectively,

to treat *advanced* breast disease; they were not granted full approval to treat *early* disease until *during* and even *after* the study period. Letrozole was fully approved in 2001, one year after the study began, however, anastrozole and exemestane did not gain full FDA approval until 2005, nearly one full year after the study ended. Thus, in this study, the odds of a patient ever receiving an AI more-than-doubled each year, and this trend is expected to continue for years to come as long as research continues to demonstrate superior efficacy of AIs.

A second major finding is that postmenopausal women (using age $\geq$55) have more than twice the odds of ever receiving an AI when compared to premenopausal women. This is an expected result because AIs, due to their mechanism of action, are only indicated for postmenopausal women. However, the current study's definition of *menopausal* is certainly limited by simply using an age cutoff. This definition does not encompass women who reach menopause at an age earlier than fifty-five, or women that have had surgically-induced menopause. Because of this, the 25 women who received AIs but were considered premenopausal by study definition were more than likely postmenopausal in reality. A self-reported indicator of menopausal status would certainly be ideal for future research.

Additionally, patients on study who had a mastectomy had marginally significant lower odds of ever receiving an AI compared to those who had BCS. This may be due to the fact that although BCS (with six weeks of post-operation radiation therapy) has equivalent long-term survival rates to mastectomy,[87] the risk for local recurrence is higher.[88] Thus, for women who forego mastectomy, the most aggressive adjuvant treatments (i.e. AI therapy) are indicated to prevent further

recurrence or the need for a post-BCS mastectomy. It may also be the case, however, that women who undergo mastectomy are not being treated aggressively enough with novel antiestrogenic treatment by their providers, and that these women are sacrificing an added protective benefit by underutilizing third generation AIs.

Furthermore, women on study with regional, distant, or unstaged cancer had more than 2.7 times the odds of ever receiving an AI (in contrast to tamoxifen only therapy) when compared to women with locally staged carcinoma. The reasons behind this are most likely two-fold. First, for late-staged tumors, more aggressive adjuvant therapy is indicated to prevent recurrence. However, similar to prescription patterns involving surgical intervention described above, not using AI therapy for women with early-staged tumors may constitute under-treatment.

Moreover, at the time the study began, AIs had FDA approval only for advanced breast disease. Thus, for at least the first year on study, aromatase inhibitors were not approved to treat early stages of disease. Therefore, as aromatase inhibitors were approved for a wider variety of treatment options, their use became more accepted and hence more widespread. Future studies should aim to clarify this relationship with causal evidence.

The final two major findings suggest differences, and perhaps disparities, in access to care. Study results indicated that (1) women who lived in urban areas had nearly twice the odds of ever being prescribed an AI compared to those who lived in a rural area, and (2) women who were hospitalized in the year prior to study initiation had almost twice the odds of ever being prescribed an AI compared to those who were not hospitalized during that time. Previous studies have demonstrated that

women who live out of metropolitan statistical areas (MSAs) were significantly less likely to receive proper breast cancer screening and have access to high-tech care,[89] and the finding that these women may have significantly lower odds of receiving novel and/or proper treatment after diagnosis should not come as a surprise. In the past, these issues of access have been linked to lack of transportation,[30] poor access to healthcare facilities,[90] an insufficient number of specialists in non-urban/non-metropolitan areas,[91] and the slow diffusion of medical innovations into clinical practice in underserved areas.[92] Additional studies should specifically explore issues of healthcare access surrounding antiestrogenic prescription patterns.

While race has been a significant predictor of breast cancer screening adherence[93] and in overall survival (both are lower in black women),[94] in this study a patient's race was not significantly associated with ever being prescribed an AI over the study period. This may be due to the fact that this study examined only individuals in the NC Medicaid population and controlled for urban/rural status, thus effectively controlling for many SES and geographical factors. One might expect African Americans to have disproportionately less access to novel treatments based on previous studies that examined screening and overall survival across race. However, African American women tend to have a lower risk of osteoporotic bones than white women, and because one of the harshest side effects of AIs is accelerated osteoporosis, some researchers have suggested that African American women may be better suited for AIs.[95] Thus, this may be disproportionately inflating AI prescription rates for African American women when compared to whites. This fact may

counterbalance the relationship between race, access, and antiestrogenic therapy type, and efforts to understand this caveat should be made in future research.

Additional examination of possible access-related predictors of therapy type showed that, unlike whether a patient was hospitalized in the year before the study, whether a patient was admitted into the emergency department, a nursing home, or home care in the year before the study was not associated with higher odds of ever receiving an AI. Furthermore, the amount of medical costs the patient accrued in the one-year period before the study began was not a predictor of the type of therapy received. This suggests—rightfully so—that whether a patient has been "high cost" in the past does not dictate their future treatment in the adjuvant antiestrogenic setting.

Moreover, physician characteristics did not predict whether or not a patient would be prescribed AI therapy. Whether or not the provider was an oncologist was not related to ever receiving AI therapy. Whether the provider practiced in the private or public setting was unrelated as well. However, because this was a Medicaid population, less than one percent of the patients visited a private provider. Moreover, fewer than twenty percent of patients saw an oncologist. In the future, these predictors will most likely have to be examined by a non-Medicaid study population to truly appreciate the results. Additionally, future studies should examine a wider variety of provider characteristics (e.g. race, size of practice, rural v. urban practice setting, board certification, US v. foreign medical schooling, etc.)

Finally, a patient's tumor size, although correlated at the univariate level, was unrelated to the type of adjuvant hormonal therapy received after controlling for

cancer stage, surgery type, and menopausal status. This fact is best explained by evidence suggesting that cancer stage, a patient's menopausal status, and whether or not the tumor is ER+, PgR+, or both are the best medical predictors of therapy type.[15]

Although this study offers many insights into what patient and physician characteristics predict adjuvant hormonal therapy type, it is not without limitations. One weakness is that the time period that this study analyzed may not be best suited to discern whether disparities exist in AI prescribing patterns. To assess levels of disparities, ideal outcomes must be fully understood. Certainly during the time of this study (2000-2004), and perhaps even today, the exact way to achieve ideal outcomes regarding AI therapy was not entirely understood. Therefore, analyzing the results of this study and interpreting them as disparities *per se* from a modern day vantage point is most likely subject to hindsight bias. That said, differences in access to novel treatment, whether completely understood or not, are always important to discern.

Another limitation of this study is limited external validity. This study analyzed Medicaid patients only in the state of North Carolina. The demographics of Medicaid patients are certainly different from the population in general, as most residents of NC and of the US do not meet Medicaid eligibility. Additionally, populations vary from state-to-state as do eligibility criteria for Medicaid. Generalizations should not be made without future study replication on more diverse populations.

A further weakness is that this study only analyzed breast cancer patients that were prescribed at least one type of adjuvant hormonal therapy. While differences and disparities may exist across those receiving *some* type of antiestrogenic therapy;

differences and disparities may also exist between those who do and do not receive *any* type of antiestrogenic adjuvant therapy. Future studies should explore this additional possibility by examining populations of breast cancer patients that consist of both women who never receive any hormonal therapy and women who do.

A more specific limitation lies in the fact that AIs were examined as one category, rather than looking individually at each of the three types of third-generation AI therapies. The study sample, however, had an insufficient number of patients prescribed letrozole or exemestane to examine this with adequate statistical power. Furthermore, this study was only able to examine race in the context of white versus African American. No data existed on individuals of other races, and data on ethnicity were sparse.

Moreover, data on patients' education and income were not available. These data are often analyzed in the context of health differences and health disparities. Psychosocial information involving a patient's beliefs, attitudes, or knowledge was also absent and should be examined in future studies.

Despite limitations, however, this study provided specific information about both patient and provider characteristics that predict antiestrogenic therapeutic prescription outcomes. While using a Medicaid population limits study generalizability and the ability to examine factors related to SES, it assures internal validity and controls for factors related to income by restricting analysis to a relatively homogeneous group. Furthermore, linking claims data with tumor registry data ensures the validity of most information and provides a list of clinically relative explanatory variables.

Today, AIs have, in the minds of many researchers and clinicians alike, replaced tamoxifen as the gold standard for breast cancer adjuvant hormonal therapy.[96] In the context of AIs, years of research seem to have paid off with a promising new treatment. Studies are currently underway to continue evaluating efficacy and to help develop more rigid treatment guidelines. Yet, as science moves forward, caution must be used. As new resources are rapidly developed in the fight against breast cancer, these resources must be distributed equitably. As more information about aromatase inhibitors is discovered, future studies like this one will be even more important. Access to appropriate antiestrogenic therapy must be monitored to tease out differences and disparities, and to make certain that the technologies of tomorrow are translated in a manner that benefits society equally and narrows the gap of inequality in breast cancer prescription practices, treatment, and care—a gap that has made the history of breast cancer a bitter sweet one.

APPENDIX

North Carolina
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Michael F. Easley, Governor
Carmen Hooker Odom, Secretary

Mark T. Benton, Director
William W. Lawrence, Jr., M.D., Senior Deputy Director

August 28, 2007

Rajesh Balkrishnan, Ph.D.
Ohio State University
500 West 12th Avenue, 136-C
Columbus, OH 43210

Dear Dr. Balkrishnan:

Your request for access to NC Medicaid data for the study entitled, "Patient Determinants Associated with Prescription of Various Adjuvant Hormonal Therapies Following a Diagnosis of Breast Cancer in Medicaid Enrolled Patients: Who is Receiving What and Why?" has been approved.

It is DMA's understanding that you are requesting approval to use NC Medicaid data that was previously obtained for a prior research project and the re-disclosed information will be used by Mr. John McLaughlin for his thesis. We further understand that all dates and identifiers have already been removed from the data. Once the study is completed you and Mr. McLaughlin will be responsible for destroying the Medicaid data. The data to be re-disclosed are listed on an attachment to this letter.

This approval does not provide for any other use of the requested data.

DMA looks forward to being apprised of relevant findings from your study. Furthermore, we would appreciate the opportunity to review any written conclusions at the time that such might be submitted for publication. If you have any questions or if we can be of further assistance to you, please feel free to contact me at (252) 756-5548.

Sincerely,

Becky Brown

Becky Brown
DMA HIPAA Privacy Official

Attachment: Data Elements to be Disclosed
Request for Access to Health Information for Research

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