Adherence to Adjuvant Endocrine Therapy among Women Diagnosed with Early Breast Cancer

Albert Farias

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Reading Committee:

Engelberta (Beti) Thompson, Chair

Steven B. Zeliadt

India J. Ornelas

Ryan Hansen

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Abstract

Adherence to Adjuvant Endocrine Therapy among Women Diagnosed with Early Breast Cancer

Albert John Farias

Chair of the Supervisory Committee:
Professor Beti Thompson
Department of Health Services

Estrogen receptor-positive (ER+) breast cancer is diagnosed in two-thirds of breast cancer cases in the US. Treatment with adjuvant endocrine therapy (AET) is recommended for five years for women with ER+ breast cancer. Despite the effectiveness of AET to improve survival and decrease cancer recurrence, adherence to recommended treatment is suboptimal. Understanding the factors that are associated with adherence to AET could improve overall breast cancer survival. Therefore, the goal of this dissertation is to identify target areas that are amenable for interventions in order to improve adherence to AET. The objective is threefold: 1) determine the association between combined out-of-pocket costs for AET medication and adherence; 2) examine how factors affect adherence to AET medication among women with very low adherence, moderately low adherence, and high adherence; and 3) understand, from the patient's perspective, how their physicians communicate with them about AET treatment. For objective 1

and 2 we conducted a retrospective cohort study using longitudinal medical and pharmacy claims data from the MarketScan Database from 2007-2011. We included women who were recently diagnosed and surgically treated for breast cancer and who filled at least one prescription for AET. For objective 3, we conducted semi structured in-depth interviews with breast cancer survivors taking AET. We found that high out-of-pocket costs for AET medication put patients at an increased risk of non-adherence. Factors associated with adherence to AET differed across the distribution of adherence and the use of mail-order pharmacies had the greatest influence on adherence. Physician-patient communication played an important role in both the initiation and management of AET. We found that women continue to take AET medication because their physician communicated key aspects of AET treatment in a way that they understood. Women also trusted and had confidence in their physicians. In summary, organizational-level interventions have the potential to improve adherence to AET. The use of mail-order pharmacies as well as lowering out-of-pocket costs may have the greatest influence on improving adherence. Women may also be more likely to continue AET treatment if physicians communicate the benefits of AET and actively engage patients in follow-up care to manage potential side effects.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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DEDICATION

To the memory of Karen Delgado, my mom.

Chapter 1. INTRODUCTION

1.1 BACKGROUND

Over the past two decades there have been important improvements in the rates of screening and the types of treatment for women with breast cancer. Yet, despite these improvements, breast cancer remains the second leading cause of cancer death for women.[1] In 2013, approximately 39,600 women were expected to die from breast cancer.[1] One way to significantly reduce breast cancer mortality is to improve adherence to recommended treatment.[2] Adherence to guidelines for systemic adjuvant endocrine therapy (AET) is associated with improved disease-free survival for women with early stage breast cancer.[3-7] It is estimated that treatment with Tamoxifen, a form of adjuvant endocrine therapy (AET), can reduce five-year mortality by up to 26%.[3,5,8] These studies have led to the National Comprehensive Cancer Network's (NCCN) recommendations of adjuvant endocrine treatment for pre- and post-menopausal women with estrogen hormone receptor-positive (ER+) early stage breast cancer.[9]

Generally, adjuvant therapy for breast cancer is any treatment given after primary treatment to increase the opportunity for long-term survival. Adjuvant therapy for breast cancer can include chemotherapy, endocrine therapy, the targeted drug trastuzumab (Herceptin®), radiation therapy, or any combination of these treatments. This dissertation focuses on the oral agents for adjuvant endocrine therapy (AET) following initial treatment of breast cancer with chemotherapy or radiation. AET includes Tamoxifen and the hormonal therapeutic drugs exemestane, anastrozole, and letrozole. Tamoxifen deprives the breast cancer cells of the hormone estrogen which breast tumors need to grow while the aromatase inhibitors prevent the body from producing estrogen.

Tamoxifen and aromatase inhibitors have different side effects and long-term complications. Both classes of drugs contribute to hot flashes, night sweats, and vaginal dryness. In clinical trials, aromatase inhibitors are associated with musculoskeletal symptoms, osteoporosis, and increased rate of bone fracture while Tamoxifen is associated with an increased risk for uterine cancer and deep venous thrombosis.[9] Despite the potential harms, the reduction in breast cancer recurrence outweighs the risk of side-effects and the NCCN recommends that for women with early breast cancer who are postmenopausal at diagnosis, receive an aromatase inhibitor as initial adjuvant therapy for 5 years, Tamoxifen for 2 to 3 years followed by an aromatase inhibitor to complete 5 years of adjuvant endocrine therapy, or 5 years of aromatase inhibitor therapy depending on the tolerance of the drugs. The panel also recommends that postmenopausal women who have a contraindication to aromatase inhibitors use Tamoxifen alone for 5 years. Premenopausal women at diagnosis are not recommended aromatase inhibitors and should be given Tamoxifen for the first five years after which women who become postmenopausal at that time should consider extended therapy with an aromatase inhibitor for up to 5 years or 5 additional years of Tamoxifen.[9] In general, the drugs are typically prescribed every day for 5 years and may involve switching between medications due to complications and/or menopausal status.[1]

Despite the effectiveness of AET to improve survival and decrease cancer recurrence, adherence rates for recommended treatment remain low. It is estimated that between 55-75% of breast cancer patients possessed greater than 80% of the recommended adjuvant endocrine medication in a one-year period[10] while the results for adherence to Tamoxifen are mixed and range from 25% to 96% for women with early-stage breast cancer. The rates of adherence vary significantly by demographic characteristics[11,12] and are lower for non-white women[11] and may contribute to the

disparity in breast cancer mortality observed by racial/ethnic subgroups. The number of other medications prescribed for comorbidities[13] and the side-effects of initial cancer treatment[10,14-18] are predictive factors of low adherence to treatment. What is known about adherence to AET is predominately non-modifiable, and understanding how to improve adherence rates can inform effective interventions to improve breast cancer outcomes. Therefore, the goal of this dissertation was to identify target areas that are amenable for interventions in order to improve adherence rates to adjuvant endocrine therapy. The objective was threefold: 1) determine the association between combined out-of-pocket costs for AET medication and adherence; 2) examine how factors affect adherence to AET medication among women with very low adherence, moderately low adherence, and high adherence; and 3) understand, from the patient's perspective, how their physicians communicate with them about AET treatment.

1.1 Specific Aims

Study One: ***The association between out-of-pocket costs and adherence to adjuvant endocrine therapy among newly diagnosed breast cancer patients.***

The specific aim in Chapter 2 was to measure one-year adherence to AET among women diagnosed and surgically treated with breast cancer who initiate AET within the first year in a large commercially insured population and to determine, a priori, the association between combined out-of-pocket costs for AET medication and adherence. A thirty-day supply of an aromatase inhibitor is $590. Even among a privately insured population, copayments and out-of-pocket expenses for AET prescription drugs may vary from $0 to more than $90 per month. To save money, women may take less medication, refill fewer prescriptions, or discontinue treatment.

Study two: ***Adherence to Adjuvant Endocrine Therapy: A Quantile Regression Analysis.***

The specific aim in Chapter 3 was to understand how factors influence adherence among women across low and high levels of adherence. Studies using logistic regression or ordinary least squares regression draw conclusions about how factors influence adherence among high adherers (greater than 80% of medication filled) or at the cohort average adherence in the cohort. Quantile regression statistical methods provide a complete picture about the patterns of adherence among low adherers who often represent a smaller yet important proportion of study cohorts in the medication adherence literature.

Study three: ***Physician-patient communication influences women's use of adjuvant endocrine therapy among breast cancer survivors.***

The specific aim in Chapter 4 was to understand, from the patient's perspective, how their physicians communicate with them about AET treatment. One potentially influential interpersonal factor that can influence the use of AET is the physician-patient interaction. The role of the physician can both positively and negatively affect medication adherence. For example, whether an oncologist encourages patients about the benefits of adherence to AET, how clearly that message is communicated, whether the support the oncologist offers such as a well-defined AET treatment plan, the tracking and follow-up of refills, and the availability for managing any side effects of AET may all influence adherence.

1.2 Conceptual Framework

This dissertation utilizes components of the socio-ecological framework to examine the association between modifiable factors of the health care delivery system, women's perceptions of

AET, and adherence. The conceptual framework describes the relationship between characteristics of the health care delivery system, patient perceptions, and adherence to AET.

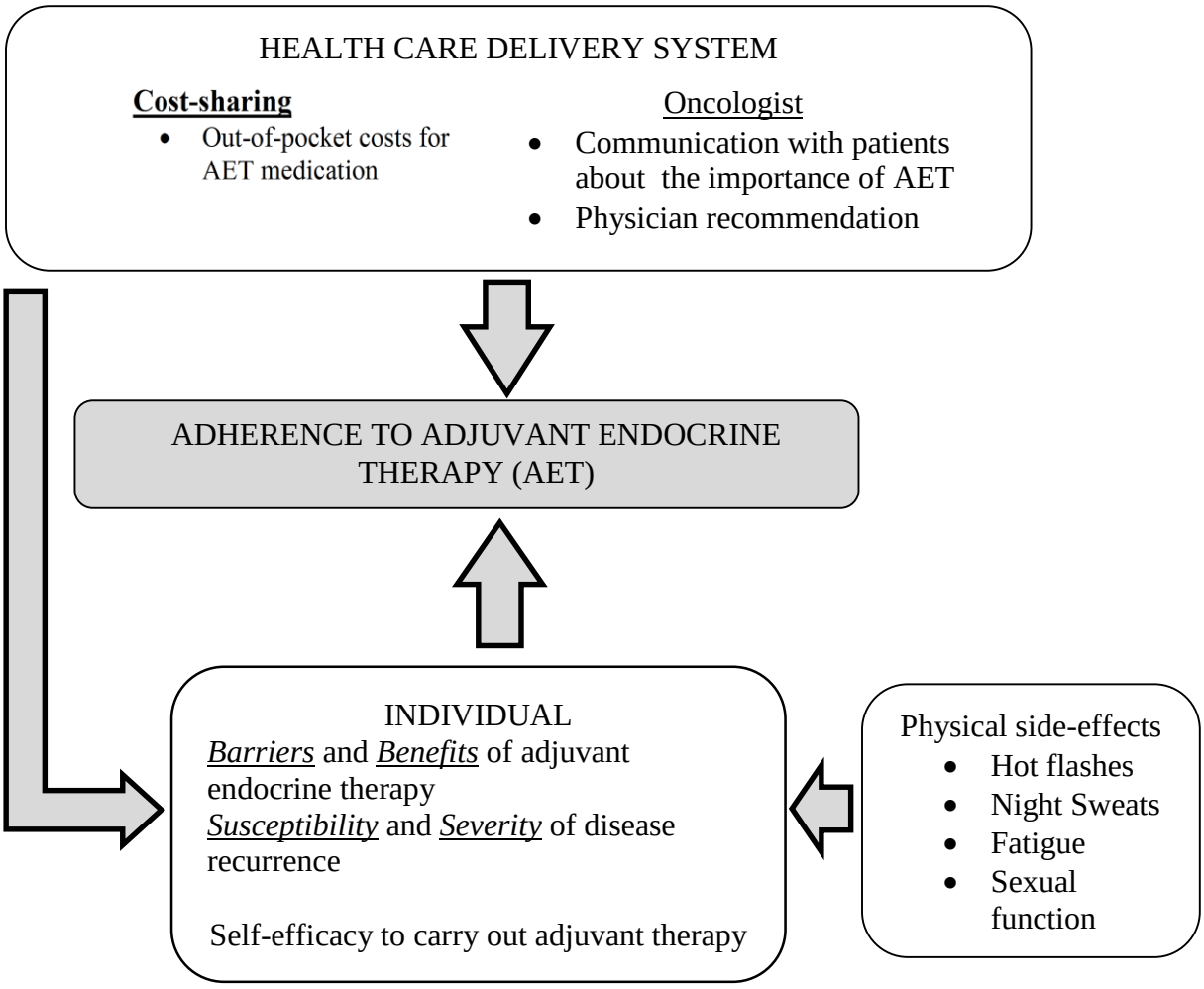

Figure 1-1 Conceptual framework that describes the factors associated with adherence to adjuvant endocrine therapy.

Health Care Delivery System

Out-of-pocket Costs. In the conceptual framework (Figure 1-1), out-of-pocket costs are hypothesized, generally, as a characteristic of the health care delivery system and have a direct association with adherence to AET.

With the roll out of the Patient Protection and Affordable Care Act (PPACA) more than 8 million people have signed up for health insurance and now have access to medical care through private or public insurance.[19] The private insurance products offered through the health insurance exchange market vary in the level of cost sharing. It has been established by the RAND Health Insurance Experiments (HIE) that higher cost sharing reduces the demand for care and the overutilization of some services such as emergency department visits for non-emergency related visits.[20] And while cost-sharing may not pose a barrier when care is urgent, it does have unintended consequences by decreasing prevention and prescription services.[20] The Affordable Care Act recognizes the importance of prevention and requires that all preventive services be offered by insurers free of charge to members. Despite comprehensive coverage and accessible preventive care, AET will still include out-of-pocket expenses and copayments for prescription drug coverage which may be a barrier towards filling and refilling prescription medication. Much like ambulatory care, the HIE also found that the cost-sharing response for prescriptions drugs was similar and led to a decrease in pharmacy utilization.[21-23] Goldman and colleagues estimated that price elasticity--for every 1% increase in cost sharing for prescription drugs--ranged from a 2% to 6% decline in prescription drug use or expenditures.[22] The focus of this dissertation was on the commercially and privately insured populations who incurred prescription drug costs. While the PPACA rollout occurred prior to the study period in question, important policy recommendations about modifications to copayments for prescription drugs are still a relevant topic.

The dollar amount of copayments for a 90-day supply of AET varies by insurance type and level of coverage and ranges from $0 to over $90.[24,25] Despite insurance status, out-of-pocket expenses for medical costs can lead to differences in rates of adherence for low-income women diagnosed

with breast cancer.[26] This finding is consistent with the fundamental causes theory proposed by Link and Phelan.[27] They posit that the uneven distribution of resources, money, and power can lead to differences in health outcomes because those from low socioeconomic status lack the resources to improve health. Increases in co-payments leads to a significant reduction in use of medications for chronic conditions.[28] In a retrospective US study in the US consisting of 30 employers and 52 health plans with varying levels of health plan benefit designs doubling co-payments was associated with between 25-44% reduction depending on the type of medications such as in the use of antidepressants, anti-diabetics, anti-hypertensive, or anti-asthmatics.[28]

In the conceptual model, the health care delivery system plays a vital role in influencing a patient's adherence to AET. Higher copayments for prescription drugs for AET are associated with a decrease in adherence.[10,24,25] Neugut et. al examined mail-in prescription drug orders for adjuvant hormonal therapy using a medical claims database from Medco Solutions and found that women with a copayment between $30-$89.99 for a 90-day prescription was associated with lower one-year adherence compared to women with a copayment of less than $30 (OR 0.69; 95% CI 0.62 to 0.75) especially among women that were older after controlling for the number of comorbidities, number of other prescriptions, geographical region, income, and race/ethnicity.[24] Sedjo and colleagues also looked at 1-year adherence to adjuvant hormonal therapy in the MarketScan database and found that a copayment of >$30 was associated with non-adherence compared to women with a copayment of <$10 in an unadjusted model.[25] This study, however, was an exploratory analysis whose aims were to examine any and all predictors of adherence to AHT. These studies both have methodological limitations in that they included all women who initiated adjuvant hormonal therapy and not women in the FDA recommended subgroup or focused on

mail-in prescription orders only. The studies did not control for all potential confounders such as the number of comorbid conditions, number of prescription drugs, and/or the amount of copayments for other prescription drugs. These potential confounders are important especially since 55% of Medicaid women in the North Carolina Central Cancer Registry (NCCR) diagnosed with breast cancer have a Charlson Comorbidity Index of 4 or greater on a scale of 0 to 15, and 72% have 10 or more unique medications in a one-year period.[13] More evidence is needed to determine the association between copayments for AET medication and adherence among women diagnosed with early breast cancer.

Role of oncologists. The conceptual model highlights important oncologist behaviors that have the potential to influence adherence rates. First, oncologists predominately influence adherence to AET because of their interactions with patients. Davidson and colleagues examined discussions between patients and oncologists and found that discussions about adjuvant endocrine therapy did not address potential difficulties of remaining adherent.[29] Discussions of adherence were usually monologues addressing the current state of study data and were not linked to the patient, the importance of adherence, or how the study data related to the patients' situation.[29] The study highlights the importance of physician communication about AET and how variations could arise in adherence.

Higher quality patient-physician relationships have been associated with higher reported adherence to treatment for HIV. Physician attributes such as general communication skills, overall patient satisfaction, trust in the physician, provision of HIV specific information, and satisfaction with physician approach to discussion about medication adherence were all associated with greater

adherence of treatment.[30] In a study of female diabetes patients, patient-provider communication was identified as the most significant factor impacting patient adherence.[31]

Individual level factors

Numerous studies have found that individual level factors related to adherence are important such as race/ethnicity, extreme ages (younger and older), type of initial treatment, side effects from initial treatment, and comorbid conditions.[10,13,24,25,32]

1.3 DATA SOURCE

1.3.1 *MarketScan® Commercial Claims and Encounters Database*

For Chapter 2 and 3, we used data from the MarketScan® Commercial Claims and Encounters Database for the period January 1, 2007 to December 31, 2011, yielding five years of complete data. The database represents a nationwide, employer-based, non-institutionalized, commercially insured population. The database contains claims and encounters from working individuals who are under the age of 65 and their dependents including spouses and children. Medical diagnosis, services, and pharmacy utilization are based on the International Classification of Diseases, Ninth Revisions, Clinical Modification Codes (ICD-9-CM codes), Current Procedural Terminology (CPT) codes (4th Edition), and generic product identifier (GPI) codes.

The database has a total of 150 million unique and commercially insured persons covered by employee sponsored insurance. The database captures person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, and prescription drug services from a selection of large employers, health plans, and government and public organizations. MarketScan links paid claims and encounter data to detailed patient information across sites and types of

providers, and over time. The dataset represents approximately 58.3% of the insured US population.

For each year, 2007-2011, the claims and encounter database is divided into 8 tables: Inpatient admissions table, facility header table, inpatient services table, outpatient services table, aggregated populations table, outpatient pharmaceutical claims table, annual enrollment summary table and enrollment detail table.

1.3.2 *Qualitative In-Depth Interviews*

For Chapter 4, we developed an in-depth interview guide using a theory-driven approach to explore factors related to a provider and patient undergoing breast cancer treatment. Theory suggests that physician-patient communication functions such as information exchange, responding to emotions, making decisions, and enabling self-management can have direct and indirect effects on health outcomes.[33] Information exchange refers to communication about aspects of care and can influence the use of AET if the physician successfully communicates information about the risks of treatment and clinical evidence on the effectiveness in a way that is understood by patients.[33,34] When medical decisions are a shared responsibility of the patient and physician, they come to an agreement based on the available clinical evidence and what is feasible to implement.[35] Physicians can also encourage patients to manage important aspects of their illness such as seeking appropriate care, coping with treatment effects, and finding health related information.[36,37] Finally, physicians that can help patients manage emotions and uncertainty about their illness can reduce distress and help the patient to cope with the disease, build self-confidence, and a sense of worth.[38] In this context, I interviewed breast cancer survivors to explore how physician-patient communication functions influence continued use of AET.

A qualitative design was the best analytical method to determine the attitudes, knowledge, and behaviors related to AET, especially since little is known from prior research. Results from qualitative research were best suited to meet the aim of Chapter 4 because the questions focus on experiences, actions, and behaviors; opinions and values; on feelings or emotional responses; and on what breast cancer survivors knew or believed to be true in certain situations.[39] A qualitative study in Chapter 4 allowed us to provide a deeper meaning of the factors related to AET.

We used a semi-structured interview guide to collect data. In-depth interviews allowed us to delve more deeply into the experiences of breast cancer survivors undergoing AET by exploring the variables and concepts indicated in the conceptual framework (Figure 1-1). In-depth interviews are best suited to learn about individual experiences and perspectives on a given set of issues such as with adherence to AET.[40] In-depth interviews are widely used in health care to create richer meanings on a particular topic with interviewees by soliciting experiences in a one-on-one manner.[40]

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Chapter 2. THE ASSOCIATION BETWEEN OUT-OF-POCKET COSTS AND ADHERENCE TO ADJUVANT ENDOCRINE THERAPY AMONG NEWLY DIAGNOSED BREAST CANCER PATIENTS.

Albert J. Farias[1], Ryan N. Hansen[2], Steven B. Zeliadt[1,3], India Ornelas[1], Christopher Li[4,5], Beti Thompson[1,5]

[1] Department of Health Services, University of Washington, Seattle, WA USA

[2] Department of Pharmacy, University of Washington, Seattle, WA USA

[3] Health Services Research and Development Center of Excellence, Department of Veterans Affairs Puget Sound Health Care System, Seattle, WA USA

[4] Department of Epidemiology, University of Washington, Seattle, WA USA

[5] Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA USA

2.1 ABSTRACT

Purpose: To determine how combined out-of-pocket costs for adjuvant endocrine therapy (AET) medication including copays, coinsurance, and deductibles affects adherence among women newly diagnosed with breast cancer with private health insurance who initiate therapy.

Methods: We examined medical and pharmacy claims for the 1-year period after initiating AET using the Truven Health Analytics MarketScan® database. Adherence was defined as ≥80% proportion of days covered (PDC). Mean out-of-pocket costs for AET fill were measured as the sum of copayments, coinsurance, and deductibles and adjusted to 30-day amounts. Using a multivariable logistic regression model we calculated adjusted risk ratios controlling for age,

comorbidities, type of surgery, use of chemotherapy and/or radiation therapy, average out-of-pocket costs for other services, and pharmacy use characteristics.

Results: Of the 6,863 women younger than 65 years who were diagnosed with breast cancer and initiated AET, 73.9% were adherent (PDC≥80%). A total of 19% of patients had less than $5 monthly out-of-pocket costs for AET, 30% had $5-$9.99, 17% had $10-14.99, 10% had $15-19.99, and 25% had $20 or greater. Patients with out-of-pocket costs for AET between $10-14.99, $15-$19.99, and greater than $20 were 6-8% less likely to be adherent compared to patients paying less than $5.00, after controlling for covariates ($p<0.05$). Out-of-pocket costs for inpatient, outpatient, and other pharmacy services were not associated with adherence.

Conclusion: A substantial proportion of privately insured patients are non-adherent to AET and out-of-pocket costs for AET medication are significantly associated with a greater likelihood of non-adherence.

Key words: Adherence, Adjuvant Endocrine Therapy, Breast Cancer, out-of-pocket costs

2.2 INTRODUCTION

Estrogen receptor-positive (ER+) breast cancer is present in two-thirds of breast cancer cases in the US.[1,2] In addition to a combination of surgery, chemotherapy and/or radiation, the standard of care for ER+ breast cancer for post-menopausal women is endocrine therapy with third generation aromatase inhibitors (AI) such as exemestane, anastrozole, or letrozole for at least 5 years, although up to 10 years may be effective.[3-6] Similarly, the National Comprehensive Cancer Network (NCCN) recommends that pre-menopausal women receive treatment with tamoxifen for up to 5 years or until menopause at which time women may switch to the AIs.[6]

The use of adjuvant endocrine therapy (AET: aromatase inhibitors and/or tamoxifen) to reduce the risk of subsequent breast cancer and the rate of mortality versus non-users has been shown to be effective in both clinical trials and in diverse cohorts of women in pragmatic trials.[4,7-10] Compared with non-users, the reduction in subsequent breast cancer risk ranges from 40% to 66% across the AET groups depending on the degree of adherence.[9] Treatment with tamoxifen for 5 years has been shown to reduce the rate of recurrence by 39% throughout the first decade, and reduces breast cancer mortality by about one-third throughout the first 15 years.[10] However, women with a prescription benefit plan who discontinued AET early, were non-adherent, had a significantly higher mortality rate compared with those who finished the full course of therapy.[11] Thus, this suggests that improvements in adherence rates to AET can reduce the morbidity and mortality of women with ER+ breast cancer.

Despite the improvement in disease prognosis among patients treated with AET, approximately 21-50% of patients are non-adherent within 4-5 years.[12] In a retrospective longitudinal study, only

72-81% of patients were adherent (MPR≥80%) to anastrozole after 1 year with the mean percentage of adherent patients decreasing over a 3-year period.[13]

While studies have examined the association between co-payments and adherence to AET, they do not include out-of-pocket costs such as the coinsurance or deductibles paid by the patient at the time of a prescription fill for AET, do not control for other out-of-pocket costs, and/or they examine women anytime during AET treatment rather than during the first year following breast cancer diagnosis and treatment.[14-17] Therefore, we sought to measure 1-year adherence to AET among women diagnosed and surgically treated with breast cancer who initiate AET within the first year in a large commercially insured population and to determine, *a priori*, the association between combined out-of-pocket costs for AET medication and adherence.

2.3 METHODS

2.3.1 *Data Source*

We conducted a retrospective cohort study using longitudinal inpatient, outpatient, and prescription claims data from a nation-wide, employer-based, commercially insured population in the United States. We used the Truven Health Analytics MarketScan® Commercial Claims and Encounters Databases from January 1, 2007 to December 31, 2011. The MarketScan® databases capture person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, and prescription drug services. All data were de-identified in accordance with the Health Insurance Portability and Accountability Act requirements.

2.3.2 *Sample Selection*

We identified women under the age of sixty-four with at least one prescription claim for an AI, or tamoxifen between January 1, 2008 and December 31, 2010 (Figure 2-1). Initiation of AET was defined as no AET prescription claims for at least six months before the first claim (index claim). Next, women were included in the cohort if they were diagnosed and surgically treated for breast cancer within twelve months prior to the index claim. Breast cancer diagnosis was defined as a diagnostic International Classification of Diseases, Ninth Revisions, Clinical Modification code (ICD-9-CM) for ductal in situ carcinoma (ICD-9-CM: 233.0), primary invasive breast cancer (ICD-9-CM: 174.0 to 174.9) or primary invasive breast cancer with axillary lymph node involvement (ICD-9-CM: 196.0-196.3, 196.5-196.6, or 196.8-196.9) in inpatient records. Surgical treatment was defined as an ICD-9-CM code or Current Procedural Terminology (CPT) code (4th Edition) for bilateral mastectomy, mastectomy, or breast conserving surgery/lumpectomy.[18-20] We restricted our sample to women continuously enrolled in a health plan that included prescription drug coverage for at least six months prior to and 12 months after the index claim. We excluded women with multiple primary cancers or metastatic breast cancer to distant organs any time prior to initiation and during the study period.

Outcome. The primary outcome was medication adherence to AET calculated using the proportion of days covered (PDC).[21] We assumed women did not take more than one AET medication at a time.[22] PDC was calculated based on the fill dates and the number of days' supply for each prescription. The numerator was the total number of days covered by the prescription fill during the 12-month study period. We created coverage periods to reflect the dates that were encompassed by each prescription fill. We shifted the start date of each period so that women did not have overlapping days of coverage. We assumed that women did not take the refilled medication before

exhausting the previous prescription.[23] The denominator was 365, the number of days between the index claim and the end of the follow-up study period (12 months after the index claim). The ratio was multiplied by 100 to obtain the percentage of the proportion of days covered. We categorized patients as being adherent if the PDC was 80% or greater.[24]

Time to discontinuation. We examined the time to AET discontinuation among patients considered non-adherent (PDC<80%). We assumed that a woman discontinued AET if she went at least four consecutive months (>120 days) without medication.[13] A woman was considered to discontinued treatment the month in which she filled her last prescription; therefore we could only measure up to eight months.

Out-of-pocket costs for AET. The main exposure of interest was the mean out-of-pocket costs for a 30-day supply of AET medication. Out-of-pocket costs were defined as the sum of the co-payments, deductibles, and coinsurance paid by the subject at the time that the prescription was filled. Out-of-pocket cost amounts for 60- or 90-day prescriptions were adjusted to 30-day amounts. Out-of-pocket costs for AET were categorized into quintiles of less than $4.99, $5.00 to $9.99, $10.00 to $14.99, $15.00-19.99, and more than $20.00 so that each category represented an equivalent dollar amount and an approximately equal distribution of patients.

Other out-of-pocket costs. Other out-of-pocket costs paid by the patient at the time services were rendered were calculated for inpatient and outpatient services, and pharmacy medications (excluding AET medication). Other out-of-pocket costs were calculated for each refill period and adjusted to reflect an average 30-day out-of-pocket costs from the index date until the patient no longer had AET medication on-hand, up to 365 days. Other out-of-pocket costs for 30-days were categorized into quintiles of less than $49.99, $50-99.99, $100-149.99, $150-199.99, and greater

than $200 so that each category represented an equivalent dollar amount with an approximately even distribution of patients.

Co-morbidities. We used the Elixhauser index to control for comorbidities using inpatient and outpatient diagnoses (IDC-9-CM codes) during the time period prior to the index date. The Elixhauser comorbidity set contains 30 chronic conditions.[25] Subjects were assigned a value based on the number of comorbidities.

Additional Subject Characteristics. Subject characteristics were limited to those variables that were available in the MarketScan® Database. Age in years and a variable to indicate whether subjects used mail or retail pharmacy was calculated based at the index date. Age was evaluated categorically (less than 40, 40-49, 50-59, and 60-64 years of age). We created breast cancer treatment variables for surgery (bilateral mastectomy, mastectomy, or lumpectomy), and the receipt of chemotherapy and/or radiation using ICD-9-CM and CPT codes from inpatient and outpatient claims up to twelve months prior to their first AET prescription fill. We assessed whether women had an oophorectomy prior to initiating AET as identified using inpatient ICD-9-CM and CPT codes.[18-20] We included a categorical variable for the duration of time from surgical treatment to the index date (0-3, 4-6, 7-9, and 10-12 months). Pill burden was calculated as the count of unique drug classes filled 90 days prior to the index date. We included a categorical variable for geographic region (Northeast, North Central, South, and West), and health plan type (health maintenance organization, preferred provider organization, other). We calculated the number of times a patient switched AET during the study period. Women switched medication if they filled a prescription for any other AI or tamoxifen different than the index drug and were categorized as not switched, switched once, or switched 2 or more times.

2.3.3 *Statistical Analysis*

Unadjusted differences in the percentage of non-adherent (PDC<80%) and adherent (PDC≥80%) women were evaluated using the Pearson X^2 test for categorical variables.

We used a multivariate logistic regression model with robust standard error estimates to calculate the odds of being adherent to AET versus being non-adherent in a one-year period. All previously described variables were included in the model and were considered to be clinically significant and potential confounders based on prior studies.[14-17,26] We used the direct substitution method to determine the adjusted risk ratio (ARR) and adjusted risk difference (ARD) since adherence was not considered to be a rare event thus avoiding inappropriately reporting odds ratios, which cannot be properly interpreted as the risk of an event in this setting.[27] The ARR is the ratio of the mean predicted probabilities and is a measure for the probability of adherence for each category of co-payment after controlling for potential confounders. The ARD is the difference of the mean predicted probabilities and represents differences in the absolute risk of adherence. All analyses were conducted using Stata 13.1 SE (StatCorp™ College Station, TX).

2.4 RESULTS

During the 3-year study period, 6,863 women were identified in the MarketScan databases who were between the ages of 18-63 years and initiated AET following a diagnosis and surgical treatment of early breast cancer. Among this cohort, 26.1% of patients were non-adherent because they had fewer than 80% of AET medication days covered (PDC<80%) during the first year of therapy.

Table 2-1 lists characteristics of the study cohort by the proportion of subjects who were adherent to AET medication (PDC≥80%). In the cohort, 59% of the patients were between 50-64 years of age. The majority had early breast cancer without lymph node involvement (68%), were enrolled in a PPO health plan (60%), filled prescriptions using a retail pharmacy (84%), received chemotherapy treatment (57%), did not have a pre-existing diagnosis of a major condition (62%), and did not switch AET during the 12 month follow-up period (84%). Half of the patients initially filled a prescription for tamoxifen (51%). The mean out-of-pocket costs for a 30 days' supply of AET medication was $17.10 (SD 22.4) while the mean 30-day out-of-pocket costs for other prescriptions and inpatient and outpatient services was $176.50 (SD: 172.20).

In the unadjusted analysis, adherence to AET was associated with age, treatment with chemotherapy, geographical region, AET drug type, the number of times a patient switched AET medication, the number of prescription drugs filled 90-days prior to index date, and the pharmacy type that the patient used. A greater proportion of patients were less likely to be adherent to AET with increasing out-of-pocket costs for AET medication ($p<0.05$).

2.4.1 *Out-of-Pocket Costs for AET Medication*

The adjusted analysis presented in Table 2-2 are the ARR and ARD of adherence to AET for each of the covariates. On average, copayments accounted for approximately 89% of the total out-of-pocket costs for a 30-days' supply of AET medication, while deductibles and coinsurance accounted for 6% and 5%, respectively. We found that 30-day out-of-pocket cost for AET medication was significantly associated with the adjusted risk of adherence ($p<0.001$, Table 2-2). On average, patients with a mean monthly out-of-pocket cost for AET medication between $10-

$14.99 were 7% less likely to be adherent to AET compared to patients with an out-of-pocket cost of less than $4.99, after controlling for covariates (95% CI, 0.88 to 0.98). This association was similar for each increased category of out-of-pocket costs for AET medication. Patients with a $15.00-$19.99 30-day out-of-pocket cost for AET were, on average, adherent six percentage points less often than patients with an out-of-pocket cost of less than $4.99, controlling for all other covariates (ARD: -0.06; 95% CI, -0.06 to -0.02). Patients with a $20 or greater 30-day out-of-pocket costs for their AET medication were 6% less likely to be adherent compared to patients with an out-of-pocket cost of less than $4.99, after controlling for covariates (95% CI, 0.8 to 0.99).

Copayments, deductibles, and coinsurance accounted for 46.3%, 18.6%, and 35.2%% of 30-day out-of-pocket costs for other prescription medication, and inpatient and outpatient services (data not shown). Other out-of-pocket costs were not associated with adherence to AET medication.

2.4.2 *Other Patient Characteristics*

Older women were more likely to be adherent to AET compared to younger women (60-64 versus 18-39 ARR: 1.17, 95% CI: 1.11-1.22). Women in the geographical south of the US and the West were significantly less likely to be adherent to AET compared to women in the Northeast (South ARR: 0.89, 95% CI 0.85 to 0.93; West ARR: 0.94, 95% CI: 0.89 to 0.99). Women who used a mail pharmacy compared to a retail pharmacy for their first AET prescription fill were more likely to be adherent to AET (ARR: 1.15, 95% CI: 1.11 to 1.19). Patients were less likely to be adherent to AET for every increase in pre-existing condition that a woman had (ARR: 0.98, 95% CI: 0.96 to 0.99) and for every time she switched AET medication (2 or more times versus no switching ARR: 0.83, 95% CI: 0.73 to 0.95). Women with more time between surgical treatment and index

claim were less likely to be adherent to AET (10-12 months versus 0-3 months ARR: 0.91, 95% CI: 0.84 to 0.98).

2.4.3 *Time to Discontinuation*

We examined the time to discontinuation of AET medication among women who were considered non-adherent (PDC<80) (n=1,790). The mean PDC among non-adherent patients (PDC<80) was 50%. Figure 2-2 depicts the percentage of patients, by month, who went greater than 120 consecutive days without medication, considered to have discontinued AET medication during the first year. The mean number of days between prescription fills among non-adherent patients that were persistent was 45 days (SD 29.4; median 35 days). Among non-adherent patients, 19.1% discontinued after the first month of AET prescription fill. After 8 months, 46.7% of non-adherent patients discontinued therapy. Of the non-adherent women (PDC<80%), 53.3% were not considered to have discontinued therapy but had intermittent prescription refills throughout the 12-month study period, although not enough to have greater than 80% of medication on-hand. Patients who discontinued therapy during the study period had a mean 30-day out-of-pocket costs for AET of $19.47, compared to $18.04 for women who were non-adherent but who had not discontinued therapy.

2.5 DISCUSSION

In this study, we found that 73.9% of women who initiated AET after a diagnosis of early breast cancer had filled prescriptions to have pills for at least 292 days (80%) over the first year. We observed that women with higher out-of-pocket costs for AET medication fills was significantly

associated with a 6-8% lower likelihood adherence to AET among a privately insured cohort of women with a prescription drug plan. The fact that low adherence is influenced by out-of-pocket costs for AET medication is important because low adherence to AET is associated with 10-49% higher breast cancer-specific mortality compared to women who are adherent.[11,28]

The finding on the association between higher out-of-pocket costs for AET and lower risk of adherence is similar to other retrospective cohort studies that have found, on average, co-payments decrease the odds of adherence to AI's or tamoxifen.[13,14,16,17] These studies, however, examined the effect of co-payments and not total out-of-pocket costs. In our study, we found that 5-6% of the total out-of-pocket costs were from coinsurance and deductibles at the time of AET prescription fill.

In our study we did not find that out-of-pocket costs for other prescription pharmacy, and inpatient or outpatient services was associated with adherence. Sedjo and colleagues found that other out-of-pocket costs were associated with adherence to AET, however, out-of-pocket costs were included as the sum for the entire 12-month follow-up period even if women had discontinued filling prescriptions for AET, likely over-inflating the association with adherence to AET medication.[17] In our study we calculated other out-of-pocket costs as a 30-day average limited to the time that women had filled prescriptions for AET medication. This is important since over one-quarter of the cohort were non-adherent.

Our findings on adherence rates are consistent with reports using similar claims-based methodology among insured women which found 12-month adherence to AET were ranged

between 72-81% (MPR≥80%).[13,15-17] We found that discontinuation among non-adherers (PDC<80%) was greatest after the first month of initiation (19%) and then decreases to 4%-7% per month, thereafter. This trend is similar to a study by Partridge and colleagues who found that the greatest percent of women who went greater than 120 days without medication was after the first month, although continued to increase thereafter.[13] Additionally, we found that among non-adherers (PDC<80%), over half of the patients (53.3%) had intermittently filled prescriptions throughout the 12-month follow-up but did not go more than 120 days without medication on-hand. Thus, pharmacists and oncologists could encourage women to regularly fill prescriptions, particularly after the first month of AET initiation in order to increase subsequent refills.

Similar to other research studies, we found that, on average, older women, women who used mail order versus retail pharmacies, and women with fewer comorbidities was associated with a higher probability of adherence.[13,15-17] Studies have also found that patients who experience side effects from AET are more likely to be non-adherent.[7,8,12,29] In our study, there was a 15% decreased probability of adherence among women who switched AET medication once compared to those that did not switch ($p<0.001$). In a chart review study, approximately 84% of breast cancer survivors who took anastrozole switched to another AI due to side effects.[30] Thus, medication switching may partially be correlated with medication side effects. We attempted to control for side effects from initial breast cancer treatment by including the time from surgery to initiation and found that the more time that elapsed, the more the probability of adherence decreased. This is an important finding because women who allow more time to elapse may have greater side-effects from initial treatment and leads them to delay initiating AET medication.

Our study had limitations. The measure of adherence using pharmacy claims is how much medication a woman has procured over a 12-month period, but may not reflect actual medication consumption and does not reflect issues such as lost medications. Clinical and prognostic factors such as date of diagnosis, stage of disease, and ER+ status are not readily available from claims and billing data, therefore we had to develop procedural and diagnostic algorithms for these measures which may have misclassified patients. We do not know from claims if each woman in our sample had an appropriate indication for AET treatment. We assumed that if a woman filled a prescription for AET following treatment for a newly diagnosed non-metastatic breast cancer, she met NCCN treatment recommendations for AET and is likely to have ER+ breast cancer. It is possible that the index date we identified may not have been their first AET fill, although we restricted our sample to women with no evidence of recurrent breast cancer and no evidence of prior AET use. Several potential predictors such as socioeconomic factors and race/ethnicity were not available. Out-of-pocket costs for AET may be a surrogate for SES factors, however, we did not find a significant difference between other out-of-pocket costs and adherence to AET as we did with out-of-pocket costs specific to AET medication therefore limiting the plausibility of this assumption. Furthermore, a study by Hershman and colleagues did not find a significant association between socioeconomic status, race/ethnicity, and adherence to AET in a group of commercially insured patients.[15] Unmeasured factor(s) such as side effects from initial treatment and AET medication may also be a contributing factor to the findings, however our inclusion of a variable to measure time from surgery to first prescription refill and medication switching may limit the impact of treatment side effects on adherence. Finally, all of the women in the study were commercially insured in a plan that offered prescription coverage and are likely healthier and younger than the general population of breast cancer patients.

Our findings have important implications. High out-of-pocket cost for AET medication are significantly associated with non-adherence and may put patients at an increased risk of cancer recurrence and increased morbidity if they cannot access medication.[4,5,9,11] Further research should focus on interventions to lower out-of-pocket costs for AET medication by exploring the role that pharmacists can play by identifying patients that belong to plans that have high cost sharing and make recommendations to select generic versus brand name drugs that are in alternate drug plan tiers.[14] Even among commercially insured patients with a prescription drug plan in the United States, adherence to AET is suboptimal. Efforts to lower the out-of-pocket costs for AET medication could significantly improve adherence.

Table 2-1. Baseline characteristics of women newly diagnosed with early breast cancer who initiate adjuvant endocrine Therapy (n=6,863)

	Total cohort		Adherent rate (PDC ≥ 80%) by category	
	%	n	%	p-value[±]
Overall cohort	100	6863	73.8	
Breast Cancer				<0.01
DCIS	1.9	127	69.3	
Early Stage	68.2	4683	73.0	
Axillary lymph node involvement	29.9	2053	76.3	
Age, years				<0.001
18-39	8.0	552	64.3	
40-49	33.4	2292	71.4	
50-59	41.3	2834	75.7	
60-64	17.3	1185	79.0	
Comorbidities[≠]				
Hypertension	18.1	1240	74.0	0.92
Chronic pulmonary disease	5.6	386	72.8	0.61
Diabetes, uncomplicated	4.8	330	69.7	0.07
Hypothyroidism	6.6	455	75.8	0.34
Obesity	5.1	350	75.4	0.51
Fluid and electrolyte disorders	2.6	180	68.3	0.08
Deficiency anemias	3.7	254	68.9	0.06
Depression	4.4	303	69.3	0.06
Elixhauser Conditions Composite				0.31
0	61.5	4219	74.4	
1	25.4	1744	73.9	
2	8.3	568	73.6	
3	3.0	207	69.6	
≥4	1.8	125	68.0	
Surgery				0.65
Mastectomy	28.6	1963	74.6	
Bilateral mastectomy	4.6	318	74.8	
Breast Conservative Surgery/ Lumpectomy	66.8	4582	73.6	
Time from surgical treatment to first AET fill, months				0.12
0-3	39.2	2689	74.3	
4-6	30.7	2105	74.9	
7-9	23.1	1588	73.2	
10-12	7.0	481	69.9	
Chemotherapy	57.1	3920	75.1	0.01
Radiation Therapy	33.6	2303	74.4	0.50
Oophorectomy	2.2	152	72.4	0.67

Health Plan Type				0.12
HMO	18.2	1246	71.6	
PPO	60.1	4125	74.5	
Other	21.7	1492	74.3	
Initiation year of AET				0.04
2008	31.6	2165	72.8	
2009	34.7	2383	73.1	
2010	33.7	2315	75.8	
Region				<0.001
Northeast	16.8	1153	78.8	
North Central	21.0	1440	76.5	
South	40.8	2801	70.1	
West	20.6	1411	75.1	
Unknown	0.9	58	69.0	
AET drug type at index date, % (n)				<0.001
Exemestane	1.9	128	73.4	
Anastrozole	30.0	2057	78.0	
Letrozole	17.0	1166	72.6	
Tamoxifen	51.2	3512	72.0	
Number of times AET medication switched				<0.001
0	83.9	5758	75.9	
1	14.1	966	63.6	
2 or more	2.0	139	65.5	
Pharmacy type at baseline				<0.001
Retail	84.3	5783	72.3	
Mail order	13.5	923	85.5	
Unknown	2.3	157	66.2	
Number of prescriptions filled 90-days prior to the index date				<0.001
0	5.0	340	62.7	
1-5	56.8	3900	74.7	
6-10	31.6	2166	73.8	
Greater than 10	6.7	457	76.4	
Out-of-pocket costs for 30 days' supply of AET medication, $				<0.001
0-4.99	19.0	1306	75.7	
5.00-9.99	29.6	2029	76.4	
10.00-14.99	16.8	1154	70.3	
15.00-19.99	10.1	694	71.6	
20.00 or greater	24.5	1680	73.0	
Other out-of-pocket costs, 30 day average, $[¥]				0.60
0-49.99	18.9	1300	73.9	
50-99.99	21.0	1442	75.2	
100-149.99	15.0	1032	73.5	
150-199.99	13.3	910	74.7	
200 or greater	31.8	2179	73.0	

[≠]Comorbidities presented were the most prevalent of the 30 Elixhauser conditions among members in the cohort. The Elixhauser comorbidities excludes metastatic cancer and solid tumors without metastasis since these were included as part of the exclusion criteria for cohort entry.

[±]p-values correspond to the Pearson's Chi square for unadjusted analysis to test for differences between adherent and non-adherent proportions for each categorical variable.

[¥]Other out-of-pocket costs include services for outpatient, inpatient, and medications (other than AET) during the follow-up period for which patients had AET medication on-hand.

Table 2-2. Adjusted risk ratio (AAR) and adjusted risk difference (ARD) of adherence to AET medication among women with breast cancer (n=6,863)

Characteristics	**ARR**	**95% CI**			**ARD**	**95% CI**		
Out-of-pocket costs for 30 days' supply of AET medication, $								
0-4.99	1.00							
5.00-9.99	1.01	0.97	to	1.05	0.01	-0.03	to	0.04
10.00-14.99	0.93	0.88	to	0.98	-0.05	-0.09	to	-0.01
15.00-19.99	0.92	0.85	to	0.98	-0.06	-0.11	to	-0.02
20.00 or greater	0.94	0.89	to	0.99	-0.04	-0.08	to	0.00
Other out-of-pocket costs, 30 day average, $¥								
0-49.99	1.00							
50-99.99	1.01	0.97	to	1.06	0.02	-0.02	to	0.04
100-149.99	0.98	0.93	to	1.04	-0.01	-0.05	to	0.03
150-199.99	1.01	0.96	to	1.06	0.00	-0.03	to	0.04
200 or greater	0.99	0.95	to	1.04	0.00	-0.04	to	0.03
Breast Cancer								
DCIS	1.00							
Early Stage	1.04	0.94	to	1.16	0.04	-0.05	to	0.11
Axillary lymph node involvement	1.09	0.99	to	1.19	0.06	-0.01	to	0.13
Age, years								
18-39	1.00							
40-49	1.08	1.03	to	1.13	0.06	0.03	to	0.09
50-59	1.15	1.09	to	1.21	0.10	0.07	to	0.14
60-64	1.17	1.11	to	1.22	0.12	0.08	to	0.16
Health Plan Type								
HMO	1.00							
PPO	1.01	0.97	to	1.05	0.01	-0.02	to	0.04
Other	0.99	0.95	to	1.04	0.01	-0.04	to	0.03
Initiation year of AET								
2008	1.00							
2009	1.00	0.96	to	1.03	0.00	-0.03	to	0.02
2010	1.03	0.99	to	1.06	0.02	-0.01	to	0.05
Region								
Northeast	1.00							
North Central	0.96	0.91	to	1.01	-0.03	-0.07	to	0.01
South	0.89	0.85	to	0.93	-0.08	-0.12	to	-0.05
West	0.94	0.89	to	0.99	-0.04	-0.08	to	-0.01
Unknown	0.90	0.75	to	1.07	-0.08	-0.20	to	0.04
AET drug type at index date, % (n)								
Exemestane	1.00							

Anastrozole	1.03	0.93	to	1.13	0.02	-0.05	to	0.09
Letrozole	0.98	0.88	to	1.09	-0.02	-0.10	to	0.06
Tamoxifen	0.97	0.88	to	1.08	-0.02	-0.10	to	0.06
Pharmacy type at baseline								
Retail	1.00							
Mail order	1.15	1.11	to	1.19	0.11	0.08	to	0.14
Unknown	0.94	0.84	to	1.04	-0.05	-0.12	to	0.03
Number of times AET medication switched								
0	1.00							
1	0.84	0.80	to	0.89	-0.12	-0.15	to	-0.09
2 or more	0.83	0.73	to	0.95	-0.12	-0.21	to	-0.04
Surgery								
Mastectomy	1.00							
Bilateral mastectomy	1.01	0.95	to	1.08	0.01	-0.04	to	0.06
Breast Conservative Surgery/Lumpectomy	0.99	0.96	to	1.02	-0.01	-0.03	to	0.02
Time from surgical treatment to first AET fill, months								
0-3	1.00							
4-6	0.97	0.93	to	1.01	-0.03	-0.05	to	0.00
7-9	0.94	0.89	to	0.99	-0.05	-0.08	to	-0.01
10-12	0.91	0.84	to	0.98	-0.07	-0.12	to	-0.02
Chemotherapy (yes versus no)	1.08	1.04	to	1.12	0.06	0.03	to	0.09
Radiation Therapy (yes versus no)	0.99	0.96	to	1.03	-0.01	-0.03	to	0.02
Oophorectomy (yes versus no)	1.02	0.94	to	1.12	0.02	-0.05	to	0.08
Number of prescriptions filled 90-day prior to follow-up period (continuous)	1.01	1.00	to	1.01	0.00	0.00	to	0.01
Elixhauser Conditions Composite (continuous)	0.98	0.96	to	0.99	-0.02	-0.03	to	-0.01

*Indicates the p-value for a test of trend using the continuous variable for mean 30-day out of pocket costs for AET medication, F-test statistic with all dummy variables

¥Other out-of-pocket costs include services for outpatient, inpatient, and medications (other than AET) during the follow-up period for which patients had AET medication on-hand.

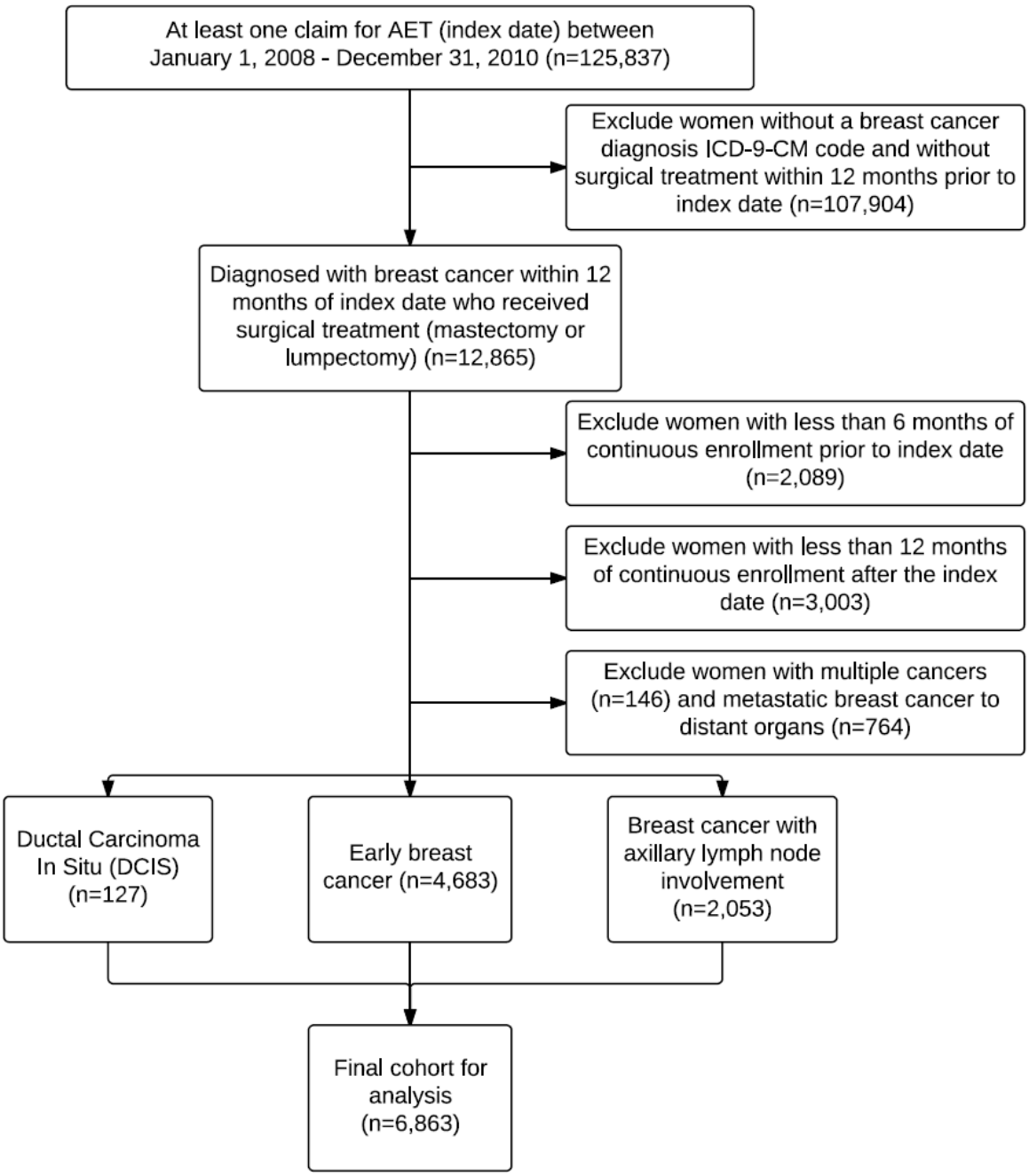

Figure 2-1. Study cohort selection and subject exclusion

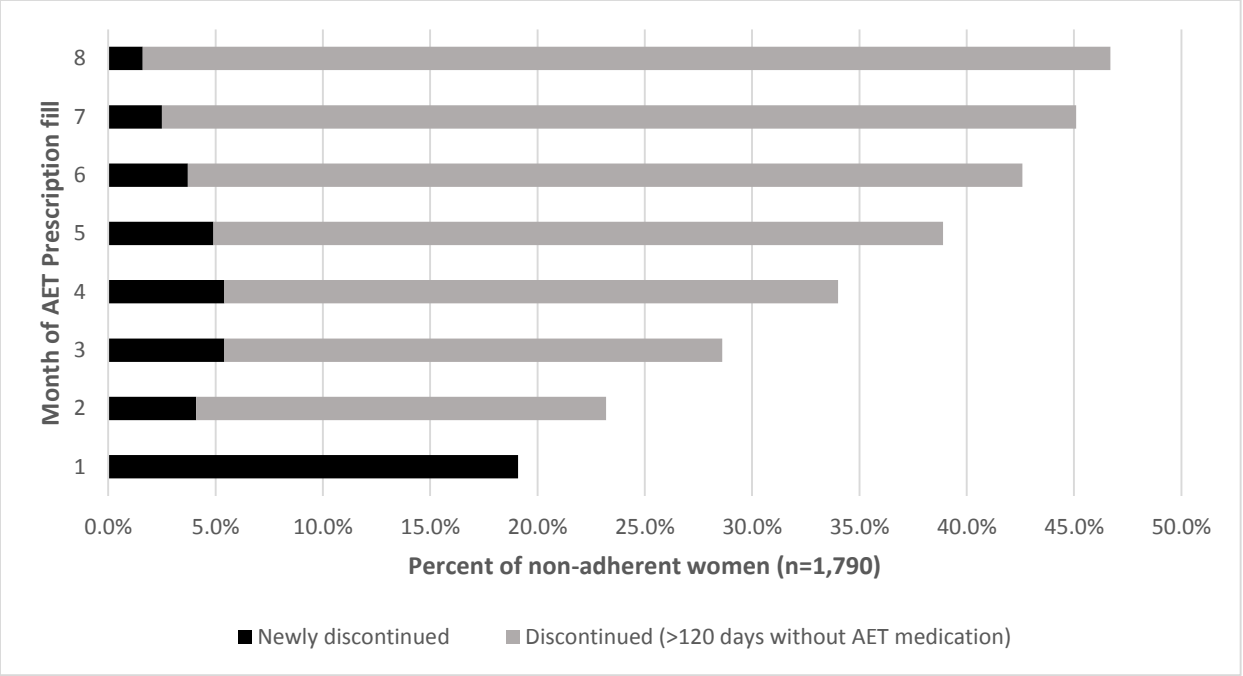

Figure 2-2. Proportion of non-adherent patients who discontinued adjuvant endocrine therapy, (n=1,790)

2.6 REFERENCES

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Chapter 3. ADHERENCE TO ADJUVANT ENDOCRINE THERAPY: A QUANTILE REGRESSION ANALYSIS.

Albert J Farias[1], Ryan N Hansen[2], Steve Zeliadt[1,3], Christopher Li[4,5], India Ornelas[1], Beti Thompson[1,5]

[1] Department of Health Services, University of Washington, Seattle, WA USA

[2] Department of Pharmacy, University of Washington, Seattle, WA USA

[3] Health Services Research and Development Center of Excellence, Department of Veterans Affairs Puget Sound Health Care System

[4] Department of Epidemiology, University of Washington, Seattle, WA USA

[5] Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA USA

3.1 ABSTRACT

Objectives: Adherence to adjuvant endocrine therapy (AET) for estrogen receptor-positive breast cancer remains suboptimal. Our objective was to understand how factors influence adherence among women across low and high levels of adherence.

Study Design: Retrospective evaluation using the MarketScan database from 2007-2011.

Methods: Privately insured women aged 18-64 recently diagnosed and treated for breast cancer who initiated AET within 12 months of primary treatment were assessed. Adherence was measured as the proportion of days covered (PDC) over a 12-month period. We used simultaneous multivariable quantile regression to assess the association between treatment and demographic

factors, use of mail-order pharmacies, medication switching, and out-of-pocket costs and adherence. We examined the effect of each variable at the 40th, 60th, 80th, and 95th quantile.

Results: Among the 6,863 women in the cohort, mail-order pharmacies had the greatest influence on adherence at the 40th quantile, associated with a 29.6 percent (22.2-37.0) higher PDC compared to retail only pharmacies. Out-of-pocket cost for a 30-day supply of AET greater than $20 was associated with a 8.6 percent (2.8-14.4) lower PDC versus $0-9.99. The main factors that influenced adherence at the 95th quantile were mail-order pharmacies, associated with a 4.4 percent lower PDC (3.8-5.0) versus retail only and switching AET medication two or more times, associated with a 5.6 percent lower PDC versus not switching (2.3-9.0).

Conclusions: Factors associated with adherence differed across quantiles. Addressing the use of mail-order pharmacies and out-of-pocket costs for AET may have the greatest influence on improving adherence among low adherers.

3.2 INTRODUCTION

Estrogen receptor (ER+) positive breast cancer is diagnosed in two-thirds of women in the United States.[1] Five years of adjuvant endocrine therapy (AET) is the standard of care for women with ER+, early-stage breast cancer.[2] Treatment with tamoxifen is recommended for premenopausal women, whereas post-menopausal women are treated with aromatase inhibitors such as letrozole, anastrozole, or exemestane.

Treatment with AET has been shown to reduce the rate of cancer recurrence by 39% and reduce breast cancer mortality by about one-third compared to nonusers.[3] However, despite the clear evidence of the benefits of treatment, adherence to recommended treatment over a 12-month period is suboptimal and ranges from 31% to 81%.[4,5]

Policies and interventions that address factors most influential at low levels of adherence will have the most impact at improving breast cancer outcomes among the most vulnerable group of survivors. Studies reveal that more than two-thirds of the population are adherent to AET and therefore draw conclusions about the association with factors among the highest adhering population.[4,6-8] Such studies show factors associated with medication adherence to AET are out-of-pocket costs for medication [6-9], using mail or retail pharmacies [7,8], and the number of times AET medication is switched in a 12 month period.[8] Little evidence exists to be able to determine the influence of these factors at low levels of adherence.

Quantile regression methods provide a complete picture about the patterns of adherence among low adherers who often represent a smaller yet important proportion of study cohorts in the

medication adherence literature.[10-12] Quantile regression has been used to study the association of factors affecting low adherers taking anti-hypertensive, anti-diabetic and anti-inflammatory medications.[10-12] Studies using logistic regression methods use a binary variable of adherence (MPR≥80%) and factors may influence adherence differently at low and high adherence levels rather than at the commonly used cut-point of 80%.[7-9,13] In addition, conducting an ordinary least squares (OLS) regression with a continuous measure of adherence provides evidence of how the average adherence in the study cohort varies with each factor, which is strongly influenced by patients with high utilization and does not allow us to make inferences among patients with low medication utilization. Quantile regression methods offer the best statistical method to examine the influence of factors at low levels of adherence to AET.

We apply a quantile regression method using prescription claims and encounter data to examine how factors affect adherence to AET drugs across levels of adherence among privately insured women treated for newly diagnosed breast cancer.

3.3 METHODS

3.3.1 *Data Source*

We conducted a retrospective cohort study using prescription claims and encounter data from a nationwide, commercially insured patient population in the United States. The Truven Health Analytics MarketScan® Commercial Claims and Encounters Databases contain medical utilization and expenditures across inpatient, outpatient, and prescription claims. All data were de-identified in accordance with the Health Insurance Portability and Accountability Act requirements. Follow-up data were available through December 31, 2011. The study was deemed not human subjects research because the data for the study is publicly available and is de-identified.

3.3.2 *Sample Selection*

We identified women in the database under the age of sixty-four with at least one prescription claim for an aromatase inhibitor (anastrozole, letrozole, and exemestane), or tamoxifen between January 1, 2008 and December 31, 2010 (Figure 3-1). AET initiation was defined as no evidence of AET prescription for at least six months before the first claim (index claim). Women were included if they were diagnosed with ductal carcinoma in situ (ICD-9-CM 233.0), primary invasive breast cancer with or without axillary lymph node involvement (ICD-9-CM 174.0-174.9 with/out 196.0-196.3, 196.5-196.6, or 196.8-196.9) and surgically treated with bilateral mastectomy, mastectomy, or breast conserving surgery/lumpectomy within twelve months prior to the index claim [14-16]. Study inclusion was limited to women continuously enrolled in a health plan with prescription drug coverage for at least six months prior to and 12 months after the index claim. Women were excluded if they had multiple primary cancers or metastatic breast cancer to distant organs anytime during the study period.

Outcome The primary outcome was medication adherence to AET defined as the proportion of days covered (PDC). PDC was calculated based on the fill dates and the number of days' supply for AET prescription in a 12-month study period.[17,18] The numerator was the number of days covered by the prescription fill and days were adjusted so that women could not have overlapping days of coverage. We assumed that women did not take the refilled endocrine therapy before exhausting the previous prescription.[19] The denominator was 365 days. We multiplied the ratio by 100 to obtain a percent of the proportion of days covered.

3.3.3 *Study Variables*

Age was calculated at the index date and evaluated as a categorical variable similar to other studies.[6-8] We used the Elixhauser comorbidity index using all inpatient and outpatient diagnoses

(ICD-9-CM) during the time period prior to the index date.[20] Medication burden was calculated as the count of unique drug classes filled 90 days prior to the index date. We included US geographic region for the Northeast, North Central, South, and West.

Initial breast cancer treatments were identified using ICD-9-CM and CPT codes from inpatient claims to identify whether the patient had a mastectomy, bilateral mastectomy, or a breast conserving surgery/lumpectomy. Similarly, we identified whether the patient had chemotherapy and/or radiation completed prior to the index date.[14-16] We included a categorical variable for the duration of time from surgical treatment to the index date (0-3, 4-6, 7-9, and 10-12 months).

We calculated out-of-pocket costs for AET medications by summing together co-insurance, deductibles, and copayments associated with AET pharmacy claims. AET costs were standardized to 30-day amounts when prescriptions were for longer periods and categorized as 0-$9.99, $10.00 to $19.99, or more than $20.00. We also calculated the average 30-day standardized out-of-pocket costs for all other health care expenses that occurred between prescription refills until the patient no longer had AET medication on-hand and categorized as less than $49.99, $50-99.99, $100-149.99, $150-199.99, and greater than $200.

Patients were categorized into three groups based on the type of pharmacy used during the follow-up period: retail pharmacies only, mail pharmacies only, or at least one mail and one retail pharmacy. We calculated the number of times a patient switched AET medication if they filled a prescription for any aromatase inhibitor or tamoxifen that differed from the index medication and categorized as not switched, switched once, or switched 2 or more times. A categorical variable

was also included for health plan type: health maintenance organization, preferred provider organization, or other.

3.3.4 *Statistical Analysis*

We calculated the frequencies for each study variable based on the proportion of women with 1) less than or equal to 146 days of medication coverage, 2) between 146-346, and 3) greater than 346 days. We chose these categories to most appropriately group women with different levels of adherence from very low adherence to fully adherent into meaningfully sized groups. We evaluated unadjusted differences across patient groups using the Pearson X^2 test for categorical variables.

We used a simultaneous multivariable quantile regression model to examine the differential effects of each independent variable on the conditional quantile of adherence.[21] We used the STATA 'sqreg' command with 1000 bootstrap replications to estimate the standard errors, analogous to robust standard error estimates in linear regression.[22] In the quantile regression we regressed specific quantiles of the dependent variable, PDC, on each variable described.[21] We used one quantile regression with four simultaneous unconditional models set equal to the 40^{th}, 60^{th}, 80^{th}, and 95^{th} quantile of the distribution of the PDC [10]. Quantile regression predicts the effect of each independent variable at the conditional quantile rather than the mean.[21] For comparison purposes, we used a multivariable regression model using ordinary least squares (OLS) and robust standard error estimates to determine the association between each of the covariates and the mean adherence (PDC).

We constructed multiple models of the data and therefore we could reject the null hypothesis at the 0.01 level of statistical significance.[21] All analyses were conducted using Stata 13.1 SE (StatCorp™ College Station, TX).

3.4 RESULTS

A total of 6,863 women were between the ages of 18-64 years and initiated AET following a diagnosis and surgical treatment of breast cancer. Characteristics of the study cohort across a range of days of medication coverage are shown in Table 3-1. Approximately 8% of the cohort had less than 146 days of medication coverage in the 12-month study period and are considered low adherers, whereas 47.6% of the cohort had greater than 347 days of medication coverage and are considered high adherers. The proportion of women with days of medication covered differed significantly on a number of demographic, clinical, treatment, and cost variables. Women with less than 146 days of medication coverage compared to women with greater than 347 days tended to be younger than 49 years (47.3% of women versus 36.4% of women), not receive chemotherapy (46.9% of women versus 56.3% of women), not switch medication (15.1% versus 11.6%), and received care in the southern US (45.1% versus 36.5%). A greater proportion of high adhering women compared to low adhering women (<146 days of medication coverage) had mean out-of-pocket costs for 30 days' supply of AET between $0-9.99 (51.4% versus 44.0%), and had used mail pharmacies to fill AET prescriptions (20.2% versus 2.9%).

Multivariable quantile regression

The difference in the percent points of adherence (PDC) at the 40th, 60th, 80th, and 95th quantiles are shown in Table 3-2**.** For comparison purpose, the difference in the percent points of adherence, on average, are also presented in the right hand column.

Higher out-of-pocket costs for AET medication were consistently associated with lower adherence ($p<0.01$). On average, women with a mean 30-day out-of-pocket cost for AET of $20.00 or greater had an adherence to AET that was 3.3 percentage points lower than women with out-of-pocket costs for AET less than $9.99 after controlling for all other variables (95% CI: 4.9 to 1.6). However, at the 40^{th} quantile of adherence, the influence of out-of-pocket costs for AET medication was greater since women with out-of-pocket cost for a 30-day supply of $20.00 or greater for AET medication had a PDC of 8.6 percentage points lower than women with out-of-pocket cost of less than $9.99 among (95% CI: 14.4 to 2.8). At the 95^{th} quantile of adherence, the influence of out-of-pocket costs, although significant was minimal (β: -0.9, 95% CI: -1.6 to -0.2). Mail-order pharmacies to fill prescriptions for AET was significantly associated with higher adherence to AET ($p<0.01$). On average, women who used only mail-order pharmacies had adherence that was 9.2 percentage points higher than women who used retail pharmacies only (95% CI: 7.9 to 10.6). The effect of using only mail-order pharmacies was even greater in the model fit to the 40^{th} quantile (β: 29.6, 95% CI: -22.2 to 36.9) and was lowest at the 95^{th} quantile (β: 4.4, 95% CI: 3.8 to 5.0).

On average, an increase in age significantly increased adherence to AET ($p<0.01$). In the model that we fit examining the 40^{th} quantile, age was not significantly associated with adherence.

However, at the 95th quantile, women aged 60-64 years, had a PDC 5 percentage points higher than women less than 40 years (95% CI 3.1-6.8) after controlling for other covariates. The effect of higher adherence with increasing age was the most influential at the 60th, 80th, and 95th quantile ($p<0.01$).

On average, women who received chemotherapy had 4.1 percentage points higher adherence than women who did not receive chemotherapy (95% CI: 2.7 to 5.6). Women receiving chemotherapy had significantly higher adherence compared to women who did not receive chemotherapy in the 40th, 60th, and 80th quantile and not in the 95th quantile ($p<0.01$). Overall, the relationship among women who received chemotherapy appeared to be consistently reduced between the 40th and 95th quantile.

We also found that living in the South versus the Northwest, women with an increase in pre-morbid condition, and switching AET medication 2 or more times compared to not switching was significantly associated with lower adherence overall and in all fitted quantiles except the 40th quantile.

3.5 DISCUSSION

Our findings show that predictors have a differential influence on adherence across levels of adherence. Although there were factors that were significantly associated with adherence in all fitted models, certain factors such as out-of-pocket costs for AET, pharmacy type, and receipt of chemotherapy had the greatest effect on adherence at the 40th quantile, whereas switching AET medication, pharmacy type, and age had the greatest effect on adherence at the 95th quantile.

The association between out-of-pocket costs for AET medication and adherence have been demonstrated in previous studies.[6-9] The quantiles of medication adherence (40th quantile versus 95th quantile) can be an indicator of a complex combination of inter- and intra- personal factors. For instance, this study demonstrates that at the 95th quantile, out-of-pocket costs for AET medication had a minimal influence on adherence. One reason could be because they have a comprehensive understanding of the importance of taking the medication despite the costs.[23] Similar to other studies, we found that using mail-order pharmacies to fill prescriptions was associated with greater adherence compared to using retail pharmacies.[7,8] Mail-order pharmacies may increase adherence to AET because they may eliminate the need for travel to the pharmacy for patients with time and transportation constraints. Patients using mail-order pharmacies may also be more inclined to purchase more medications than patients using retail pharmacies.[24] However, unmeasured self-selection factors such as race/ethnicity could also account for the observed association since non-Latino whites are more likely to use mail-order pharmacies.[25] However, unlike other studies, the impact on adherence for women who used mail pharmacies versus retail pharmacies was greatest in the 40th quantile of adherence compared to the 95th quantile. This suggests that mail-in pharmacies may substantially limit barriers to accessing medication among low adherers.

We found that women treated with chemotherapy were more likely to be adherent to AET compared to women not treated with chemotherapy across all quantiles of adherence. The effects were greatest in the 40th quantile compared to the 95th quantile. It is possible that women not treated with chemotherapy were misclassified into the study cohort because they filled one prescription

of AET when they were not ER+. A study by Wang and Du found that 82% of women with ER+ breast cancer, treated with chemotherapy, initiated AET treatment versus 68% for women not treated with chemotherapy.[26] They also found that women treated with chemotherapy who are diagnosed at a later stage are more likely to initiate AET compared to women who are diagnosed at an earlier stage and may be more likely to continue AET to minimize the chance of recurrence.[26] Finally, women who received chemotherapy may be less likely to discontinue AET medication because they may have a higher tolerance for side-effects.[27,28] We also observed that switching AET medication was associated with lower adherence at the 95th quantile, however, women who filled fewer prescriptions had fewer opportunities to switch medication.

This study has several strengths. We used a large cohort of privately insured women with a prescription drug coverage plan who were continuously insured for at least 18 months. Women in the cohort were recently diagnosed and treated with breast cancer and therefore we were able to study adherence to AET during the first year of treatment which may be the most critical period to address suboptimal adherence.[4] Next, we included detailed baseline characteristics such as pill burden, time from treatment to initiation of AET, and the presence of comorbid conditions which may have confounded the observed associations with adherence.

Our study also has some limitations. First, calculating adherence using prescription claims assumes that patients are taking medications as often as they fill prescriptions, however, using pharmacy records is the most accurate and validated estimate of actual medication use in large populations over periods of time.[29,30] Second, while claims and encounter data are a reliable source to determine prescription drug usage and medical procedures, clinical factors such as stage of disease

are based on procedural and diagnostic algorithms which may have misclassified patients that did not have observable codes. Third, our study was not able to control for sociodemographic characteristics such as race/ethnicity, education, or income since these factors may be important confounders in our findings, however, a study by Hershman et. al did not find a significant association between these factors and adherence to AET in a group of commercially insured patients.[6] Furthermore, all women in this study had employer sponsored health insurance and may not be representative of women with low socioeconomic status. Fourth, while we utilized data from the MarketScan® databases which contains data on more than 180 million commercially insured Americans, the women in our cohort are more likely healthier and younger than the general population and may limit the generalizability of these findings beyond this population of women with breast cancer.

These results add to the literature on adherence to AET medications for women newly diagnosed with breast cancer. The quantiles of the distribution of adherence are a better measure than the mean because in modeling the mean of skewered distributions such as adherence, the behavior of the mean often represents what is happening in the tails of the distribution.[21] Even among a privately insured population, a suboptimal proportion of patients had less than 146 days of AET medication coverage in a 12-month period. Quantile regression allows us to draw conclusions about how each of the factors influence adherence at lower quantiles of adherence.

Our study has implications for future research. The use of mail-order pharmacies, and impact of out-of-pocket costs should be explored with patients that are low adherers of AET medication. This information could provide greater insight to capture important aspects of non-adherence

among groups of patients that are least likely to continue medication. Also, randomized controlled trial should be used to establish the efficacy and safety of mail-pharmacies on adherence to AET medication.

Conclusion

This study provides evidence that factors such as the use of mail-order pharmacies, and 30-day out-of-pocket costs for AET medication influence adherence differently across levels of adherence even among a group of privately insured patients. Health insurance plans which allow patients the option to fill AET medication using mail-in pharmacies may improve adherence, particularly among low adherers. The Affordability Care Act allows patients to access free preventive care and certain medications, however, including the aromatase inhibitors which prevent cancer recurrence at no out-of-pocket costs may also improve adherence to AET.

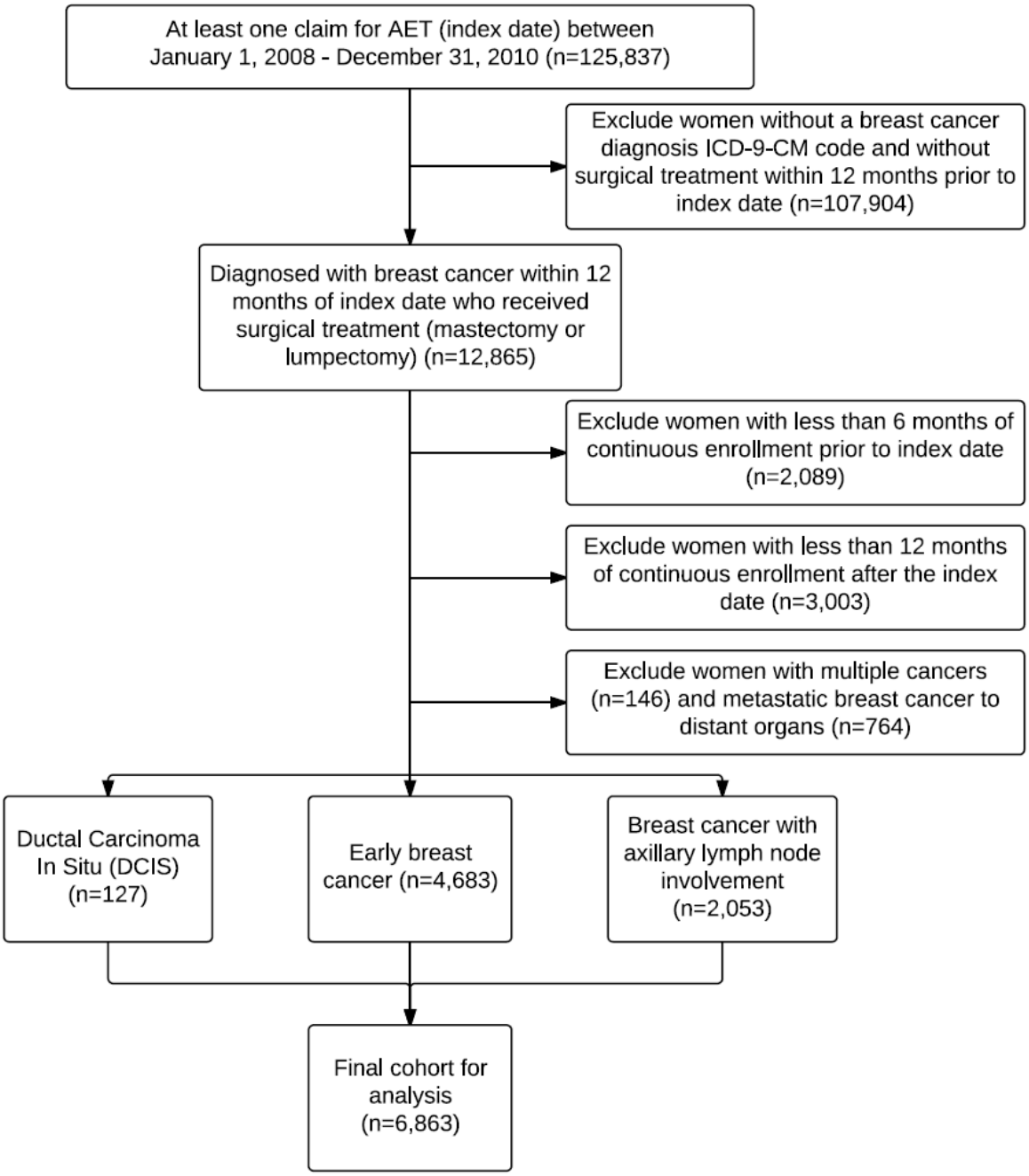

Figure 3-1. Consort diagram for study cohort selection

Table 3-1. Sample characteristics across the range of adherence, proportion of AET medication days covered in a 365 day period (PDC) (n=6,863)

	Less than 146 day's covered	Between 146-347 day's covered	Greater than 347 day's covered	p-value
Overall, % (n)	8.0% (548)	44.4% (3047)	47.6% (3268)	
Breast cancer stage				<0.01
DCIS	2.0%	1.9%	1.8%	
Early Stage	75.4%	67.3%	67.9%	
Axillary lymph node Involvement	22.6%	30.8%	30.3%	
Age, years				<0.001
<40	11.3%	9.6%	6.0%	
40-49	36.0%	36.2%	30.4%	
50-59	40.0%	39.6%	43.1%	
60-64	12.8%	14.6%	20.5%	
Comorbidities[a]				
Hypertension	17.5%	17.4%	18.8%	0.37
Chronic pulmonary disease	5.1%	6.2%	5.2%	0.18
Diabetes, uncomplicated	5.1%	5.1%	4.5%	0.59
Hypothyroidism	6.6%	5.9%	7.3%	0.08
Obesity	6.2%	5.0%	5.0%	0.47
Fluid and electrolyte disorders	3.7%	2.7%	2.4%	0.24
Deficiency anemias	5.1%	4.4%	2.9%	<0.01
Depression	5.7%	5.1%	3.6%	0.01
Elixhauser Conditions Composite				0.34
0	58.2%	61.7%	61.8%	
1	26.6%	24.6%	26.0%	
2	9.5%	8.5%	7.9%	
3	3.8%	3.1%	2.9%	
≥4	1.8%	2.1%	1.5%	
Surgery				0.26
Mastectomy	28.7%	27.7%	29.5%	
Bilateral mastectomy	5.3%	4.2%	4.9%	
Breast Conservative Surgery/ Lumpectomy	66.1%	68.1%	65.6%	
Time from surgical treatment to first AET fill, months				<0.001
0-3	40.2%	36.3%	41.7%	
4-6	27.7%	31.6%	30.3%	
7-9	22.8%	24.5%	22.0%	
10-12	9.3%	7.7%	6.0%	
Chemotherapy	46.9%	59.8%	56.3%	<0.001
Radiation Therapy	31.9%	34.5%	32.9%	0.28
Oophorectomy	3.3%	2.3%	2.0%	0.16
Health Plan Type				<0.01
HMO	22.6%	18.5%	17.0%	
PPO	60.2%	59.5%	60.6%	

Other	17.2%	21.9%	22.3%	
Initiation year of AET				0.11
2008	34.7%	31.2%	31.4%	
2009	36.9%	34.7%	34.4%	
2010	28.5%	34.2%	34.2%	
Region				<0.001
Northeast	12.8%	15.4%	18.8%	
North Central	20.3%	19.7%	22.3%	
South	45.1%	44.7%	36.5%	
West	20.8%	19.4%	21.6%	
Unknown	1.1%	0.9%	0.8%	
AET drug type at index date, % (n)				<0.001
Exemestane	2.9%	1.7%	1.9%	
Anastrozole	24.5%	27.4%	33.3%	
Letrozole	16.4%	17.8%	16.3%	
Tamoxifen	56.2%	53.1%	48.5%	
Number of times AET medication switched				<0.001
0	84.9%	78.8%	88.5%	
1	13.5%	18.3%	10.3%	
2 or more	1.6%	2.9%	1.3%	
Pharmacy type				<0.001
Retail only	91.4%	77.9%	60.6%	
Mail order only	5.7%	8.8%	19.3%	
Retail and mail	2.9%	13.4%	20.2%	
Number of prescriptions filled 90-days prior to the index date				<0.001
0	9.1%	5.4%	3.9%	
1-5	57.7%	55.6%	57.8%	
6-10	29.0%	32.0%	31.6%	
Greater than 10	4.2%	7.0%	6.8%	
Out-of-pocket costs for 30 days' supply of AET medication, $				<0.001
0-9.99	44.0%	46.4%	51.4%	
10.00-19.99	28.1%	26.8%	23.4%	
20.00 or greater	27.9%	26.9%	25.2%	
Other out-of-pocket costs, 30 day average, $[b]				0.03
0-49.99	24.5%	18.2%	18.8%	
50-99.99	20.8%	20.3%	21.8%	
100-149.99	13.9%	15.1%	15.2%	
150-199.99	11.5%	13.5%	13.4%	
200 or greater	29.5%	33.1%	30.9%	

[a] Comorbid conditions displayed were the most prevalent of the Elixhauser conditions in the cohort.
[b] Other out-of-pocket costs include costs paid by the patient for inpatient, outpatient, and medication (other than AET).
P-values correspond to the Pearson's Chi Square test of independence

Table 3-2. Difference in the percent points of the proportion of days covered (PDC) for adjuvant endocrine therapy medication where each model represents the 40th, 60th, 80th, and 95th percentile of PDC (n=6,863)

	40th Quantile of PDC			60th Quantile of PDC			80th Quantile of PDC			95th Quantile of PDC			OLS		
	β	(95% CI)		β	(95% CI)		β	(95% CI)		β	(95% CI)		β	(95% CI)	
Out-of-pocket costs for 30 days' supply of AET medication															
0-9.99	Reference			Reference			Reference			Reference			Reference		
10.00-19.99	-6.8	-11.7	-1.8	-6.7	-11.2	-2.3	-3.3	-5.7	-0.8	-1.0	-1.7	-0.3	-2.9	-4.3	-1.4
20.00 or greater	-8.6	-14.4	-2.8	-6.2	-11.2	-1.3	-2.6	-5.2	-0.1	-0.9	-1.6	-0.2	-3.3	-4.9	-1.6
Other out-of-pocket costs for services and medication															
0-49.99	Reference			Reference			Reference			Reference			Reference		
50-99.99	4.9	-1.8	11.6	2.9	-2.6	8.5	0.6	-2.1	3.4	0.5	-0.3	1.4	1.1	-0.7	3.9
100-149.99	3.6	-4.1	11.3	1.7	-4.2	7.5	-0.5	-3.3	2.3	0.4	-0.5	1.2	0.2	-1.7	2.2
150-199.99	4.8	-2.9	12.6	1.7	-4.5	8.0	-0.1	-3.4	3.1	0.3	-0.6	1.2	1.0	-1.0	3.1
200 or greater	5.3	-1.8	12.4	1.1	-4.3	6.6	-0.2	-2.9	2.5	0.4	-0.5	1.2	0.7	-1.1	2.5
Breast Cancer															
DCIS	Reference			Reference			Reference			Reference			Reference		
Early Stage	-3.2	-18.5	12.2	0.8	-12.0	13.6	3.9	-4.5	12.3	0.9	-1.6	3.4	0.7	-3.6	4.9
Axillary lymph node involvement	3.7	-12.0	19.5	4.8	-8.1	17.8	6.4	-2.1	14.9	1.3	-1.2	3.9	2.7	-1.7	7.1
Age, years															
Less than 40	Reference			Reference			Reference			Reference			Reference		
40-49	5.2	-1.3	11.7	7.8	1.0	14.7	6.4	0.9	11.9	2.9	1.1	4.7	3.3	1.1	5.6
50-59	7.4	0.5	14.2	12.6	5.7	19.5	9.7	3.9	15.5	4.2	2.4	6.0	5.4	3.0	7.8
60-64	9.4	0.6	18.1	13.2	5.8	20.6	11.8	5.8	17.7	5.0	3.1	6.8	6.8	4.1	9.6
Health Plan Type															
HMO	Reference			Reference			Reference			Reference			Reference		
PPO	-2.4	-8.1	3.2	3.1	-1.9	8.0	1.9	-1.3	5.2	0.1	-0.7	0.9	0.5	-1.2	2.1
Other	2.5	-3.9	8.9	3.5	-1.6	8.6	0.2	-3.3	3.7	-0.2	-1.0	0.6	0.1	-1.7	1.9
Initiation year of AET															
2008	Reference			Reference			Reference			Reference			Reference		
2009	1.2	-3.9	6.2	2.1	-2.0	6.2	0.9	-1.3	3.1	0.0	-0.5	0.6	-0.3	-1.6	1.1
2010	3.1	-2.0	8.3	4.8	0.9	8.6	2.3	0.3	4.4	0.1	-0.4	0.7	1.1	-0.3	2.4
Region															
Northeast	Reference			Reference			Reference			Reference			Reference		
North Central	-3.9	-10.3	2.5	-3.2	-7.9	1.4	-0.7	-2.9	1.5	-0.4	-1.0	0.2	-1.5	-3.2	0.1

South	-5.6	-11.6	0.4	-6.4	-11.0	-1.9	-3.9	-6.4	-1.5	-1.7	-2.4	-1.0	-3.5	-5.0	-2.0
West	-4.0	-11.3	3.2	-2.8	-7.4	1.9	-1.8	-4.4	0.8	-0.2	-0.8	0.4	-2.2	-3.9	-0.4
Unknown	-8.1	-26.5	10.4	-17.3	-36.0	1.4	-5.1	-25.4	15.1	-1.1	-5.6	3.4	-4.5	-11.2	2.3
AET drug type at index date, % (n)															
Exemestane	Reference			Reference			Reference			Reference			Reference		
Anastrozole	12.6	-5.6	30.7	8.0	-7.1	23.1	3.0	-6.6	12.5	-0.3	-2.8	2.3	2.9	-1.8	7.6
Letrozole	6.5	-11.5	24.5	2.0	-13.5	17.5	-0.3	-9.9	9.4	-0.9	-3.5	1.6	1.3	-3.5	6.1
Tamoxifen	5.7	-12.7	24.1	4.0	-11.2	19.2	1.4	-8.3	11.1	-0.6	-3.2	2.0	0.9	-4.0	5.7
Pharmacy type															
Retail only	Reference			Reference			Reference			Reference			Reference		
Mail only	29.6	22.2	36.9	22.6	18.5	26.8	13.5	11.3	15.7	4.4	3.8	5.0	9.2	7.9	10.6
Mail and retail	31.4	26.4	36.4	21.2	17.3	25.0	12.4	10.3	14.5	4.2	3.6	4.8	9.8	8.6	10.9
Number of times AET medication switched															
0	Reference			Reference			Reference			Reference			Reference		
1	-3.4	-8.1	1.4	-8.5	-12.7	-4.3	-10.0	-13.2	-6.8	-4.9	-6.3	-3.4	-4.6	-6.1	-3.0
2 or more	-2.5	-12.6	7.6	-10.5	-20.1	-0.8	-10.8	-19.6	-2.1	-5.6	-9.0	-2.3	-5.1	-8.6	-1.5
Surgery treatment															
Mastectomy	Reference			Reference			Reference			Reference			Reference		
Bilateral Mastectomy	-3.0	-13.0	7.1	2.2	-7.4	11.9	3.0	-0.7	6.7	0.5	-0.6	1.5	0.1	-2.6	2.9
Breast Conserving Surgery	-0.2	-4.9	4.6	0.7	-2.8	4.2	-0.1	-2.0	1.7	-0.4	-0.9	0.1	-0.4	-1.6	0.8
Chemotherapy	13.6	8.4	18.9	10.9	6.9	14.9	4.9	2.4	7.4	0.7	0.0	1.3	4.1	2.7	5.6
Radiation Therapy	-3.0	-7.9	1.8	0.1	-3.4	3.5	0.1	-1.7	1.9	-0.2	-0.7	0.4	-0.3	-1.6	0.9
Oophorectomy	-2.2	-15.8	11.5	-3.9	-18.6	10.9	0.4	-8.8	9.5	0.1	-2.2	2.3	-1.0	-5.2	3.2
Time from surgical treatment to first AET fill, months															
0-3	Reference			Reference			Reference			Reference			Reference		
4-6	-1.3	-6.7	4.1	-1.9	-6.0	2.2	-2.6	-5.1	-0.2	-0.8	-1.5	-0.1	-2.0	-3.6	-0.5
7-9	-5.2	-11.3	0.8	-3.6	-8.1	0.9	-3.3	-6.0	-0.5	-1.1	-1.9	-0.4	-2.9	-4.7	-1.2
10-12	-9.2	-16.9	-1.4	-11.6	-18.8	-4.4	-8.5	-14.4	-2.7	-2.2	-3.8	-0.6	-5.4	-8.0	-2.8
Number of prescriptions filled 90-day prior to follow-up period	0.5	-0.2	1.2	0.4	0.0	0.8	0.2	-0.1	0.5	0.0	0.0	0.1	0.2	0.00	0.4
Elixhauser Conditions Composite	-1.7	-3.9	0.4	-1.4	-3.1	0.3	-1.3	-2.2	-0.3	-0.4	-0.7	-0.2	-0.8	-1.4	-0.2
Intercept	18.0	-9.9	46.0	34.5	11.9	57.0	62.6	47.9	77.4	90.9	86.6	95.3	75.8	68.5	83.1

Coefficients are points of the proportion of days covered (PDC)

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Chapter 4. PHYSICIAN-PATIENT COMMUNICATION INFLUENCES WOMEN'S USE OF ADJUVANT ENDOCRINE THERAPY AMONG BREAST CANCER SURVIVORS

Albert J. Farias[1], India Ornelas[1], Sarah Hohl[2], Steven B. Zeliadt[1,3], Ryan N. Hansen[4], Christopher Li[2,5], Beti Thompson[1,2]

[1] Department of Health Services, University of Washington, Seattle, WA USA

[2] Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA USA

[3] Health Services Research and Development Center of Excellence, Department of Veterans Affairs Puget Sound Health Care System, Seattle, WA USA

[4] Department of Pharmacy, University of Washington, Seattle, WA USA

[5] Department of Epidemiology, University of Washington, Seattle, WA USA

4.1 ABSTRACT

Objective: Adherence to adjuvant endocrine therapy (AET) remains suboptimal despite the effectiveness of these treatments at reducing breast cancer recurrence and mortality for women with estrogen positive-receptor status. The objective of this study is to understand, from the patient's perspective, how physicians communicate with them about using AET treatment.

Methods: Qualitative methods using semi-structured in-depth interviews were conducted in 2014-2015 with women (n=22) diagnosed with breast cancer who filled a prescription for AET in the previous 12 months. Eighteen open-ended interview questions aimed to elicit participants' experiences with initial breast cancer treatment and use of AET. We reviewed and coded interview transcripts using qualitative principles of deductive reasoning to identify concepts and themes from the interview data.

Results: We grouped themes into four major functions of physician communication: (1) information exchange, (2) decision-making, (3) enabling patient self-management, and (4) emotional support. Physicians exchanged information with patient's in a way that they understood and enhanced the women's health literacy regarding the treatment benefits, and knowledge of AET care. Many women expressed trust in their physician and confidence in the care that they received. Women reported a high degree of self-efficacy regarding the medication and were continuing AET treatment despite the side effects.

Conclusions: Women may be more likely to continue AET treatment if physicians communicate information related to treatment benefits, purpose, and expectations to them in a way that they understand. Physicians play an important role in determining breast cancer patients' use of AET.

4.2 INTRODUCTION

Estrogen receptor-positive breast cancer is diagnosed in two-thirds of breast cancer cases in the US.[1,2] Treatment with adjuvant endocrine therapy (AET) is recommended for five years for women with ER+ breast cancer.[3] AET includes tamoxifen and the aromatase inhibitors exemestane, letrozole, and anastrozole. Treatment with tamoxifen is recommended for pre-menopausal women and aromatase inhibitors are recommended for post-menopausal women.[3] Women treated with AET experience improved disease-free survival.[4-8] However, despite the effectiveness of AET to improve survival and decrease cancer recurrence, adherence rates to recommended treatment remain low. It is estimated that between 73-88% of breast cancer patients are adherent to medication in the first year and up to 50% of patients become non-adherent within 4-5 years of initiating treatment.[9-11]

Factors associated with adherence to AET are predominately drawn from large samples of medical claims and insurance data and are limited to the measured clinical and billable factors. Factors related to adherence have focused predominately on the demographic and disease-specific characteristics related to breast cancer treatment.[9,12-15] For example, the rates of adherence vary significantly by age,[16,17] the number of other medications prescribed for comorbidities,[14] cost of medication,[9,15,18] and type of initial breast cancer treatment.[9,10] Health beliefs are also important factors that contribute to adherence to AET.[19] For example, perceived risk of disease recurrence and assessing the cost and benefits of treatment influence adherence to initial breast cancer treatment.[17,20] However, little evidence exists about the interpersonal factors that influence the use of AET.

One potentially influential interpersonal factor is the physician-patient interaction. The role of the physician can both positively and negatively affect medication adherence.[21] Theory suggests that physician-patient communication functions such as information exchange, responding to emotions, making decisions, and enabling self-management can have direct and indirect effects on health outcomes.[22] Information exchange refers to communication about aspects of care and can influence the use of AET if the physician successfully communicates information about the risks of treatment and clinical evidence on the effectiveness in a way that is understood by patients.[22,23] When medical decisions are a shared responsibility of the patient and physician, they come to an agreement based on the available clinical evidence and what is feasible to implement.[24] Physicians can also encourage patients to manage important aspects of their illness such as seeking appropriate care, coping with treatment effects, and finding health related information.[25,26] Finally, physicians that can help patients manage emotions and uncertainty about their illness can reduce distress and help the patient to cope with the disease, build self-confidence, and a sense of worth.[27] Generally, these communication functions can lead to greater patient trust in the physician, enhanced health literacy, and a greater willingness to follow through with treatment.[22]

Greater physician trust and physician recommendation of treatment during the decision making process are associated with higher rates of medication adherence.[21,28,29] However, little evidence exists about the influence of physician-patient communication on the use of AET. The objective of this study is to understand, from the patient's perspective, how their physicians communicate with them about AET treatment.

4.3 METHODS

4.3.1 *Study Design*

We conducted semi-structured in-depth interviews with breast cancer survivors in order to understand their experiences and perspectives regarding the complex issue of adherence to AET.[30] By using this approach, women were encouraged to talk openly about their experiences with AET in a conversational manner yet we were able to systematically collect similar information about each participant's experience.[31] The study was approved by the University of Washington's Institutional Review Board.

4.3.2 *Participant Recruitment*

Eligible women were defined as breast cancer patients who filled at least one prescription for tamoxifen, exemestane, anastrozole, or letrozole in the last 12 months. Women were recruited from two geographic regions in the United States between September 2014 and April 2015. In Los Angeles, California, women were recruited with informational flyers sent to email list serves of breast cancer support/survivorship groups, and placed in oncologist's offices. Flyers contained the purpose of the study, eligibility criteria, and staff contact information. In Houston, Texas, women were recruited from breast cancer survivorship support groups that were identified from an internet search. Study staff contacted the groups, presented the purpose of the study, handed out flyers, and answered questions during a monthly meeting. Participants contacted the first author and were screened over the telephone to ensure that they met study inclusion criteria. We then scheduled a face-to-face interview at a time and place that the participant felt most comfortable being interviewed. The majority of the interviews took place in study rooms at public libraries, and at the participant's workplace.

4.3.3 *Data Collection and Analysis*

Interviews were designed to allow an open conversation about each woman's experiences with AET. Prior to the interview, the researcher introduced himself, reiterated that the purpose of the interview was to learn about their experiences with AET, and obtained informed consent from the participant. The semi-structured interview guide consisted of 18 open-ended questions that were developed to understand how social, cultural, and health care factors influence women's experiences with AET (Appendix A). Specifically, we were interested in how these factors influenced participants' barriers and benefits to use AET, and their perceptions of the susceptibility and severity cancer recurrence. Interview topics included the history of breast cancer diagnosis and treatment, experiences with side-effects from the initial breast cancer treatment, relationship with physicians during the initial treatment, treatment decision making, views about cancer survivorship, and experiences and side-effects of subsequent hormonal therapy. In this paper, we focus our findings regarding the participant's relationship with her physician. Demographic information including place of birth, age, income, household composition, marital status, and education and these were recorded at the end of each interview. All interviews were conducted in English by the first author who was trained to conduct in-depth interviews. Each interview lasted between 35-60 minutes. Case summaries were written at the conclusion of each interview; each described the interview setting, general impressions, and/or salient themes that emerged from each interview. Women were given a $25 gift card at the conclusion of the interview. The first author conducted all of the interviews until he reached saturation in which no new data emerged from the interviews.

The interviews were recorded using a digital audio device, professionally transcribed verbatim, and were checked for accuracy and to distinguish inaudible words by the interviewee. Three interviews were inaudible because of the recording quality and could not be transcribed.

The transcripts were uploaded into Atlas.ti, version 7, a qualitative data analysis software program (Atlas.ti, Berlin, Germany). A list of codes were developed using an *a priori* approach, based on the interview questions and study goals.[32-35] We used a deductive, constant comparison approach to identify concepts and themes from the interview data. The first four interview transcripts were coded line by line by two coders to check for reliability and familiarity with codes. Each coder then separately coded six or seven transcripts. The final two interview transcripts were double-coded to check for consistency in coding and inter-rater reliability. We met weekly, in an iterative process, to refine the codebook by adding, removing, and revising codes to capture emerging themes. The first three authors and senior author met regularly to discuss themes from the data, to determine linkages across participants and thematic categories, and to corroborate on exemplary quotes to represent each theme.

4.4 RESULTS

We interviewed twenty-two women. The interviewed women were predominately white (59.1%); however, African American women accounted for over one-quarter of the participants (27.3%) (Table 4-1). Fifty-three percent of the women were under the age of 55 years old. The majority (63.6%) of the women had a household income of $50,000 or more, lived with one or more people (59.1%), and nearly three-quarters of the women (72.7%) had at least a bachelor's degree. Women reported currently taking either aromatase inhibitors (exemestane or anastrozole) (50%), or tamoxifen (50%). Most of the participants (72.7%) were interviewed in Los Angeles, CA.

Based on our theoretical framework described by Street and Epstein, we grouped the emergent themes into the four functions of physician-patient communication: (1) information exchange, (2) decision making, (3) patient self-management, and (4) response to emotions and uncertainty (Table 4-2).[22]

4.4.1 *Information Exchange*

All of the women in the study described their interactions with their physician when deciding to take AET and to continue treatment. The women reported that their physician talked to them about the purpose, benefits, and treatment duration of AET medication. All of the women were able to articulate the way in which the drugs worked and stated that their physician described their cancer as "estrogen-fed", "slow growing and extremely hormonally positive", and "growing because of the hormones." The women reported that their physician said that they "needed to starve the cancer of estrogen to prevent it from growing", and to "slow the cells down." The women understood from their physician that using AET would help "reduce the [cancer] recurrence rate" and to "contain the estrogen". Almost all women used phrases such as "clinical studies with the latest information", "published studies", or "new research" to describe how physicians talked to them about the benefits of AET to reduce cancer recurrence. One woman reported that their physicians called AET the "five year pill", while other women said that that they would have to take "one pill per day for five years". Some women even understood that they may have to be on AET treatment for up to 10 years because of "new research".

4.4.2 *Decision Making*

The women understood that the decision to take and continue AET was ultimately up to them and was based on a discussion of the information exchanged with their physician and their physician's recommendation. One woman explained:

> "I need my questions answered in whatever way that she [the oncologist] can statistically, because she can't say personally what's going to happen to me. And then I'm going to have to decide which [AET treatment] I want."

The recommendation to take AET was often a discussion about the information described in the previous section. As another woman described:

> "I saw her a month or two ago and I was discussing it and basically, I don't make instant decisions, and she's telling me, well this is this. This is that. So, what do you want to do?"

The women ultimately make the decision to take AET treatment but know that it is a choice based on the physician's recommendation as one woman noted:

> "It basically was brought on by my oncologist…well of course, you don't have to take it if you don't want to"… "I reached the conclusion [to take AET] with the doctor's help, of course".

4.4.3 *Enabling Patient Self-management*

Many women noted that physicians aided in the self-management of their disease. Women were actively engaged in managing their own care by asking questions during routine follow-up care where physicians addressed concerns and treatment side effects. All of the women knew exactly when they had their next routine visit to manage their care with the physician. Many women described "I see my oncologist every 90 days" or "every three months". When asked what they talk about during these visits, one woman said:

> "We're primarily making sure that the hormone levels have dropped enough or dropped or risen, depending on what they're looking for. So, it's for blood work and just to monitor side effects from the tamoxifen."

Women reported that physicians were helping them actively manage the side effects of AET. This involved both medicinal and non-medicinal strategies. Active management of side effects

increased the woman's self-efficacy to continue on AET. For example, when one woman was asked how confident she was that she would be able to continue with treatment for five years, she responded:

> "It should be fine, I mean, if I start having any problems then I'll let her [oncologist] know and see if we can't find something to help."

All women in the study, at one point during AET treatment, experienced hot flashes. One woman said that:

> "They [doctors] recommended I take it [AET] in the evening so that I'm not dealing with being hot during the day. So it was more just controlling when I was going to have them because that's a common side effect with it."

Another woman indicated that her physician prescribed an antidepressant to help with hot flashes:

> "It's an antidepressant... But, for whatever reason, that medicine does decrease hot flashes."

And another woman indicated that:

> "My oncologist recommended to try to take over-the-counter supplement first, if it does not work, then she would prescribe me something."

We found that patients were actively engaged in follow-up care because physicians fostered relationships where women felt comfortable talking to the physician about any issues related to AET treatment or cancer recurrence.

> "Some women can't take [Arimidex], some women can. And that's why it's important to stay on with your oncologist, because you can tell them the symptoms that you have…in order to help yourself, you have to talk to your doctor and that's what I'm doing now."

4.4.4 *Responding to Emotions and Managing Uncertainty*

When describing their care, almost all participants focused on the personality traits of their physician. Common descriptions of their physicians were: "he was nice", "he's very positive but he's realistic", "the doctor was very present and caring", and "very respectful and not condescending".

In general, we found that the communication with their physician made women to feel respected and cared for. One participant noted that:

> "He [oncologist] knew me by my name, my face. When I came in, it was like they treated you like you were a person and not just cattle coming through". "He used to call me his most delicate patient."

We found that women often described their doctors as "very well respected and prominent in the field" and as someone who "does a lot of research with tests", and is someone that is a "respectable person". Women placed a lot of value on the level of expertise of their physician and it was evident that they trusted that their physician provides the best care. When asked why she was continuing with treatment despite all of the side effects that she was experiencing, one woman stated:

> "Why am I continuing with it? I think a lot of it has to do with kind of the confidence in my doctor…she is the doctor and she knows what the clinical trials are showing."

4.5 DISCUSSION

Our study described the interactions between physicians and patients with ER+ breast cancer currently using AET. The interviews showed that physician-patient communication plays an important role in both the initiation and management of AET for women with breast cancer. Specifically, we found that information exchange, shared-decision making, emotional support, and patient-self management of care were aspects that encouraged the use and continuation of AET. Despite the concerns about potential future side-effects of AET, many patients expressed reassurance that their provider would help them manage these problems if they occurred so they would not need to discontinue treatment. For women who experienced hot flashes, they described a willingness to continue taking AET because of the trust and confidence they have in their physicians, and the help they received from their physicians in managing discomfort of hot flashes.

One goal of health information exchange is for the physician to offer a clear understanding of what to do to improve one's health, why it is being done, and precisely, how to do it.[36] Information exchange that focuses on understanding the medical issues of a patient's condition is most successful when patients understand the information explained to them by their physician.[23] Successful health information exchange and enhanced health literacy can be exemplified when the patients can "teach back", or repeat the information provided by their physician.[36] We found that every woman in the study had a high degree of health literacy regarding AET treatment by the way they described the information given to them by their physician. Health literacy regarding the disease or treatment efficacy has been shown to improve treatment adherence [37]. Evidence suggests that patients' strong belief in the necessity of a treatment also improves adherence to medication.[38,39]

Elwyn et. al describe a shared decision making model for clinical practice in which the physician describes the choices and helps patients explore preferences and make decisions[40]. In our study, participants understood that the decision to take and continue AET treatment was a choice for which they took responsibility, using the information and recommendations that their physician provided. When patients are part of the decision-making process by actively participating in the encounter, regardless of who assumes responsibility for the final decision, they often have less regret about the decision and anxiety and experience better health.[41,42] Treatment decision-making that involves patient input is associated with higher adherence to antidepressants, asthma-controller medications, and diabetes medication.[43,44]

Physicians can help patients manage the emotional aspects of their treatment experience by interacting with them in a way that builds their trust in the care that they are receiving.[22] Physician behaviors that build trust generally fall into categories of competency, communication, caring, honesty, and partnering.[45] It is no surprise that our findings about how women described their interactions with their physician by emphasizing caring personality traits and reputation led to greater trust in their physician. Physician trust has been shown to improve adherence to antihypertensive medication and may also be important with the use of AET medication.[46-48]

Patient self-management is aimed at enabling patients to cope with treatment effects and seek appropriate care.[22] Physicians can encourage self-management by providing guidance and advice on better self-care.[22] Women often experience side effects such as hot flashes, joint aches, and sleep disturbances while taking tamoxifen and the aromatase inhibitors. [49-51] Side effects are associated with lower adherence and early discontinuation of AET treatment.[49-51] In our study, physicians were actively involved in the management of breast cancer treatment which eased women's fear of potential side effects from AET and women felt empowered to manage their own treatment. Physicians that encourage self-management empower patients to have a sense of control, or self-efficacy, over any health issues that may arise from treatment.[22] Lower perceived patient self-efficacy with regard to medicine intake is associated with lower adherence to AET.[52] Therefore, physicians that enable patient self-management of AET treatment may improve women's self-efficacy and lead to higher medication adherence.

Because women in our study were highly educated, had an income at or above the median household income in the US, and were actively using AET treatment, we may not have identified

aspects of the patient-physician interaction that serve as barriers to AET use, such as the cost of AET medication. Eligibility criteria included women who had filled a prescription for AET medication in the past 12 months which may explain why women were actively taking medication. A longer time period for prescription refills may yield more women who discontinue taking AET. The results from our study, however, provide insight into the physician-patient interactions surrounding the use of AET. We identified important functions of physician communication that could be addressed in order to improve the use of AET. Our findings are supported by a theoretical framework that demonstrates that these functions operate to improve adherence to medications and health outcomes.[22] Physicians are just one of the interpersonal factors that might influence a woman's decisions about AET use. Future research should explore the influence of the social and cultural environment and how these relationships support the use of AET.

Conclusions

Our study highlights that physicians, particularly oncologists, play an important role in the continuum of care of breast cancer survivors. At the very least, physicians who provide care to women currently taking AET treatment should assess patients' understanding of the way that the drugs work and the benefits of AET treatment, as well as actively engaging them in follow-up care for treatment side-effects. Women may be more likely to continue AET treatment if physicians can communicate these key pieces of information to them in a way that they understand. These physician-patient communication functions could improve trust, health literacy, and self-efficacy of women taking AET. Future research should examine the physician-patient interactions of patients who discontinue or never initiate AET treatment and whether or not interactions differ by race/ethnicity.

Physicians are an important interpersonal relationships of breast cancer patients that can support the use of AET. Adherence to AET could be enhanced by understanding and addressing how physicians interact with patients to exchange information about the effectiveness of AET treatment, foster the decision to take AET, encourage self-management of treatment, and respond to patients' emotions.

Table 4-1. Sample characteristics (n=22)

Characteristic	n (%)
Age, years	
<45	5 (22.7)
45-55	7 (31.8)
55-65	6 (27.3)
>65	4 (18.2)
Race/ethnicity	
White	13 (59.1)
African American	6 (27.3)
Asian	2 (9.1)
Hispanic	1 (4.5)
Adjuvant Endocrine Therapy	
Aromatase Inhibitor	11 (50.0)
Tamoxifen	11 (50.0)
Income	
Less than $15,000	2 (9.1)
$15,000-$50,000	6 (27.3)
$50,000 or more	14 (63.6)
Household Composition	
Alone	9 (40.9)
1	6 (27.3)
2 or more	7 (31.8)
Marital Status	
Single	6 (27.3)
Married	10 (45.5)
Divorced	4 (18.2)
Widowed	1 (4.5)
Geographic Region	
Houston	6 (27.3)
Los Angeles	16 (72.7)
Educational Attainment	
High school or lower	1 (4.5)
Some college, technical school	5 (22.7)
Bachelor degree	10 (45.5)
Master degree	5 (22.7)
Doctorate degree	1 (4.5)

Table 4-2. Themes and subthemes pertaining to patient report of their physician's communication to take adjuvant endocrine therapy treatment.

Emergent themes	**Subthemes**
1. Information exchange between physicians and patients about AET treatment	Benefits of AET citing clinical trials
	Description of the way AET works
	AET treatment duration and expectations
2. Decision making to take and continue AET treatment	Physician recommendation
	AET treatment is an option
3. Enabling patient self-management	Physicians actively involved in the management of side-effects of treatment
4. Emotional support	Physician personality traits
	Professional expertise
	Trust and confidence in physician's care

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Chapter 5. CONCLUSIONS AND IMPLICATIONS

5.1 CONCLUSIONS

Approximately 70% of breast cancer cases are estrogen-receptor positive and are recommended for treatment with aromatase inhibitors or tamoxifen.[1,2] Recent research underscores the effectiveness of five years of adjuvant endocrine therapy to reduce the risk of breast cancer recurrence and the 10-year breast cancer mortality rate. Our research findings suggest adherence to medication is suboptimal even after the first year of initiation among a group of newly diagnosed breast cancer patients that are privately insured with a prescription drug benefit plan. The results from this dissertation underscore the important aspects of the health care delivery system that should be addressed in order to improve adherence among patients least likely to continue AET.

Our research identified factors that influenced a woman's continued use of adjuvant endocrine therapy and identified some that are amenable to interventions. We explored the role of the health care delivery system in Chapter 2 by identifying the association between out-of-pocket costs for AET and adherence. We found that 73.9% of women were adherent 12 months after initiating AET treatment. Discontinuation of treatment was greatest in the first month of initiation and over half of patients had intermittently filled prescriptions. Most importantly, higher out-of-pocket costs for AET medication was significantly associated with a 6-8% lower likelihood of adherence to AET among a privately insured cohort of women with a prescription drug plan. In Chapter 3, we examined how treatment and demographic factors, the use of mail-order pharmacies, medication switching, and out-of-pocket costs influence adherence among women least likely to fill prescriptions. We found that factors associated with adherence to AET differed across all levels of adherence. The use of mail-order pharmacy and lowering out-of-pocket costs for AET may have

the greatest influence at improving adherence among low adherers. Finally, in Chapter 4 we explored the role of the physician-patient interaction. We identified that physician-patient communication plays an important role in both the initiation and management of AET for women with breast cancer. Information exchange, shared-decision making, emotional support, and patient self-management of care were aspects that encouraged the use and continuation of AET. Despite the potential of side-effects from AET medication, most women continue AET because of the trust and confidence they have in their physicians.

5.2 Implications and Future Research

Our findings have important implications for the development of interventions and future research. High out-of-pocket costs for AET medication may put patients at increased risk of non-adherence. Interventions aimed to lower out-of-pocket costs should explore the role of the pharmacist. The pharmacist may be more likely to identify patients that belong to plans that have high cost sharing and can make recommendations to select generic versus brand name drugs that are in alternate drug plans.[3] The Affordable Care Act allows patients to access free preventive care and preventive medications with no out-of-pocket costs. Including the aromatase inhibitors to the list of preventive medications because of the efficacy of the drugs to significantly prevent or reduce the risk of cancer recurrence could eliminate out-of-pocket costs for AET medication to improve adherence. Next, health insurance plans which allow patients the option to fill AET medication using mail-order pharmacies may improve adherence. Finally, interventions can improve physician-patient communication so that physicians communicate key pieces of information about AET to patients in a way that they understand. Interventions should target the oncologist and assess patients'

understanding of the way that the AET medication work, the benefits of treatment, and whether physicians actively engage patients in follow-up care for treatment side-effects.

While we identified key aspects of the health care delivery system that influence adherence to AET, we were not able to study other important factors such as the role of social support, religion, and health beliefs. Future research should examine the social and cultural influences on adherence to AET. For instance, social networks and family support may influence women's perceived susceptibility and severity of breast cancer recurrence which may serve as motivation to continue AET treatment despite the barriers. Future research should also examine the physician-patient interactions of patients who discontinue or never initiate AET treatment. We were able to study important factors that also affect minority women such as issues related to costs of medication, using mail-order pharmacies which may decrease barriers of transportation and time compared to using retail pharmacies, and trust in physicians; however, future research should examine how all of these factors influence adherence to AET among breast cancer survivors from a diverse group of race/ethnicities. Finally, adherence to AET is suboptimal within the first year of initiation; however, the adherence rate may be even lower because women with ER+ breast cancer may never fill a prescription for AET. Future research should examine factors associated with women who never fill a prescription but who are indicated to take AET.

Our work provides evidence that interventions which address organizational level factors of the healthcare delivery system such as out-of-pocket costs for AET medication, using mail-order pharmacies, and improving the quality of the patient-physician communication may improve adherence to AET. Together, these results improve our understanding of the factors that influence

a woman's continued use of AET treatment and help identify ways in which we can improve adherence in order to potentially reduce the rates of breast cancer recurrence and mortality.

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APPENDIX A: IN-DETPH INTERVIEW GUIDE

SCHOOL OF PUBLIC HEALTH
UNIVERSITY of WASHINGTON

Adherence to Adjuvant Therapy among Breast Cancer Survivors

ELICITATION INTERVIEW GUIDELINES

Thank you again for agreeing to take part in our research study. The interview should take about 45 minutes and it is being audio recorded so we can review the information you give us at a later time. As mentioned in the informed consent you signed earlier, you have the right to stop the interview at any time or refuse to answer any question.

We will now begin the interview. We are specifically interested in your experiences with your doctor regarding your breast cancer treatment. We are particularly interested in how your doctors, friends, and family influence your thoughts about continuing with hormonal treatment. We will not keep anybody's name or any identifying information and you can use a fake name today if you wish.

Do you have any questions before we begin? [*Start recording]*

This is (Interviewer name) **_____ speaking with participant** (Participant ID #) **_____.**

Thank you so much for taking the time to speak with me. We are going to start off with a few simple questions just so we can get comfortable with how this process works.

ICE BREAKERS (Choose 1)

A. Please describe for me your typical day from the time that you get up until the time that you go to bed.
B. Can you please describe for me the neighborhood where you live now?
C. Can you describe for me the place that you grew up? What was it like?

Thank you for sharing with me. Now we will move into the questions for the interview. The process will go just like the first question did. I will ask a question and then you can respond just like we are talking to one another.

In this interview, we would like to learn about the experience of being a cancer survivor and your opinions about the needs of cancer survivors. So please, feel free to respond openly and provide as much detail as you feel comfortable providing.

CANCER DIAGNOSIS AND INITIAL TREATMENT EXPERIENCE

First I want to talk to you a little about having cancer and your treatment experience.

1. What type of cancer do you have?
    a. Can you describe to me the stage of your breast cancer?
    b. Can you describe for me any type of the tumor characteristics, if you cannot, that is ok? [PROBE: We are looking for estrogen/progesterone receptor status, her2/neu positive or negative, etc.]

2. What do you think caused your breast cancer?

3. Where did you have your treatment for breast cancer? [PROBE: We are interested to know if they received treatment in the US or abroad, the type of facility and place, whether it was in a hospital, outpatient facility, community clinic, etc.]

4. What type of medical treatment did you have for your breast cancer?
    a. [PROBE: Let them first respond and then ask for the following: surgery, radiation, and chemotherapy.]
        I. What was the purpose of the treatment that you received from your doctor?
        II. What type of side-effects did you experience from treatment? (nausea, hair-loss, low energy, etc.)

5. What were the options that your doctor gave you for your treatment?
    a. How did you decide the treatment that you had?

6. Do you believe that the treatment worked? If so, why?

7. Alongside the medical care your doctor gave you, did you use any other traditional medicine, such as acupuncture, herbs, etc. to treat your cancer?
   a. (if yes) [**Make sure participant describes the traditional medicines**.]
      i. What was the purpose of the traditional medicine you used?
      ii. Do you believe they worked? If so, why?
      iii. Do you continue to use traditional medicine for your cancer?
      iv. Do you believe it is better than the treatment that you received from your doctor?
   b. (if no) Ok.

8. In this next question we are interested in finding out about your experiences with getting treatment for your breast cancer. Can you describe for me how your doctors and nurses treat you?
   a. What do they do that makes you think that you are treated well?
   b. What do they do that makes you think that you are treated poorly?
   c. Has anyone at your doctors, hospital, pharmacy, or lab ever made you feel unhappy, angry or upset? What happened?
   d. How does your experience with the way you are treated make you feel about coming back to the doctors for more care for your breast cancer?

9. Where did you find emotional support or comfort for your emotions during the time you were going through treatment?

   [NOTES: Response can refer to the time they were actually receiving treatment (i.e., literally during chemotherapy) BUT we are also looking for what comforted them or where did they find support during that time in their life more generally].

   a. [PROBE: During the time you were in treatment, was there a person or something you did that often helped you emotionally? If so, can you please describe it for me?]
   b. [PROBE: If participant did not discuss in above questions, what role did spirituality or religion have in your life during the time you were in treatment?]

10. Is there anything that would have helped you to better deal with your cancer diagnosis and treatment?
    a. [PROBE: For instance, what type of information from your doctors might have been helpful for you?]
    b. [PROBE: Have you thought about other kinds of support or service that may have helped you during treatment?]

CANCER SURVIVORSHIP AND LONG-TERM ADJUVANT TREATMENT

Ok, thank you. Now I want to ask you some questions about your life now, after your initial treatment. Many women are recommended by their physician to take long-term adjuvant hormonal therapy for estrogen receptor positive tumors. Such medications can include pills that they get from a pharmacy such as Tamoxifen or aromatase inhibitors such as anastrozole (Arimidex), Exemestane, or Letrozole. We would like to talk to you about current treatment (aside from surgery, radiation, or chemotherapy).

11. After receiving treatment, some people experience being very tired, have pain, or trouble with their memory, do you have any of these?
    a. Do you experience any of these on a regular basis?
        i. (if yes) What do you do when the *[name the symptom]* happen?
            1. Do you experience anything else that might be associated with your cancer?
            2. Is there anything you think you can do to help the *[name the symptom]*?
        ii. (if no) Do you experience any other symptoms?
            1. (if yes)
                a. Can you tell me about that?
                b. Is there anything you can do to help the [name the symptom]?
            2. (if no) Why do you think that is?

ADJUVANT HORMONAL THERAPY

12. Are you currently going to the doctors for your breast cancer?
    a. What type of doctor do you see? (Probe: cancer doctor such as an Oncologist or from their primary care physician)

b. How often do you see them?

13. Are you currently taking any medication for your breast cancer?

(**If yes)**

a. What type of medication and treatment? [Tamoxifen, anastrozole (arimidex), exemestane, letrozole]
    I. How often do you take these pills?
    II. What, if any, side-effects do you have from these treatment(s)?
    III. Has your doctor ever told you how long you should be taking these medications?
        a. How confident do you feel that you will be able to continue with the treatment?
    IV. What did your doctor tell you were the benefits of taking the medication?
    V. What do you believe are the benefits of taking the medication?
b. Why are you continuing with your treatment?
c. How difficult is it for you to regularly take medication for your breast cancer? [PROBE: We would like to focus this question on potential barriers or factors that enable them to continue treatment [probe] for barriers such as costs of the medication (copayments, deductibles, etc.).]
d. What made you decide to receive additional treatment?
    I. Who did you talk to help you decide to receive adjuvant hormonal treatment?
    II. What has your doctor told you that you should do to keep your cancer from coming back?

(If no)

a. What has your doctor told you that you should do to keep your cancer from coming back?
b. How would you feel if your doctor prescribed for you to take a pill once a day for up to 5 years to help your cancer from coming back?

14. Has your doctor told you how often you should see him/her or another doctor?

I. If so, what type of doctor?

15. What would be the most challenging thing to keep you from taking the medication?

16. Do you ever think about the cancer coming back?
    a. (if yes)
        i. How often do you think about it?
        ii. What are some of the thoughts you have?
        iii. Does anything help you get rid of the thoughts when you have them?
    b. (if no)
        i. Is there anything you can do to stop the cancer from coming back?
        ii. What do you think will happen if it does come back?

17. Have ever talk to a doctor about your cancer coming back?
    a. (if yes) What kind of things did you talk about?
        i. Is there anything else you would like to know from your doctor?
    b. (if no) Why haven't you talked to your doctor about your cancer coming back?
    c. Is there anything else that you would like to talk about with your doctor regarding your cancer?

18. People who have had cancer often call themselves "cancer survivors".
    a. Do you see yourself as a cancer survivor?
        i. (if yes) Why?
            1. What makes you a cancer survivor?
        ii. (if no) Why do you not see yourself as a cancer survivor?
            1. Would you call yourself something else?

SOCIODEMOGRAPHIC QUESTIONS

We are almost finished. Finally, I would like some information about you that will help us understand differences among people in responding to these questions.

19. Where were you born?

20. How many years have you lived in this country? _____ years

21. Are you:
    a. married or living as married
    b. single
    c. divorced
    d. widower
22. What is your household composition?
23. What is the highest level of education you completed?
    a. no education or kindergarten
    b. elementary school (1-6)
    c. middle school
    d. high school diploma or equivalent (GED)
    e. some college, Associate's degree, Vocational or Technical College
    f. Bachelor's degree
    g. Master's or doctoral degree
24. I am going to read some income categories. Please tell me into which category your total household income for one year falls.
    □ Less than $15,000
    □ $15,000 to less than $20,000
    □ $20,000 to less than $25,000
    □ $25,000 to less than $30,000
    □ $30,000 to less than $35,000
    □ $35,000 to less than $40,000
    □ $40,000 to less than $45,000
    □ $45,000 to less than $50,000
    □ $50,000 or more

CLOSING

Before we end this interview, do you have any other thoughts about your experience with cancer or about your needs as a cancer survivor that you would like to share?

Thank you for your time.

VITA

Albert John Farias grew up in Azusa, CA. He graduated with a Bachelor of Science degree in Biology from the University of California, Los Angeles in 2005. He began conducting research in the field of breast cancer research as a graduate student at Columbia University in 2006. He completed his Masters of Public Health in Health Promotion and Disease Prevention from the Mailman School of Public Health at Columbia University in the Department of Sociomedical Sciences in 2007. In 2010, he began his doctoral training at the University of Washington, and completed his dissertation in August 2015. He will be an NCI-funded (R25) Postdoctoral Fellow at the University of Texas Health Sciences Center at Houston, School of Public Health in the Department of Epidemiology and a member of the Center for Health Services Research.