Predicting adherence to aromatase inhibitor therapy in patients with breast cancer using protection motivation theory

Monita Karmakar

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A Thesis

Entitled

Predicting Adherence to Aromatase Inhibitor Therapy in Patients with Breast Cancer
Using Protection Motivation Theory

By

Monita Karmakar

Submitted to the Graduate Faculty as partial fulfillment of the requirements for the
Masters of Science Degree in Pharmaceutical Sciences, Administrative Pharmacy Option

Dr. Sharrel Pinto, Committee Chair

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The University of Toledo
May, 2013
An Abstract of

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ABSTRACT

Objective: Review of the literature suggests that there is a gap in understanding the psychosocial factors affecting adherence to Aromatase Inhibitors (AI). The aim of this study is to identify and assess the factors affecting adherence to Aromatase Inhibitor Theory in breast cancer patients using the Protection Motivation.

Methods: Cross-sectional retrospective study. 288 patients, taking aromatase inhibitors as adjuvant therapy, were identified using a cancer registry managed by a University-based medical center. A survey instrument measuring patient’s medication taking behavior was developed using the Protection Motivation Theory, which was mailed to the patients. The
Morisky Scale was used to measure adherence to Aromatase Inhibitor, on a scale of 0-8. ANOVA, Pearson’s correlation and Multiple Regression were used to analyze the data using SPSS with significance being measured at the 0.05 alpha level.

Results: 145 responses were received bringing the response rate to a 54.10%. Out of the 145 patients, 6 who had discontinued Aromatase Inhibitor therapy on doctors’ orders were removed from the final analysis. The patients scored a mean of 6.84 (±0.66) and a median of 7.75 on the Morisky Scale. Using the mean as a cutoff, 38% of the patients were non-adherent to their medications including 6 who had discontinued therapy for reasons other than doctors’ orders. The level of protection motivation showed a significant positive correlation with the adherence scale (r=0.310). Multiple regression revealed that Coping Appraisal was a better predictor of adherence (β=0.437), while Threat Appraisal did not show a significant correlation. Pearson’s Correlation revealed that Self Efficacy (r=0.485) and Response Efficacy (r=0.206) showed a positive correlation with adherence while Response Cost (r=−0.235) showed a negative correlation. A second multiple regression showed that Self Efficacy was the only significant predictor of adherence (β = 0.429). Other factors attributing to lower adherence were younger and older age, not being married, insurance status (private insurance and Medicare), lower income and presence of more than 3 comorbid conditions.

Conclusion: The results of the study indicate that Protection motivation theory was somewhat useful to explain adherence to Aromatase Inhibitor in breast cancer patients.
Thank you, Mom, Dad and my sister, Nabaruna for being a constant source of support even when we are miles apart. You motivate me to be my very best. Special thanks to all the breast cancer survivors for inspiring me. This is for you all…
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As I reflect on the last two years, I take this moment to thank and express my gratitude to the people who have been instrumental to this project. It has indeed been a journey from the inception of the idea to the final form that is presented before you. First and foremost, I give many thanks to God Almighty for His presence in my life and showering me with his love and blessings.

I would like to start by acknowledging all the breast cancer survivors who have taken the time to fill out my survey. I would also like to thank Dr. Iman Mohamed for allowing the project to be carried out at her clinic and providing partial funds for the project. Dr. Hameed, thank you for your help acquiring the data from the cancer registry a smooth process. A special thanks to Dr. Steve Martin for believing in me and providing me funds to carry out this project. I would also like to thank all the staff at the cancer center especially Colette Gaba and Tiffany Robinson for their effort to make sure everything proceeds smoothly.

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CHAPTER ONE: INTRODUCTION

Background

According to the World Health Organization (WHO), “Adherence” is defined as the “extent to which a person’s behavior, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.” Adherence to medication has been chronicled as a major barrier to successful interventions with drug therapy. The average rate of adherence in United States is about 50%. It has been reported that 33% to 69% of the hospital admissions in the United States are due to medication non-adherence. The cost of medication non adherence was estimated to be around $177 billion annually. This study is an evaluation of adherence to oral adjuvant hormonal therapy in patients having breast cancer and the factors affecting adherence using a patient reported outcome questionnaire.

The Center of Disease Control and Prevention (CDC) reported that, in 2007, in the United States approximately 207,090 women were diagnosed with breast cancer while 39,480 of total deaths in that year were attributed to breast cancer. It has been identified as the second leading type of cancer diagnosed in women. Not only is it the most prevalent type of cancer, it also places a heavy economic burden on the society and patients. A review of studies dealing with the economic burden of breast cancer revealed that the average out of pocket costs for a patient to treat breast cancer ranges from $300 to $1,180 per month during active treatment and was about $500 per month 1 year after
Treatment options for breast cancer include surgery, radiation therapy, hormone therapy, chemotherapy and targeted therapy. In this paper, I will focus mainly on hormonal therapy, which includes two classes of drugs, mainly tamoxifen, a selective estrogen receptor modulator and aromatase inhibitors like anastrazole and letrozole among others. These drugs have gained great importance and attention in recent years essentially as adjuvant therapy. Clinical trials have established their efficacy as maintenance drugs and improving survival of the patients by preventing recurrence of cancer. These drugs are usually administered in the form of a chronic regimen for 3 to 5 years in non-metastatic breast cancer patients who show the presence of estrogen and progesterone receptor in the cancer cells. As with any chronic regimen, the literature has revealed that adherence to therapy is a major issue in these classes of drugs, thus interfering with the disease prognosis. This problem is further complicated by the severe side-effect profile of these drugs ranging from cardio-vascular to gynecological problems which can deter patients to comply with the prescribed regime.

A review of the studies conducted in women with breast cancer revealed that adherence to these hormone therapies range from 55% to 93%. The most alarming trend in this research is the decreasing level of adherence as the therapy progresses and discontinuation of hormone therapy before the completion of the regimen. Discontinuation and non-adherence may increase chances of mortality in women due to remission of the cancer. Most of these studies deal with analysis of the pharmacy and other administrative databases to measure the medication possession ratio (defined as the ratio of the total of days’ supply divided by the index period) and to identify the
predictors of low adherence or non-adherence.\textsuperscript{15-21} The main criticism of this methodology is that it does not take into consideration the complete medication taking behavior (especially the psycho-social predictors of adherence) among patients.\textsuperscript{22}

A few researchers studying medication adherence in breast cancer have attempted to document patients’ attitudes and beliefs regarding their medication to evaluate their adherence to cancer therapies.\textsuperscript{23-26} With the exception of one study, these studies either lacked a theoretical framework or failed to identify one. A study conducted in United Kingdom used the decisional balance concept of the Trans-theoretical model to explain this behavior.\textsuperscript{26} However, due to the difference in the background, settings, and health care systems, the results of this study may not be able to be generalized to patients in the United States.

In the past, many studies have successfully explored the use of various behavioral theories to explain this particular behavior as it relates to other diseases. These comprehensive theories have the advantage of giving a holistic picture of any behavior, taking into regard patients’ attitudes, beliefs and other psychosocial aspects across several ecological levels to explain why an individual would behave in a certain way. The most commonly used theories include health belief model\textsuperscript{27, 28, 29, 30, 31} and the theory of reasoned action/ theory of planned behavior.\textsuperscript{32, 33, 34, 35} World Health Organization has identified a multi-dimensional theory called the “Medication Adherence Model”, which incorporates various constructs from the existing health behavior theories.\textsuperscript{1}

Protection Motivation Theory (PMT) is one such behavioral theory, which explains the cognitive processing of fear. The theory devised by Rogers et. al. suggests that people may be motivated to change their behavior if presented with a threat.\textsuperscript{36}
According to this theory, a person’s motivation to perform a recommended health behavior is influenced by his threat appraisal and coping appraisal. The threat appraisal is the cognitive processing of fear and is comprised of two components namely, the individual’s perceptions of the severity of the threat (perceived severity) and the individual’s perceptions of his vulnerability to the threat (perceived vulnerability). The coping appraisal is the process by which an individual copes with the threat, or the appropriate response behavior. This process includes three components mainly, the individual’s perceptions about the effectiveness of the response behavior (response efficacy), the individual’s perceptions about the tangible and intangible costs and disadvantages of carrying out the behavior (response cost) and the individual’s power to carry out the required behavior (self-efficacy). The PMT suggests that a higher threat appraisal and higher coping appraisal will lead to higher protection motivation or motivation to change behavior to avoid the threat which will result in adoption of the protective or response behavior. This study will incorporate the protection motivation theory to evaluate patients’ adherence to adjuvant endocrine therapy.

**Problem Statement**

Review of the literature suggests that many breast cancer patients exhibit low levels of adherence adjuvant hormonal therapy as the therapy progresses. This may cause these patients to experience a higher risk breast cancer recurrence. There is a lack of understanding of the factors associated with low adherence amongst these women.
Need For The Study

The severity of breast cancer would ideally motivate a patient with the disease to be adherent to their medication regimen. However, studies of the real world data suggests otherwise. The review of the pertinent literature shows that there is a gap in understanding the various psychosocial aspects that contribute to this non-adherence and early discontinuation of hormonal therapy amongst breast cancer patients. This suggests the need for this study, which aims to utilize various constructs of the protection motivation theory to evaluate current adherence in patients with breast cancer.

Significance

This study will incorporate the Protection Motivation Theory developed by Rogers et.al. modified slightly in order to evaluate the patients’ beliefs and attitudes regarding taking their medications. The findings from this study will help to identify factors associated with poor adherence. This will in-turn help health care providers to design suitable interventions so as to encourage patients with breast cancer to be adherent to their adjuvant endocrine therapy regimen.

Goal

To assess adherence to aromatase inhibitors and identify the factors affecting suboptimal adherence using the Protection Motivation Theory in patients with breast cancer.
Objectives

1. To assess adherence to aromatase inhibitors amongst patients with breast cancer.
2. To examine the relationships that exist among the variables described in the model.
3. To identify predictors for adherence to aromatase inhibitors.

Research Questions and Hypotheses

1. What is the pattern of adherence to aromatase inhibitors amongst patients with breast cancer?
2. How do the different variables described in the model relate to each other?
   
   Null hypothesis #1: There are no significant relationships between the variables described in the model.
   
   Alternate hypothesis #1: There are significant relationships between the variables described in the model.
3. What are the significant predictors of adherence to aromatase inhibitors?
   
   Null hypothesis #2: After controlling for all the external factors, the constructs of the PMT do not predict the patients’ level of adherence.
   
   Alternate hypothesis #2: After controlling for all the external factors, the constructs of the PMT significantly predict the patients’ level of adherence.
CHAPTER TWO: LITERATURE REVIEW

This chapter gives an overview of the existing literature in the area of breast cancer and medication adherence.

Breast Cancer

Breast cancer is the cancerous growth of the epithelial cells that are present in the ducts and the lobules in the breast. It can occur in men, but the number of cases is very low. Hence, in this paper we will restrict the topic of our discussion to breast cancer in women.

Risk Factors

Several risk factors for breast cancer have been identified in women. According to the American Cancer society, some of the risk factors for breast cancer include older age, history of breast cancer, exposure to radiation during treatment, family history of breast cancer, lack of physical activity, obesity, and alcohol. Certain genetic changes especially in the BRCA1 or the BRCA2 gene mutation is a considerable risk factor for acquiring breast cancer. History of taking diethyl-stilbesterol (a drug that was given to prevent miscarriage in women during the 1970’s) is another predictor for increased chances of acquiring breast cancer. Early onset of menstrual cycle (before the age of 12 years), late menopause (after the age of 55 years) and reproductive history (like having no biological
child or having the first child after the age of 30 years) are also risk factors for developing breast cancer in women.\textsuperscript{37}

\textit{Epidemiology}

CDC reports suggest that breast cancer is one of the leading types of cancer that is diagnosed and the second leading cause of cancer related death among women in the United States.\textsuperscript{7} It is estimated that approximately one in eight women would be diagnosed with breast cancer based on a lifetime risk starting from her birth discounting her current age. The lifetime risk of a 30-year old woman to develop breast cancer is 123 per 1,000 women.\textsuperscript{38} According to the CDC, in 2007, an estimated 207,090 women were diagnosed with breast cancer, while 39,480 of total deaths that year were due to breast cancer.\textsuperscript{7}

\textit{Economic Burden}

Apart from being the most prevalent type of cancer, breast cancer places a huge economic burden the disease on the patient and society as a whole. A study to estimate the economic burden of metastatic breast cancer was conducted in 2004 on the Medicare population of the United States by Rao et.al. The population was mostly comprised of women over the age of 65 years. He calculated the direct medical costs associated with treating breast cancer in this population and estimated that the mean cost per patient over a 16 month period was approximately $35,164.\textsuperscript{39}

A synthesis of the cost of illness studies conducted for breast cancer revealed that approximately $4.2 billion per year was attributed to direct medical costs for treating breast cancer in the United States. The review also showed that there was a lack of studies detailing the societal and various other indirect costs attributed to treating breast
cancer. Another systematic review estimated that the mean out of pocket costs in women being treated for breast cancer ranged from $300 to $1,180 per month during active treatment, and approximately $500 per month one year after diagnosis. These were direct medical costs while direct non-medical costs ranged from $137 to $174 per month during active treatment and $200-$509 per month one year or more after diagnosis.

Staging of Breast Cancer

The different stages of the cancer are used to describe the size of the tumor and the extent to which the cancer has spread in the body and is hence determined based on the following criteria: a) whether the cancer is invasive or not, b) number of lymph nodes involved, c) whether the cancer has spread to other parts of the body.

The most common system used to describe the stages of breast cancer is the one developed by the American Joint Committee on Cancer (AJCC) known as the TNM system. According to this system, each tumor is classified using the following nomenclature:

- T followed by a number from 0 – 4 stands for tumor size,
- N followed by a number from 0 – 3 indicates if the tumor has spread to axillary lymph nodes near the breast and
- M followed by 0 or 1 indicates whether the tumor has metastasized or spread to distant organs.

Hence, the size of the tumor, the degree of spread of the tumor to other lymph nodes and metastasis to distant organs forms the basis of this classification. The cancer is classified into 9 stages from Stage 0 to Stage 4 with Stages 1, 2 and 3 having many sub-
divisions. Stage 0 is called ductal in situ carcinoma (DCIS) where the tumor is confined within the duct and the lobule of the breast. The cancer is classified as Stage 4 when the tumor has metastasized to distant organs such as the lungs, bone, liver, brain and others. This information is then used to determine the stage of the cancer which in turn determines the type of treatment that should be administered to the patient.\textsuperscript{40}

The odds of survival of the patient decrease as the later the stage of diagnosis of the cancer. According to the research by Bland et.al. the 10 year survival rate for patients in Stage 0 of the cancer is 95%, with survival rate decreasing at each successive stage and lowest being 7% in Stage IV of the cancer when the cancer is metastatic in nature. The following is the stage-wise 10-year survival rate as reported after the analysis of the data from the patients diagnosed of breast cancer in the year 2001 and 2002 National Cancer Database.\textsuperscript{41}

\textit{Table 1: 10-year survival rate of breast cancer patients diagnosed in 2001 and 2002 by stage in the United States.}

<table>
<thead>
<tr>
<th>Stage of cancer</th>
<th>10-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>95%</td>
</tr>
<tr>
<td>Stage I</td>
<td>88%</td>
</tr>
<tr>
<td>Stage II</td>
<td>66%</td>
</tr>
<tr>
<td>Stage III</td>
<td>36%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>7%</td>
</tr>
</tbody>
</table>

\textit{Source: Adapted from Bland et.al.\textsuperscript{41}}
Intrinsic Subtypes of Breast Cancer

The tumor is also classified according to the presence or absence of certain markers and receptors or binding sites for certain hormones. This type of classification forms the basis for decisions about administering targeted therapy. Certain tumors have increased expression of receptors or binding sites for the hormones, estrogen and progesterone. These tumors require the presence of these hormones for their proliferation. Estrogen and progesterone is normally required by the mammary cells for its normal proliferation. Increased expression of the binding site or receptor results in increased entry of these hormones into the cells. This leads to increased proliferation of the cells which throws the cells out of the normal cell cycle.

Another marker usually found in these cells is the HER2/neu protein. HER2 stands for Human Epidermal Growth Factor Receptor 2 and is a protein usually found in cells, which under normal conditions this protein initiates the process of cell growth. Under abnormal circumstances, this protein is expressed in the form of HER2/neu protein, which is an abnormal protein. Over-expression of this abnormal protein in the mammary cells leads to cancer via uncontrolled division of these cells.

Based on the presence or absence of these markers, breast cancer is classified into the following five categories:

1) Basal-like: in this type of breast cancer, the cancer cells do not express any of the three receptors (estrogen receptor (ER), progesterone receptor (PR) or the HER2/neu (HER2) protein). Hence the tumors are ER-/PR-/HER2- or triple negative.
2) Luminal A: in this case, the cancer cells express estrogen receptor and are hence ER+ and/or PR+ tumors but are of low grade because of higher density of receptor present on the tumor.

3) Luminal B: in this case, the tumor cells are ER+ and/or PR+ but are more aggressive than the A-type as they have lower number of the said receptors on the tumors.

4) HER2/neu enriched: this is a more aggressive type of cancer due to the presence of HER2/neu protein. Advances in medicine have made it possible to achieve better outcomes with this type of tumor.

5) Normal Breast Like: these tumors have characteristics that are similar to the normal breast tissue. This classification is based on the gene expression profile of the cells and is done using DNA microarray technologies. Recent studies have shown that the receptor status and the gene expression profiling is a good indicator of the risk of metastasis, relapse free survival and overall survival of the patients. These gene expression profiles also provide a good strategy to select patients who would benefit from the different types of adjuvant therapies, such as chemotoxic therapy, hormone therapy, and targeted therapy.

Treatment options

Treatment decisions for breast cancer are based on the stage of the disease and presence or absence of hormone receptors and abnormal proteins. Treatment options include surgery, radiation therapy, hormone therapy, chemotherapy and targeted therapy and are broadly classified into two major subgroups: local and systemic therapy.
Surgery and radiation therapy are mostly used to remove the tumor from the breast tissues and are types of local therapy. Hormone therapy, chemotherapy and targeted therapy are systemic therapies used to control the spread of the cancer throughout the body.

Chemotherapy includes therapy with general antineoplastic drugs such as alkylating agents, antimetabolites and others aimed at killing the cancer cells in the system. Trastuzumab is a recently developed drug which is used to treat HER2/neu protein enriched breast cancers. It is a type of monoclonal antibody which specifically targets the HER2/neu proteins on the cells killing the cancer cells. Hormone therapies are used in women who show the presence of estrogen receptors in the cancer cells. In this case, the cancer cells require the presence of the hormone estrogen for its growth and proliferation. Hormone therapies are targeted to block the action of this hormone or stop the production of this hormone.\textsuperscript{10,37} Since both Trastuzumab and the hormonal therapies specifically target the cancer cells leaving the normal body cells intact, they are also called as targeted therapy.\textsuperscript{11} For the purpose of this study, our discussion will be limited to these aromatase inhibitors, which are a type of hormone therapy.

**Hormonal Therapy**

Hormone therapy is usually used as adjuvant therapy following a surgery or treatment with radiation to limit the spread of any residual cancer cells.\textsuperscript{11} Hormone therapies fall under two categories a) selective estrogen receptor modulator (SERM) and b) aromatase inhibitor (AI).\textsuperscript{10,37,46} Presented below is a brief discussion about these drugs.
Mechanism of Action

Tamoxifen is the first kind of hormonal therapy that was approved by the United States Food and Drug Administration (USFDA) in 1977. It is effective both in post and pre-menopausal women and is a type of Selective Estrogen Receptor Modulator (SERM). Once in the body, tamoxifen competes with estrogen to bind to the estrogen receptor on the tumor cells blocking the binding of estrogen to these receptors. It also exerts a partial estrogen antagonistic effect on the breast tissues.

Aromatase inhibitors (AI) like Anastrazole and Letrozole on the other hand act by inhibiting the action of the cytochrome enzyme, known as aromatase. This enzyme, aromatase, is responsible for the aromatization of androgens present in the body to form estrogen. Inhibition of this enzyme limits the production of estrogen and hence the proliferation of the cancerous breast tissues. Aromatase Inhibitors were developed during the 1980’s and the early 1990’s from aminogluthethimide, originally an anticonvulsant which showed some antiestrogen activity. This was followed by the 1st, 2nd and 3rd generation Aromatase Inhibitors in the order they were developed. Aromatase Inhibitors are of two types: Type1 and Type 2 Aromatase Inhibitors. Type 1 Aromatase Inhibitors are steroidal in nature and bind irreversibly to the enzyme, aromatase. An example of a 3rd generation Type 1 Aromatase Inhibitor is exemestane. Type 2 Aromatase Inhibitors are non-steroidal in nature and bind reversibly to the enzyme, aromatase. Examples of 3rd generation Type 2 Aromatase Inhibitors are anastrazole and letrozole. Anastrazole was the first Aromatase Inhibitor that was approved for use by the USFDA.
Figure 1: Mechanism of Action of Aromatase Inhibitors and Tamoxifen

Source: Smithe et al. 200348

Clinical Efficacy and Treatment Regimen

The first clinical trial for Tamoxifen was held in 1971 in which, out of the 46 patients in the treatment group, 10 showed a good response. In 1998, the Early Breast Cancer Trialists Collaborative Group (EBCTCG) obtained information on 55 randomized clinical trials conducted worldwide to prove the efficacy of tamoxifen and performed a meta-analysis. The trial compared outcomes for patients who were on adjuvant tamoxifen
monotherapy for 1 year, 2 years and 5 years with patients who were not on any kind of tamoxifen therapy. They found significant reduction in recurrence and mortality in each of the cohort. For patients on a 1 year therapy, the reduction of recurrence and mortality during the 10 year follow up period was 21% and 12% respectively. Patients on a 2 year trial reported a 29% reduction of recurrence and 17% reduction in mortality while those on a 5 year therapy reported 47% reduction of recurrence and 26% reduction in mortality due to breast cancer during the 10 year follow up period.\textsuperscript{11}

Since its approval in 1977, tamoxifen was considered the “gold standard” of care for women with breast cancer for many years. It was found effective in the treatment of breast cancer in both pre and post-menopausal women. The advent of aromatase inhibitors revolutionized the treatment of Estrogen Receptor (ER) positive breast cancer in postmenopausal women. Various clinical trials proved that it was more efficacious than tamoxifen in treating breast cancer in postmenopausal women. However, Aromatase Inhibitors are not effective in premenopausal women. This is due to the increased secretion of gonadotropins due to the negative feedback system.\textsuperscript{10}

A meta-analysis of randomized trials of Aromatase Inhibitors compared with monotherapy with tamoxifen in post-menopausal women found significant improvements in disease outcomes with Aromatase Inhibitors as monotherapy or as a sequential therapy after initial tamoxifen therapy. It was found that, after 5 years of therapy with Aromatase Inhibitors, there was a 2.9% decrease in recurrence and a non-significant 1.1% decrease in breast cancer mortality when compared with 5 years of monotherapy with tamoxifen. After 5 years of sequential therapy (3 years of tamoxifen followed by Aromatase
Inhibitor) there was a 3.1% reduction in recurrence and 0.7% reduction in breast cancer mortality when compared to 5 years of monotherapy with tamoxifen.46

Based on these trials, tamoxifen is found to be most effective in pre-menopausal women11 and is hence considered as the treatment of choice for these women.13 The therapy should ideally be instituted for 5 years.11 In case of post-menopausal women, trials have shown that aromatase inhibitors as primary therapy for 5 years or after 2 to 3 years of therapy (sequential therapy) is considered as the treatment of choice by the American Society of Clinical Oncologists.13

Side-effects

Though proven to be clinically effective, hormone therapies have a varied side-effect profile, which should be taken into consideration when administering these therapies. These side effects differ by the type of therapy instituted (SERM or Aromatase Inhibitor).13 Side effects range from cardiovascular to musculoskeletal to gynecological problems.13 It has been found that Aromatase Inhibitors are associated with more cardiovascular side effects like ischemia, hypercholesterolemia and hypertension, while risk of developing venous thromboembolic events is higher with tamoxifen. Aromatase Inhibitors are also associated with increased loss of bone mineral density, fractures, osteoporosis, and arthralgia when compared to tamoxifen.13 Tamoxifen increases the risk of uterine cancer, benign endometrial pathologies, hysterectomies and vaginal dryness.13 Though both the types of agents make patients prone to experiencing hot flashes, incidence of hot flashes is lower with Aromatase Inhibitors than with tamoxifen. There are also reports of vaginal dryness and loss of libido as side-effects.13 The concerns
regarding the side-effects pose a challenge administering these therapies as side-effects are a leading cause of non-adherence amongst patients.²

**Medication Adherence**

This section will give a brief overview of the problem of medication non-adherence, its significance, causes and different ways to measure non-adherence. According to the World Health Organization (2003), “Adherence” is defined as the “extent to which a person’s behavior, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.” Over the years a lot of confusion has reigned regarding the use of an appropriate term to refer to this behavior of the patient.¹ The term “compliance” was used predominantly in the literature to refer to this behavior in the past. But these terms were criticized for signifying paternalism as it implied a passive behavior on the part of the patient. Hence the term “adherence” is currently being used as it signifies the importance of patient-provider relationship and collaboration in the corresponding behavior in the patient.²

**Measures of Adherence**

There are different ways to measure adherence. Measures of adherence usually fall under two categories: direct and indirect measures. Direct measures of medication adherence include measurement of the drug, its metabolites or a biological marker which may be added during formulation in blood or urine.²² Indirect measures include methods like performing pill counts, determining refilling of the prescriptions, patient self-reported
measures using different validated questionnaires, using electronic medication monitors, patients’ medication diaries.\textsuperscript{22} Though very accurate, direct measures lack feasibility of being used on a daily basis while the indirect measure lack reliability and accuracy.\textsuperscript{22} A recently developed method for measuring medication adherence includes using retrospective administrative databases to calculate medication possession ratio (MPR) and persistence.\textsuperscript{49} But these indirect methods are criticized due to their inability to capture the entire picture like medication taking behavior, that is, time the patient took the medication and following other instructions provided by the health care provider.\textsuperscript{22}

\textit{Self Reported Medication Adherence}

Another form of measuring medication adherence is via self-reports by patients through the help of validated instruments. These instruments may either be generic or disease specific.\textsuperscript{50} Some of the commonly used instruments include the Morisky Medication Adherence Scale\textsuperscript{51}, Brief Medication Questionnaire\textsuperscript{52}, Medication Taking Questionnaire\textsuperscript{53}. The Morisky scale, developed by Morisky et.al. is an eight-item questionnaire with dichotomous (yes/no) scoring system.\textsuperscript{54} The Brief Medication Questionnaire is a 9 item instrument developed by Svarstad et.al. with a dichotomous or Likert scale scoring system.\textsuperscript{52} The Medication Taking Questionnaire is a 12 item instrument developed by Johnson and Rogers and is scored on a dichotomous scale.\textsuperscript{53} The three instruments discussed above are generic instruments. Other than these, there are certain disease specific instruments.\textsuperscript{55-58}

One of the most commonly used questionnaire to measure self-reported medication adherence is the Morisky’s scale. This scale was originally developed as a 4-
item questionnaire er to assess patients' medication taking behavior *(see Appendix1)*. The items are rated on a dichotomous scale, with total scores ranging from 0 to 4 with 0 being highly non adherent and 4 being perfectly adherent. The internal reliability of the questionnaire was estimated to be 0.61.\textsuperscript{51} Four more questions were later added to the questionnaire making it an 8-item questionnaire. Three of these were rated on a dichotomous scale while one was on a 5-point Likert-type scale. The total scores ranged from 0-8 with the norm being that anyone who scored below a 6 was considered to have low adherence *(see Appendix 2)*. The internal reliability of the revised questionnaire was estimated to be 0.83.\textsuperscript{54} Hence addition of the 4 extra questions increases the reliability of the questionnaire.

*Significance of Adherence*

A vast body if literature shows the significance of optimal adherence to medication to be of prime importance in order to manage disease conditions. Low medication adherence often leads to worsening of the prevailing disease conditions, which ultimately leads to increased health care expenditures and costs.\textsuperscript{2} Low medication adherence is classified under preventable medication errors and it is estimated that each year approximately $100 billion is spent on treating these preventable medication errors, which partially explains the spiraling, and out of control increase in medical expenditure in the United States. \textsuperscript{59}
Contributing Factors

In the report on medication adherence to chronic diseases published by the World Health Organization, the author has identified five interrelated factors that affect medication adherence irrespective of the type of disease. These factors together constitute the medication adherence model, which is a multi-dimensional model compared of different health behavior theories. These factors include the socio-economic factors, health care team and system related factors, condition related factors, therapy related factors and patient related factors. Though, strong evidence is not established, poor socio-economic status, low literacy level, poverty, unemployment, lack of social support, high cost of medication and cultural beliefs about western medications constitute the social and economic factors of poor adherence to medications.

A good patient-provider relationship is crucial for enhancing medication adherence. Other factors related to the health system that predictor adherence include adequate reimbursement by health plans for the cost of medications, medication delivery system and access to medications, lack of knowledge about adequate self-management techniques and lack of effective interventions to improve medication adherence.

Condition related factors represent the characteristic of the patient due to his underlying disease or condition which affect his adherence to medications. These include factors such as level of disability (both physical and psychological), severity of the symptoms, co-morbid conditions like depression and others. Therapy related factors include factors that are related to the medications and the medication regimen such as the complexities of the medication regimen, duration of the treatment, side-effects, frequent changes in the regimen and treatment failure.
The patient related factors are related to the beliefs and perceptions of the patients about the disease and their expectations from the treatment regimen. Patients’ knowledge of the specific disease, their self-efficacy to deal with the disease and its outcomes, various illness-management behaviors employed by them, forgetfulness, anxiety about their disease and fear of recurrence, psychosocial stress, and low motivation are some of the examples that fall under this category.¹

**Medication Adherence in Patients with Breast Cancer**

The advent of hormone therapy have greatly improved the treatment outcomes for cancer patients.⁶⁰ However, as with any oral therapy, there is an associated challenge of suboptimal adherence in patients taking hormonal therapy. With the chronic nature of these drugs, there arises the need to monitor and find out reasons for non-adherence amongst the patients so that appropriate measures can be taken to ensure optimal adherence.⁶¹ Over the years, various researchers have attempted to study and document non adherence to these therapies which will be discussed in the following section.

**Non-adherence and early discontinuation**

Demissie et.al. were the first to study the pattern of adherence to Adjuvant HT in 2003. It was a prospective study with the purpose to identify predictors of adjuvant tamoxifen use, side-effects, and discontinuation. They followed 303 women followed for nearly 3 years. Of the 296 patients who responded to the telephone interviews, 189 (65%) used tamoxifen. Information about side effects was provided by only 166 patients. Hence total sample size was 166. Of these 26 people had discontinued therapy. Patients who were estrogen receptor–positive were less likely to stop taking tamoxifen during the
follow-up period, while and patients who experienced side effects were more likely to
stop taking tamoxifen. The side-effects which were associated with significantly higher
discontinuation rates were depression, nausea, vision problem and vaginal bleeding. Age,
primary therapy and other variables were not statistically significant.\textsuperscript{62}

Similar results were found in other studies analyzing adherence to or
discontinuance of tamoxifen. In 2003, Partridge et.al. analyzed the number of days
covered by prescriptions for Tamoxifen. They analyzed the prescription claims data
obtained from the patients enrolled at the New Jersey Medicaid or Pharmaceutical
Assistance to the aged and disabled program during the period 1990 to 1996. Analysis of
one year adherence to Tamoxifen revealed that only 77\% of the women had an adherence
level \(\geq 80\%\). In the cohort of patients who filled their first prescription in 1991, the mean
adherence in the first year was 83% with adherence decreasing to 50\% by the end of 4\textsuperscript{th}
year. Main significant predictor variables were age (older and younger women were at
higher odds of having low adherence), patients who visited an oncologist had
significantly higher adherence. The following graph shows the drop in adherence to
therapy in this cohort of patients.\textsuperscript{63}
Figure 2: Long Term Adherence to Adjuvant Tamoxifen Therapy in eligible patients from 1991 index cohort year.

Source: Partridge et.al., 2003. ⁶³

Lash et.al. followed 462 breast cancer patients from 1996-1999 in a prospective study, collecting data through interviews. They found a 31% of their patients had discontinued therapy through various time points. They used proportional hazards modeling to calculate crude risk ratio for discontinuation of Tamoxifen and found side effects and increased number of concurrent prescription medications as the significant predictors for discontinuation of therapy. ⁶⁴
Owusu et.al. followed a cohort of breast cancer patients who were diagnosed of cancer between 1990 and 1999 for 5 years after initial diagnosis. They reported that 49% of their patients had discontinued their medications before the stipulated 5 years of therapy. They also used Cox Proportionality Hazards modeling to find predictors of Tamoxifen discontinuance. Amongst the predictors used by them, significant ones included older age, higher number of co morbid conditions, indeterminate Estrogen receptor status. They also found that those patients who had breast-conserving surgery had a higher incidence of discontinuance versus those who had mastectomy.\textsuperscript{20}

Fink et.al. followed a cohort of 597 breast cancer patients for 2 years. They found that 17% of these patients had discontinued therapy within the 2 year follow up period. Of those who discontinued their therapy, 68% of them did so within the 1\textsuperscript{st} year of therapy. They found through their study that patients who had neutral or negative beliefs about the drug were more likely to discontinue taking the drug.\textsuperscript{65}

The first research to study the adherence pattern to adjuvant anastrazole therapy was conducted by Partridge et.al. in 2008. It was a retrospective data analysis of longitudinal claims data of two large health insurance plans obtained from MarketScan database to determine the Medication Possession Ratio (MPR), defined as the proportion of the days that the patient had medicines available to them over the observation period. They reported that the average MPR of the patients decreased from 84% in the first year to 72% in the third year while the proportion of women having MPR>80% increased from 26% in the first year to 40% in the second year. The following graph shows the change in adherence that was found in the study through three years.\textsuperscript{19}
Figure 3: Comparison of MPR and proportion of women who had MPR>80% over the three years.

Source: Partridge et.al., 2008

In 2010 Sedjo et.al. used the Market Scan database to assess one-year adherence to Aromatase Inhibitor and determine the risk factors for low adherence to Aromatase Inhibitor in post-menopausal women using a multivariate logistic regression model. The various significant risk factors observed were younger age, out of pocket payments > $30 per prescription, higher Charlson Comorbidity Index.
Few studies have looked at the problem of non-adherence from a behavioral aspect. Atkins et.al. in 2006 conducted a prospective study in UK to determine the prevalence and factors associated with non-adherence to medications in breast cancer patients through semi structured interviews. They reported that 55% of the patients in their sample population (N=131) were non adherent. They found that a low locus of control (internal and powerful others) had a significant effect on non-adherence. In 2008, Kirk et.al. conducted an Internet survey of breast cancer patients using open ended questions. They reported only 57.4% of the respondents (N = 333) claimed to have not missed a single dose of their meds. Treatment related side-effects, cost of medications, forgetfulness, were cited as some of the reasons for non-adherence.

Consequences of Non adherence or Early Discontinuation of Hormonal Therapies

A review of literature shows that adherence to hormonal therapies ranges between 53% to 93%. The most alarming trend is the decreasing adherence as the therapy progresses and discontinuance of hormone therapy before its completion. The problem of non-adherence is of major concern. Discontinuation and non-adherence may increase chances of mortality in women due to remission of the cancer.

Hershman et.al. used the Cox Hazards Proportionality ratio to analyze the risk of non-adherence and early discontinuation of adjuvant hormonal therapy on all-cause mortality in women with breast cancer. The researcher identified 8,769 breast cancer patients with a prescription for hormonal therapy through the Kaiser Permanente of North California database between 1996 and 2006. Analysis of their prescription claims showed that 31% of the patients had discontinued therapy while out of those who continued on
therapy, 28% were non adherent. An estimated 80.7% of the women who continued on therapy survived at 10 years versus 77.8% of women who discontinued. Of those who continued on therapy, survival at 10 years was 81.7% in women who were adherent and 77.8% in women who were non adherent. Hence both early discontinuation and non-adherence were independent predictors of mortality. Presented below is the Kaplan Meier Curve comparing 10 year survival in patients who continued versus who discontinued their hormonal therapy. The second curve compares survival time for patients who were adherent versus those who were non adherent to their hormonal therapy among women who continued on therapy.\textsuperscript{15}
Figure 4: Kaplan Meier Curve comparing 10 year Survival Rate amongst patients who discontinued vs. those who continued and those who were adherent and those who were non adherent.

Source: Hershman et.al., 2011. 15
Health Behavior Theories Used to Explain Medication Adherence

Various behavioral studies have been conducted using various behavioral theories or models to explain medication adherence in different disease states. But a single theory or model is not capable of painting the complete picture of the contributing factors for medication non-adherence. Hence, several multidimensional models were created for explaining medication adherence which will be presented later in this section.

**Health Belief Model (HBM) and Medication adherence**

The health belief model was born out of the research done by Rosenstock and Hochbaum concerning vaccinations and perception and beliefs held by people regarding the same. The model says that a patients’ behavior (health related) is governed by the following constructs: perceived susceptibility to a disease, perceived severity of the disease, perceived benefits of adopting the said behavior, barriers to treatment and demographic characteristics which were more of modifying factors. The application of health belief model is extensive in the field of health behavior and is probably one of the most widely used and the earliest model used to describe medication taking behavior.

Most of the studies used a validated Health Beliefs Questionnaire to capture the beliefs of the patient regarding their medication and disease, a validated Barrier’s Questionnaire to assess the perceived barriers of the patients and a Morisky’s 8-item questionnaire for self-reporting of medication adherence. Some of the exploratory studies used semi structured interview and focus groups as their methods.

Some of the early studies which used HBM reported conflicting results. They show that there is no significant difference in the beliefs of the patients with regards to their medication taking behavior in the adherent and non-adherent groups. For example,
a study done among hypertensive patients was done to find out the health beliefs of the patients classified in two groups, compliant and noncompliant using the standardized Health beliefs Questionnaire. Comparison of the two groups did not find any significant difference.⁴⁸

In a more recent study conducted in 2003, to assess the patients who showed high adherence to highly active antiretroviral therapy (HAART), the researchers used semi-structured qualitative interviewing methods. They found that the patients’ perception about the disease and the medication strongly influenced their behavior. Perceived susceptibility and severity of the disease and perceived benefits of taking the medications were positively correlated with the patients’ adherent behavior. A positive relation with the provider also showed positive correlation with the adherent behavior of the patient. Adherence was found to be higher in patients who had some form of social support.⁴⁹

A study conducted to find out the reasons for discontinuing medications in patients with a heart condition had some similar findings. Some of the barriers identified by the patients were, costs, side-effects, transportation for obtaining the medication, lack of reimbursement from the prescription benefits plan and inefficient patient-provider communication which created some degree of confusion regarding the medications. But the patients felt they were highly susceptible to the disease and that the disease was very severe. They also recognized the benefits of taking the medications.⁵⁰ Some of the other studies using self-reported validated questionnaires to assess medication adherence in AIDS patients found results along the same lines.⁵¹ In all these studies, barriers were the most predictive construct for medication adherence.
Theory of Planned Behavior and Medication Adherence

The theory of planned behavior developed by Ajzen and Fishbein suggests that a behavior is governed by intent to perform a behavior which in turn is governed by the attitude towards a behavior (beliefs and evaluation of outcome of beliefs), subjective norm (normative belief or beliefs of the significant ones and motivation to comply to these beliefs) and perceived behavioral control. Few studies have used the theory of planned behavior to assess the medication taking behavior of the patients. A brief description of the findings of these studies is presented below.

In 2003, Russell et.al. interviewed renal transplant patients regarding their medication taking behaviors using questions based on the theory of planned behavior to assess their behavior. The results suggested that the perceived advantages of adherence amongst the patients included feeling better, remaining off dialysis, remaining out of hospitals, reduced chances of rejection of organ, staying healthy for longer among others. Side effects were cited as the major disadvantage of using these medications. The subjective norm for these people comprised of beliefs held by the patients’ mother, family, friends, spouse, children and their colleagues. Some of the facilitators of adherence include organizing, tracking medication changes, using pill boxes, alarm, refill reminders, etc. Some of the barriers to adherence were recognized as forgetting to take their medication, having to adjust their routine according to their regimen, complex medication regimen among others.

A prospective study tested the theory of planned behavior to predict adherence to immunosuppressant therapy using a questionnaire. The results indicated that favorable attitudes and perceived behavioral control were predictors of intention to adhere to
medications while subjective norm was a relatively weak predictor. The theory in this case explained 41% of the variance in intention. Similar results were reported in a study done to assess the medication taking behavior in diabetes patients conducted in UK. The study found high correlation between positive behavioral beliefs and intention to adhere to medications as well as between normative beliefs and intention and control beliefs and intention. This exploratory study was a foundation for randomized controlled trial of an intervention to improve medication adherence in patients with type 2 diabetes based on theory of planned behavior and volitional action planning.

*Motivational Interviewing and Medication Adherence*

Most of the intervention regarding adherence have focused on improving the patients’ knowledge and improving their self-efficacy to manage their disease. But these strategies often focus on the basic assumption that individuals accept their condition and are ready to accept the treatment and are motivated to make the change and improve their condition. Such is not the case with everyone. A huge fraction of the people do not have the motivation for improving their condition and hence imparting knowledge to them and improving their self-efficacy would have no impact on their adherence. This calls for the application of the trans-theoretical model developed by Prochaska and Diclimente to classify patients into contemplators and non-contemplators. The two basic goals of motivational interviewing are to improve patients’ fundamental motivation to get the patient to adopt the recommended behavior and to resolve any doubts or confusion that the patient might have regarding the recommended behavior. The whole intervention is a process guided by the trans-theoretical model of behavior change.
Use of motivational interviewing and its subsequent success in improving patients’ adherence has been demonstrated by a few studies. A randomized controlled trial using motivational interviewing was used to measure its effect on adherence to hypertensive medications in African American population. The study was conducted in a community based setting and a hospital based setting. The patients were randomized to two groups a control group receiving only the standard care and an experimental group receiving standard care along with motivational interviewing. The group receiving motivational interviewing showed significantly increased adherence to medication than the control group which was assessed by Medication Event Monitoring System and self-reported Morisky’s scale. A similar study done to study the impact of motivational interviewing on glaucoma medications showed positive results.

A multidimensional approach to medication adherence

The individual theories are not enough to predict medication adherence or non-adherence. Hence various multidimensional theories are constructed to give a holistic picture of this complex behavior. One such study integrated the Health Belief Model, Theory of Planned Behavior and Self-Regulation Theory under the model, Dynamic Exchange Model for Medication Adherence Level and Comparison of Outcomes. The Medication Adherence Model is another multi-dimensional model that integrates the various existing behavioral theories into one. The main concept of this model includes the five interacting domains which influences medication adherence, mainly, socio-economic factors, health system related factors, condition-related factors, therapy-related factors and patient-related factors. A study done to test the validity of this model to the
medication adherence pattern in patients with heart failure revealed strong correlations between each of the abovementioned factors and medication adherence.\textsuperscript{73}

**Protection Motivation Theory**

The protection motivation theory was developed by Rogers et.al. to explain how individuals behave when faced with a threat. It is comprised of two major components the threat appraisal and the coping appraisal. A brief schematic for the theory is presented below:

![Protection Motivation Theory Diagram]

*Figure 5: Protection Motivation theory\textsuperscript{74,37}*

A meta-analysis of the studies done using protection motivation theory shows that there is a moderate correlation between the various constructs of the theory and the motivation
to comply with a particular behavior.\textsuperscript{75,76} This theory has been used by several researchers studying the health-related behaviors such as using sunscreen\textsuperscript{77,78}, getting vaccinated\textsuperscript{77} amongst others. Several researchers have successfully used this theory to explain and modify screening behaviors\textsuperscript{79,80} (for example getting mammogram screenings and genetic testing) and motivation to follow exercise regimen in breast cancer patients\textsuperscript{80}.

According to Rogers et. al. threat appeal fails if the necessary coping procedures are not present to help the individual cope with the presence of threat. As a result, the individual may adopt maladaptive practices which are contrary to the healthy behavior and may harm the patient’s health. According to Rogers, motivation to comply with protective behavior and ultimate adoption of the behavior is very low if the threat appraisal is high with very low coping appraisal. In this case, the person may go into maladaptive practices. If the threat appraisal is low with high coping appraisal the individual will have low motivation to adopt the behavior as he does not feel vulnerable to the health problem. Motivation to comply with the behavior is the highest when there is both a high coping as well as high threat appraisal. Fear motivates the person to adopt the behavior while the coping behavior and self-efficacy aids successful adoption of the behavior.\textsuperscript{37} The following figure helps to explain the theory.
Figure 6: Cognitive Processing of Fear\textsuperscript{74, 37}
CHAPTER THREE: METHOD

This chapter provides an overview of methodology used to conduct the study. The following topics will be discussed in this chapter: Study Population, Sampling and Power Analysis, Theoretical Framework, Instrumentation, Questionnaire Administration and Data Collection and Data Analysis.

Introduction

This is a cross-sectional study designed to assess adherence to adjuvant hormonal therapy amongst women having breast cancer who are receiving treatment at the University of Toledo Medical Center. Since the study involved collecting confidential patient data, approval for the same was obtained from the Institutional Review Board (IRB) at the University of Toledo. All the researchers involved in the project had obtained appropriate training for IRB human subjects research and Health Insurance Portability and Accountability Act (HIPPA).

Theoretical Framework

The theoretical framework for the study is a modified protection motivation theory which has been described earlier. The theoretical framework distinguishes two different kinds of factors that predict medication adherence: PMT variables and non-PMT
variables. The constructs of the PMT are the ones used in the original protection motivation theory as explained by Rogers et.al. According to this, two of the major factors that predict adherence to medications are threat appraisal and coping appraisal. Threat appraisal is comprised of two constructs, mainly perceived vulnerability to a recurrence of breast cancer and perceived severity if a recurrence of breast cancer were to occur. Coping appraisal is comprised of two constructs: beliefs about the efficacy over the cost (tangible and intangible) of the medications and self-efficacy to take the medications exactly as the doctor prescribed (this includes understanding the directions given by the doctors, ability to remember the directions and others).

The external factors for the framework were determined after reviewing the pertinent literature as discussed in the previous chapter. The socio-demographic factors include age, type of health insurance, race/ethnicity, marital status, type of pharmacy, number of concurrent prescriptions, side effects due to hormonal pills, co-morbid condition. The questions about tumor characteristics included years since initial diagnosis, stage of the cancer, type of primary therapy received, and recurrence of cancer.
Figure 7: Theoretical Framework for study
**Instrumentation**  
*(See Appendix 3)*

The survey questionnaire for this study was developed based on a comprehensive review of the literature based on medication adherence and breast cancer. It consists of the following sections:

1. **Your breast cancer medications**: The first eight questions measure the patients’ adherence to therapy. It is a Modified Morisky’s scale. The first seven questions are scored on a dichotomous scale. The eighth question is measured on a 5-point Likert scale. If a patient answers no she will receive a score of one while if he answers yes she will receive a zero score. Question 5 will be reverse coded for the final tally. The adherence was measured as a summation of the scores received on the Morisky Scale using the following formula:

   \[ \text{Adherence} = \sum \text{scores} \]

   Hence the patients will receive a maximum of 8 and a minimum of 0 on this scale. Questions 9 and 9.1 will be used to classify the patients based on whether they have continued or discontinued therapy. Those who have discontinued therapy will be categorized as non adherent patients. Question no. 9.1 will ascertain the primary reason for discontinuation of therapy. Patients who respond that they discontinued therapy because their doctor told them so, will be excluded from the sample.

2. **Perceptions about medications**: This section measures the patient’s beliefs about the response efficacy over response cost. The questions 10, 13, 19 and 22 measures response efficacy defined as the beliefs of the patient about the efficacy of their
hormone pills. They are rated on a 4-point Likert type scale ranging from strongly disagree to strongly agree. The response will be coded 1 to 4. Response Efficacy will be measured as a summated score of the above mentioned items. The potential range of this scale will be 4 to 16 with a higher score representing a higher level of response efficacy.

Questions 11, 12, 14, 15, 16, 17, 18, 12 and 20 measures response cost defined as the patients’s perceptions about the tangible and intangible costs and disadvantages of taking the hormone pills. They are rated on a 4-point Likert type scale ranging from strongly disagree to strongly agree. The response will be coded 1 to 4. Response Cost will be measured as a summated score of the above mentioned items. The potential range of this scale will be 4 to 36 with a higher score representing a higher level of response cost.

3. **Level of Self Confidence:** This section measures the patient’s level of self efficacy, defined as the individual’s level of confidence to obtain the medications on time, understanding the doctor’s directions and complying with them. This section comprises questions 23-26. They are rated on a 4-point Likert type scale ranging from very confident to no confidence. The response will be coded 1 to 4. Self Efficacy will be measured as a summated score of the above mentioned items. The potential range of this scale will be 4 to 16 with a higher score representing a higher level of self-efficacy.

4. **Side Effects:** They are rated on a 4-point Likert type scale ranging from major problem to no problem. The response will be coded 0 to 3. Inconvenience due to side-effects will be measured as a summated score of the above mentioned items. The potential range of this scale will be 0 to 27 with a higher score representing a higher level of the trait.
5. **Perceptions About Breast Cancer:** This section measures the patients’ perceived vulnerability and severity to a recurrence of breast cancer. Questions 36-40 measures the perceived vulnerability of the patients defined as the patients’ perception of the risk of a recurrence of breast cancer. They are rated on a 4-point Likert type scale ranging from strongly disagree to strongly agree. The response will be coded 1 to 4. Perceived Vulnerability will be measured as a summated score of the above mentioned items. The potential range of this scale will be 4 to 20 with a higher score representing a higher level of perceived vulnerability.

Questions 41-46 measures the patient’s perceived severity defined as the patient’s perception of the severity of a recurrence of breast cancer. They are rated on a 4-point Likert type scale ranging from strongly disagree to strongly agree. The response will be coded 1 to 4. Perceived Severity will be measured as a summated score of the above mentioned items. The potential range of this scale will be 4 to 24 with a higher score representing a higher level of perceived severity.

6. **Facts About You:** These are demographic questions and questions about tumor characteristics which constitute the external factors which have been included after an extensive literature review.

**Instrument Validation**

Face validity of the survey was established through a comprehensive review of the literature regarding medication adherence, Protection Motivation Theory, and breast cancer. A select group of patients from the Rupert Health Center reviewed the survey for its readability and aesthetics. Content validity was established by sending the
survey to a panel of experts who reviewed the structure of the questions and the validity of the questions. Suggested revisions from the expert panel were incorporated to improve the validity of the survey. A post hoc Principal Components Analysis with a Varimax rotation was performed to determine the construct validity of the survey. The results of the PCA were used to determine the specifics of the data analysis. How the theoretical items load on the constructs was assessed prior to analysis. The internal reliability of the survey was assessed by measuring the Crohnbach’s alpha for the survey. Stability reliability of the survey was established using a Pearson Correlation.

**Study Population**

Patients were recruited from the University of Toledo Medical Center. A mailing list of meeting the inclusion criteria in Dr. Iman E. Mohamed’s practice were generated from the University Cancer Registry. The inclusion criterion for being selected to participate in the study is that the patient should be diagnosed of breast cancer between 2007 and 2011 and should receive an aromatase inhibitor therapy. Any patient who has stopped taking their medications on doctor’s orders was excluded from the study as determined by their response to question no 9 and 10 on the questionnaire. Also patients who cannot read were excluded from the study. A total of 288 patients meeting the inclusion criteria were identified from the mailing list and were invited to participate in the project.
Sampling and Power Analysis

A power analysis using the G*Power software was done to ensure that the study had significant statistical power.\textsuperscript{81,82} To achieve 85\% power, for the Pearson correlations, a total of 32 respondents were required. The minimum sample size required for performing the t-tests was 146 to obtain a power of 85\%. Considering a conservative 50\% response rate, the survey will be mailed to double the number of required sample size (i.e. 292 patients) to ensure that the required sample size was achieved. A sample of 300 respondents is considered good for a factor analysis. Taking all of these into consideration, a census sampling technique will be used. All the women who are on aromatase inhibitor therapy present in the mailing list obtained from the Rupert Health Center will be invited to participate in the survey. Along with this, various other methods would be incorporated in the study to ensure maximum participation.

Data Collection

The survey was administered to the 288 breast cancer patients who met the inclusion criteria for the study (census sampling). The survey was administered via mail using a three wave mailing procedure to improve response rate. A copy of the survey on a light pink colored paper (for easy distinguishing) was enclosed along with a personalized hand signed cover letter explaining the purpose of the study in an envelope and a prepaid return envelope. These measures are taken to ensure high response rate. To further improve response rate, the mailing enclosed a one dollar bill as an incentive.\textsuperscript{83,84} The first wave of survey was sent out on August 7, 2012 followed by a second wave on August 27, 2012 and a third wave on September 16, 2012. The first 50 respondents were
sent an additional request along with another dollar bill to complete the survey for a second time for the purpose of testing the stability reliability of the survey.

The responses from the survey received were entered into SPSS spreadsheets version 19 on secure computers, which were password protected. The paper surveys will be stored for duration of two years, as per protocol in a secure location in the PCOR, in the University of Toledo, College of Pharmacy and Pharmaceutical Sciences. The data on the computer and the surveys can only be accessed by personnel who are authorized by the IRB and trained in HIPPA and IRB human subjects’ research training. The results of the study were presented as aggregates to ensure that privacy of the patients was maintained.

**Data Analyses:**

Simple descriptive statistics were performed to assess the patients’ level of adherence to aromatase inhibitors and patients’ level of protection motivation to adhere to their medications. Pearson correlation was used to measure the relationship between the PMT variables and adherence and the factors and protection motivation. One way ANOVA was used to compare the mean of the adherence across the various non-PMT variables. A multiple regression was conducted to assess whether the constructs of the PMT predicts adherence to therapy after controlling for the external factors.
CHAPTER 4: RESULTS

This chapter describes the results from the data analysis. The chapter will be discussed under the following headings: Response Rate, Missing Data Analysis and Data Imputation, Reliability and Validity of the Questionnaire, Description of the Study Population, Breast Cancer History, Side Effects Experienced By the Patients, Adherence to Aromatase Inhibitors, Protection Motivation Theory, Testing of Research Questions and Hypothesis, Summary.

Response Rate

The survey was sent out to 288 breast cancer survivors selected from the practice of Dr. Iman E. Mohamed at the University of Toledo Medical Center, Toledo, Ohio. A total of 20 surveys were not delivered or opened due to the following reasons: a) incorrect address or change in address (n = 17); b) death of the respondent (n = 3). Out of the remaining 268 patients, 145 responded, providing a response rate of 54.10%. Out of the 145 who responded, 7 were excluded from the analysis as they had stopped taking the drug on doctor’s orders. Hence final analyses were conducted on the data received from 138 respondents.
Validity Testing

Face validity and content validity of the survey were established prior to the data administration phase. After the data collection process was completed, a post-hoc Principal Components Analysis (PCA) was conducted on the data to establish the construct validity using Varimax rotation. The items from the sections of the survey thought to measure the various constructs of the PMT were included in the PCA: 1) Perception about medications, 2) Level of Confidence, 3) Perceptions about Breast Cancer. A forced extraction method was used. Any item with a loading below 0.40 was considered to be weak and was removed from the subsequent analysis. The sample size was adequate for the analysis as shown by the Kaiser-Meyer-Olkin measure of sampling adequacy (KMO = 0.747). There were no significant correlations among the factors suggesting the factors were independent. Table 1 shows the factor loadings for the specific items. The items in the table marked in red were removed from the analysis due to low factor loadings.
<table>
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</thead>
<tbody>
<tr>
<td>Perceived Vulnerability</td>
<td>39</td>
<td>Compared to other breast cancer survivors, my odds of having a return of breast cancer are low.</td>
<td>0.643</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>I feel vulnerable to a return of breast cancer at some point in life.</td>
<td>0.782</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>My chances of having a return of breast cancer are high.</td>
<td>0.813</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>My gut feelings tell me that I will NOT have a return of breast cancer.</td>
<td>0.752</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>There is a good chance that breast cancer may be developing again within my body.</td>
<td>0.761</td>
</tr>
<tr>
<td>Perceived Severity</td>
<td>37</td>
<td>If I were to have breast cancer again, it would hurt me financially.</td>
<td>0.566</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>Having a return of breast cancer would create severe problems for my loved ones.</td>
<td>0.743</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>Having another case of breast cancer would be life threatening for me.</td>
<td>0.617</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>If I were to have breast cancer again, the health consequences would be severe.</td>
<td>0.637</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>Developing breast cancer would be the worst thing that could happen to me.</td>
<td>0.580</td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>Having a return of breast cancer would have a bad effect on my quality of life.</td>
<td>0.722</td>
</tr>
<tr>
<td>Response Cost</td>
<td>11</td>
<td>Obtaining my anti-hormone pills puts a financial burden on me and my family.</td>
<td>0.200</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>I worry about the long-term effects of my anti-hormone pills.</td>
<td>0.727</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Taking my anti-hormone pills disrupts my lifestyle.</td>
<td>0.705</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>It is difficult for me to take my anti-hormone pills in exactly the way my doctor told me.</td>
<td>0.675</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>My anti-hormone pills probably do more harm to me than good.</td>
<td>0.848</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>Having to take my anti-hormone pills worries me.</td>
<td>0.798</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>My anti-hormone pills have too many negative side effects.</td>
<td>0.798</td>
</tr>
</tbody>
</table>
Table 2: PCA continued

<table>
<thead>
<tr>
<th>Construct</th>
<th>Item No.</th>
<th>Items</th>
<th>Factor Loadings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Efficacy</td>
<td>10</td>
<td>Without my anti-hormone pills, I would probably get breast cancer again.</td>
<td>0.734</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>My anti-hormone pills protect me from getting breast cancer again.</td>
<td>0.774</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>My anti-hormone pills are very effective at lowering my risk of having breast cancer again.</td>
<td>0.628</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>My anti-hormone pills work only if they are taken regularly</td>
<td>0.269</td>
</tr>
<tr>
<td>Self-Efficacy</td>
<td>21</td>
<td>Remember to take your anti-hormone pills every day.</td>
<td>0.757</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>Obtain your anti-hormone pills when your doctor prescribes them.</td>
<td>0.828</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>Follow your doctor’s orders for taking your anti-hormone pills.</td>
<td>0.843</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Take your anti-hormone pills even though it may disrupt your lifestyle.</td>
<td>0.810</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Take your anti-hormone pills even though you may experience negative side effects.</td>
<td>0.775</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>Obtain your anti-hormone pills even though they may be expensive.</td>
<td>0.692</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>Take your anti-hormone pills even though you may be taking additional medications.</td>
<td>0.806</td>
</tr>
</tbody>
</table>

* Items in red indicate the ones with weak factor loading which were removed.

The PCA revealed the following four factors guided by the PMT: 1) Perceived Severity, 2) Perceived Vulnerability, 3) Response Efficacy, 4) Response Cost and 5) Self Efficacy. These factors explained a cumulative of 60% variance in the responses and supported the validity of the scales for measuring the above mentioned dimensions. None of the items loaded on multiple components which showed that the items were one-dimensional in nature. Except for two items, all the other items loaded on the respective hypothesized scales. The validity of the Morisky Scale has been previously validated.54
1) Perceived Vulnerability

This factor was measured by the item numbers 39, 40, 41, 42 and 43 under the subsection “Perceptions about Breast Cancer” in the questionnaire. The factor loadings for these items were above 0.4 and hence were retained for subsequent analysis.

2) Perceived Severity

This factor was measured by the item numbers 37, 38, 44, 45, 46 and 47 under the subsection “Perceptions about Breast Cancer” in the questionnaire. The factor loadings for these items were above 0.4 and hence were retained for subsequent analysis.

3) Response Efficacy

This factor was measured by the item numbers 10, 12, 17 and 20 under the subsection “Perceptions about Medications” in the questionnaire. The factor loadings for the first three items were above 0.4 and hence were retained for subsequent analysis. But item no. 20, i.e., “My anti-hormone pills work only if they are taken regularly” showed a poor loading of 0.269 on the Response Efficacy scale. This may be due to the fact that compared to all the other items on this factor this is the only item that assess the efficacy of taking the medications regularly. The other items on this factor only assess the patients on their beliefs of whether the anti-hormone medications were efficacious in reducing their chances of breast cancer. Hence this item was removed from the calculation of the Response Efficacy scale.

4) Response Cost

This factor was measured by the item nos. 11, 13, 14, 15, 16, 18 and 19 under the subsection “Perceptions about Medications” in the questionnaire. The factor loadings for all the items except item no. 11 were above 0.4 and hence were retained for subsequent
analysis. The item no.11 i.e., “Obtaining my anti-hormone pills puts a financial burden on me and my family” showed a poor loading of 0.200. This item was hypothesized to predict response cost. The poor factor loading may be attributed to the improper phrasing of the item and the use of the conjunction “and”. This is an example of a double barreled question which should have been avoided. Also, all the other items within the same factor were directed at the patient and not the family members. This may explain the peculiar behavior of this item in the principal components analysis. For future research, we may consider rephrasing the item as “Obtaining my anti-hormone pills puts a financial burden on me.” This item was removed from the calculation of the Response Cost scale.

5) Self-Efficacy

This factor was measured by item nos. 21, 22, 23, 24, 25, 26 and 27 under the subsection “Level of confidence” in the questionnaire. All of these items loaded above 0.4 and hence were retained for the analysis.

Reliability Testing

The cronbach’s alpha was estimated for the entire survey as well as each of the subscales to establish the internal reliability of the survey and the subscales. Demographics were excluded from this estimation. A Cronbach’s alpha score of 0.7 is considered a generally acceptable cutoff for a reliable questionnaire. The Cronbach’s alpha for the entire survey was calculated at 0.814. The internal consistency for each of the subscales used in the survey also exceeded the 0.7 cutoff. The results of the reliability and the validity tests reveal that the survey was a strong and consistent survey which can
be used in future studies on a larger population. The internal reliability scores and the test retest reliability scores for each of the subscale are as follows:

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Internal reliability (cronbach’s alpha)</th>
<th>Test Retest Reliability (Pearson’s Correlation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morisky Scale</td>
<td>0.831</td>
<td>0.330</td>
</tr>
<tr>
<td>Perceived Severity</td>
<td>0.789</td>
<td>0.740</td>
</tr>
<tr>
<td>Perceived Vulnerability</td>
<td>0.828</td>
<td>0.683</td>
</tr>
<tr>
<td>Response Efficacy</td>
<td>0.782</td>
<td>0.795</td>
</tr>
<tr>
<td>Response Cost</td>
<td>0.835</td>
<td>0.338</td>
</tr>
<tr>
<td>Self-Efficacy</td>
<td>0.889</td>
<td>0.549</td>
</tr>
<tr>
<td>Side Effects</td>
<td>0.772</td>
<td>0.881</td>
</tr>
</tbody>
</table>

**Description of the Study Population**

Descriptive statistics revealed that the sample predominantly consisted of White Caucasians (90%; n=124) with only eight African Americans, three Hispanics and 2 Asians. The vast majority of the respondents (89%) were in the 50-79 age group, with 67% of the women who were married. One in three respondents had an educational background at or below high school graduate compared to 41% who had some college degree (which included college dropouts and associates degree holders) and 25% who were college graduates (4 or more years). Approximately 36% of the respondents had an annual income under $45,000; 32% of the respondents had an income between $45,000 and $70,000; and 24% of the respondents had income above $70,000. Nearly half of respondents (49%) had private health insurances only; and the other half (44%) had Medicare alone or along with a supplemental insurance plan. Only two of the respondents were uninsured and six respondents received healthcare through Medicaid.
Approximately 46% of the patients obtained their medications via a community pharmacy compared to 34% of the patients who got theirs through mail order, 6% through outpatient pharmacy and 12% through multiple sources. The majority of the sample reported presence of one or more comorbid condition (56%) and were on multiple medications in addition to their aromatase inhibitor (92%). (Table 3)
<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less Than 40 years</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>40-49 years</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>50-59 years</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>60-69 years</td>
<td>66</td>
<td>48</td>
</tr>
<tr>
<td>70-79 years</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>Above 80 years</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td><strong>Level of Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school graduate</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>High School Graduate of GED</td>
<td>42</td>
<td>30</td>
</tr>
<tr>
<td>Some College</td>
<td>57</td>
<td>41</td>
</tr>
<tr>
<td>College Graduate</td>
<td>35</td>
<td>25</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>124</td>
<td>90</td>
</tr>
<tr>
<td>Black/African American</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Bi-racial</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>93</td>
<td>67</td>
</tr>
<tr>
<td>Single (never married)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Divorced</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Separated</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Widow</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td><strong>Annual Household Income</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 14,999</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>$15,000 - $24,999</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>$25,000 - $34,999</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>$35,000 - $44,999</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>$45,000 - $54,999</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>$55,000 - $64,999</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>$65,000 - $74,999</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>$75,000 - $84,999</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>$85,000 - $94,999</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>More than $95,000</td>
<td>22</td>
<td>16</td>
</tr>
</tbody>
</table>
Table 4 continued

<table>
<thead>
<tr>
<th>Variables</th>
<th>N =138</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insurance Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private Insurance</td>
<td>67</td>
<td>49</td>
</tr>
<tr>
<td>Multiple Insurances</td>
<td>42</td>
<td>30</td>
</tr>
<tr>
<td>Medicare</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Medicaid</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Uninsured</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Type of Pharmacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mail-order Pharmacy</td>
<td>47</td>
<td>34</td>
</tr>
<tr>
<td>Community Pharmacy</td>
<td>63</td>
<td>46</td>
</tr>
<tr>
<td>Multiple Pharmacies</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Outpatient Pharmacy</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Comorbid Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No comorbidities</td>
<td>52</td>
<td>38</td>
</tr>
<tr>
<td>Only one comorbid condition</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>2 comorbid conditions</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>3 or more comorbid condition</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td><strong>Number of Prescription Medications</strong></td>
<td>]</td>
<td></td>
</tr>
<tr>
<td>1-3 prescription medications</td>
<td>62</td>
<td>45</td>
</tr>
<tr>
<td>4-6 prescription medications</td>
<td>55</td>
<td>40</td>
</tr>
<tr>
<td>7 or more prescription medications</td>
<td>21</td>
<td>15</td>
</tr>
</tbody>
</table>

*Percentage calculated out of N=138. Percentage may not equal 100% due to non-response and rounding
*Total number under each category may not equal 138 due to non-response.

Breast Cancer History

Most of the patients in the study population were cancer free (71%). Only 12% ever had a recurrence of cancer. Only 2% (n=3) of the respondents were in their 1st year of diagnosis compared to 24% (n=33) who were on their 2nd year, 25% (n = 35) in their 3rd year, 18% (n = 25) in their 4th year, 18% (n=25) in their 5th year and 12% (n = 17) in their 6th year of diagnosis. Approximately 69% of the people had undergone both surgical and non-surgical therapy before starting their aromatase inhibitor therapy compared 20%
who had undergone only surgery and 10% who only received only non-surgical therapy. Non-Surgical primary therapies included radiation and chemotherapy. Of the 123 patients who had undergone surgery, 51% had a lumpectomy, 33% a mastectomy, and 6% both lumpectomy and mastectomy (Table 4).

Table 5: Breast Cancer History

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage of Cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Stage 2</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Stage 3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Stage 4</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Cancer Free</td>
<td>98</td>
<td>71</td>
</tr>
<tr>
<td><strong>Cancer Recurrence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>No</td>
<td>119</td>
<td>86</td>
</tr>
<tr>
<td><strong>Year Since Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>less than one year</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>more than 1 year but less than 2 years</td>
<td>33</td>
<td>24</td>
</tr>
<tr>
<td>more than 2 year but less than 3 years</td>
<td>35</td>
<td>25</td>
</tr>
<tr>
<td>more than 3 year but less than 4 years</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>more than 4 year but less than 5 years</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>more than 5 year but less than 6 years</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td><strong>Primary Therapy Received</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no primary therapy</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>non-surgical primary therapy</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>surgery only</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>both surgery and non-surgical therapy</td>
<td>95</td>
<td>69</td>
</tr>
<tr>
<td><strong>Type of surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>45</td>
<td>33</td>
</tr>
<tr>
<td>lumpectomy only</td>
<td>70</td>
<td>51</td>
</tr>
<tr>
<td>both Mastectomy and Lumpectomy</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>No surgery</td>
<td>15</td>
<td>11</td>
</tr>
</tbody>
</table>

*Percentage calculated out of N=138. Percentage may not equal 100% due to non-response and rounding
*Total number under each category may not equal 138 due to non-response.
Side-Effects Experienced by the Patients

The patients were asked to score each medication related side-effect on a scale of 0-3 which were summated to give a total score representing the inconvenience due to these side-effects for each patients. The summated score for side-effects ranged from 0 – 25 with higher score representing more inconvenience. The minimum score observed in the sample was 0 and the maximum was 25 with a mean of $8.93 \pm 0.15$ and a median of 9. The top three side-effects of medication reported by the patients as a source of inconvenience were fatigue or tiredness (75%), joint pain (71%) and hot flashes (67%). The other side-effects as a source of problem were: decreased sex-drive (57%), mood changes (50%), flushing (49%), loss of appetite (42%), vaginal dryness/bleeding (39%) and nausea and vomiting (14%). Table 5 gives a better breakdown of the inconvenience that was faced by the patients due to these side-effects.
<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Major Problem</th>
<th>Moderate Problem</th>
<th>Slight Problem</th>
<th>No Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Percentage (%)</td>
<td>n</td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>Hot Flashes</td>
<td>25</td>
<td>19</td>
<td>32</td>
<td>24</td>
</tr>
<tr>
<td>Fatigue/Tiredness</td>
<td>18</td>
<td>14</td>
<td>47</td>
<td>35</td>
</tr>
<tr>
<td>Joint Pain</td>
<td>37</td>
<td>28</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>Vaginal Dryness/Bleeding</td>
<td>12</td>
<td>9</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Decreased sex drive</td>
<td>23</td>
<td>17</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Mood changes</td>
<td>5</td>
<td>4</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Flushing (face feeling red and hot)</td>
<td>15</td>
<td>11</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>Loss of appetite/change in weight</td>
<td>11</td>
<td>8</td>
<td>22</td>
<td>17</td>
</tr>
</tbody>
</table>
Adherence to Aromatase Inhibitors

Adherence measured in terms of the Morisky scale was scored on a range of 0-8 with a higher score representing a higher adherence. The respondents scored a minimum of 0 and maximum of 8 on the scale with a mean of 6.84 (±0.66) and a median of 7.75. Any patient who had discontinued her medication was arbitrarily assigned a score of “0” on the Morisky scale. Six respondents had discontinued the medication due to reasons other than the doctors’ orders. These six respondents were classified as non-adherent. The mean was used as a cut-off point for adherence. Any patient who scored below the mean was classified as non-adherent while patients who scored above the mean were categorized as adherent. Six out of the 138 respondents had a missing response for the items in the Morisky scale and hence were classified as non-responders. Of the 132 approximately 38% (n = 51) were non adherent, including the six who had discontinued therapy while 62% (n=81) were adherent. The percentage of adherent and non-adherent women in each year is depicted in Table 6. The percentage of non-adherent women increased as the year since initial diagnosis increased with the maximum percentage of non-adherent women being reported among those who were in their 5th year since diagnosis. Figure 1 is a graphical representation of the trend of adherence as therapy progressed.
Table 7: Adherence to Aromatase Inhibitor

<table>
<thead>
<tr>
<th>Year Since Diagnosis</th>
<th>Non Adherent</th>
<th>Adherent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>less than one year</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>more than 1 year but less than 2 years</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>more than 2 year but less than 3 years</td>
<td>11</td>
<td>33</td>
</tr>
<tr>
<td>more than 3 year but less than 4 years</td>
<td>11</td>
<td>44</td>
</tr>
<tr>
<td>more than 4 year but less than 5 years</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td>more than 5 year but less than 6 years</td>
<td>8</td>
<td>53</td>
</tr>
</tbody>
</table>

*Percentage calculated out of total number of respondents in each category

Figure 8: Trend of Adherence with the progression of therapy
Protection Motivation Theory

The PMT constructs measured the breast cancer survivors’ threat appraisal and coping appraisal regarding breast cancer and taking the recommended medications. These constructs include perceived severity; perceived vulnerability; response efficacy; response cost; and self-efficacy. The items in the survey were used to measure each of these constructs. Table 7 and 8 shows the responses received to these items on the survey by the sample population followed by a brief description of each of the constructs.
<table>
<thead>
<tr>
<th>Construct/question</th>
<th>Agree</th>
<th>Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perceived Vulnerability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compared to other breast cancer survivors, my odds of having a return of breast cancer are low.</td>
<td>97</td>
<td>37</td>
</tr>
<tr>
<td>I feel vulnerable to a return of breast cancer at some point in life.</td>
<td>85</td>
<td>50</td>
</tr>
<tr>
<td>My chances of having a return of breast cancer are high.</td>
<td>50</td>
<td>82</td>
</tr>
<tr>
<td>My gut feelings tell me that I will NOT have a return of breast cancer.</td>
<td>77</td>
<td>56</td>
</tr>
<tr>
<td>There is a good chance that breast cancer may be developing again within my body.</td>
<td>44</td>
<td>85</td>
</tr>
<tr>
<td><strong>Perceived Severity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If I were to have breast cancer again, it would hurt me financially.</td>
<td>82</td>
<td>52</td>
</tr>
<tr>
<td>Having a return of breast cancer would create severe problems for my loved ones.</td>
<td>90</td>
<td>45</td>
</tr>
<tr>
<td>Having another case of breast cancer would be life threatening for me.</td>
<td>58</td>
<td>74</td>
</tr>
<tr>
<td>If I were to have breast cancer again, the health consequences would be severe.</td>
<td>68</td>
<td>64</td>
</tr>
<tr>
<td>Developing breast cancer would be the worst thing that could happen to me.</td>
<td>38</td>
<td>98</td>
</tr>
<tr>
<td>Having a return of breast cancer would have a bad effect on my quality of life.</td>
<td>82</td>
<td>53</td>
</tr>
<tr>
<td>Response Cost</td>
<td>Agree</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>-------</td>
<td>---</td>
</tr>
<tr>
<td>I worry about the long-term effects of my anti-hormone pills.</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Taking my anti-hormone pills disrupts my lifestyle.</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>It is difficult for me to take my anti-hormone pills in exactly the way my doctor told me.</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>My anti-hormone pills probably do more harm to me than good.</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Having to take my anti-hormone pills worries me.</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>My anti-hormone pills have too many negative side effects.</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Response Efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without my anti-hormone pills, I would probably get breast cancer again.</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>My anti-hormone pills protect me from getting breast cancer again.</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>My anti-hormone pills are very effective at lowering my risk of having breast cancer again.</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Self-Efficacy (How confident are you to...)</td>
<td>Very Confident</td>
<td>Less Confidence</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>N</td>
<td>Percentage (%)</td>
<td>N</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Remember to take your anti-hormone pills every day.</td>
<td>98</td>
<td>71</td>
</tr>
<tr>
<td>Obtain your anti-hormone pills when your doctor prescribes them.</td>
<td>103</td>
<td>75</td>
</tr>
<tr>
<td>Follow your doctor’s orders for taking your anti-hormone pills.</td>
<td>107</td>
<td>78</td>
</tr>
<tr>
<td>Take your anti-hormone pills even though it may disrupt your lifestyle.</td>
<td>90</td>
<td>65</td>
</tr>
<tr>
<td>Take your anti-hormone pills even though you may experience negative side effects.</td>
<td>79</td>
<td>57</td>
</tr>
<tr>
<td>Obtain your anti-hormone pills even though they may be expensive.</td>
<td>76</td>
<td>55</td>
</tr>
<tr>
<td>Take your anti-hormone pills even though you may be taking additional medications.</td>
<td>93</td>
<td>67</td>
</tr>
</tbody>
</table>

*Perceived Vulnerability*

Perceived vulnerability to a recurrence of breast cancer was measured using 5 items. The potential scores ranged from 5-20 with a higher score meaning a higher perceived vulnerability. In the sample population it was observed that the patients scored a minimum of 5 and a maximum of 20. The mean of the score was 11.70 (±2.97) and the median was 12. Based on the mean as a cutoff, it was observed that 47% (n=65) of the survivors in our sample had a higher perceived vulnerability to a recurrence of breast cancer compared to 43% who had a lower perceived vulnerability. Fourteen responses (10%) were removed from analysis due to incomplete data.
**Perceived Severity**

Perceived severity of a recurrence of breast cancer was measured using 6 items. The potential scores ranged from 6-24 with a higher score meaning a higher perceived severity. In the sample population, it was observed that the patients scored a minimum of 6 and a maximum of 24. The mean of the score was 15.61 (±3.53) and the median was 15. Based on the mean as a cutoff, it was observed that 44% (n=61) of the survivors in our sample had a higher perceived severity of a recurrence of breast cancer compared to 48% who had lower perceived severity. Eleven responses were removed from analysis due to missing data.

**Threat Appraisal**

Threat Appraisal was calculated as a summated score of the Perceived Vulnerability and Perceived Severity. The potential range of this score ranged from 11 to 44 with a higher score representing a higher threat appraisal. In our study, we observed that the survivors reported a minimum score of 13 and a maximum of 42 with the mean of the score being 27.24 (±5.03) and the median, 27. Based on the mean as a cutoff, it was observed that 35% of the patients considered themselves to have a higher threat appraisal compared to 50% who considered themselves to have a lower threat appraisal. Twenty responses (15%) were removed due to missing data.

**Response Efficacy**

Response efficacy was measured using 3 items with a potential range of 3-12, higher score representing a higher response efficacy. Of the 138 respondents, 16 (12%) had missing values and were excluded from the final calculation. The patients scored a minimum of 3 and a maximum of 12 on this item with a mean of 8.93 (±1.68) and a
median of 9. Based on the mean as a cutoff, it was observed that 62% (n=85) of the survivors had a higher belief in the efficacy of the medication compared to 26% who had a lower belief in the efficacy.

Response Cost

Response cost was measured using 6 items with a potential range of 6-24, higher score representing a higher response cost. Of the 138 respondents, 12 (9%) had missing values and were excluded from the final calculation. The patients scored a minimum of 6 and a maximum of 21 on this item with a mean of 11.48 (±3.22) and a median of 12. Based on the mean as a cutoff, it was observed that 52% (n=72) of the survivors had a more negative attitude to the medication and thus a higher response cost compared to 39% who had a less negative attitude.

Self-Efficacy

Self-efficacy to be adherent to the medication regimen was measured using 7 items with a potential range of 7-28, higher score representing a higher self-efficacy. Of the 138 respondents, 5 (4%) had missing values and were excluded from the final calculation. The patients scored a minimum of 17 and a maximum of 28 on this item with a mean of 25.6 (±2.94) and a median of 27. Based on the mean as a cutoff, it was observed that 60% (n=83) of the survivors had a higher self-efficacy towards the behavior compared to 36% who had a lower self-efficacy to be adherent to the medication.
Coping Appraisal

Coping Appraisal was calculated as Response Efficacy – Response cost + Self Efficacy. The potential range of this score ranged from 12 to 40 with a higher score representing a higher coping appraisal. In our study, we observed that the survivors reported a minimum score of 5 and a maximum of 34 with the mean of the score being 23.10 (±5.70) and the median, 24. Based on the mean as a cutoff, it was observed that 46% of the patients considered themselves to have a higher coping appraisal compared to 39% who considered themselves to have a lower coping appraisal. Twenty one responses (15%) were removed due to missing data.

Protection Motivation

Protection Motivation was calculated as a summated score of Threat Appraisal and Coping Appraisal. The potential range of this score ranged from 23 to 84 with a higher score representing a higher coping appraisal. In our study, we observed that the survivors reported a minimum score of 36 and a maximum of 69 with the mean of the score being 50.62 (±6.74) and the median, 50. Based on the mean as a cutoff, it was observed that 36% of the patients considered themselves to have a higher protection motivation compared to 40% who considered themselves to have a lower protection motivation. Thirty three responses (24%) were removed due to missing data.

Testing of Research Questions and Hypothesis

In this section each of the research questions and hypothesis will be tested under to examine the relationship between the variables.
Relationship between the PMT Variables and Adherence

In this section the relationship between the PMT variables and adherence (measured in terms of the Morisky scale) were examined. The relationship between each of the PMT variables (Perceived Vulnerability, Perceived Severity, Threat Appraisal, Response Cost, Response Efficacy, Response Cost, Self-Efficacy, Coping Appraisal, and Protection Motivation) and the adherence was assessed using Pearson’s Correlation. Weak positive correlation was observed between adherence and Protection Motivation (r = 0.310; p = 0.001). Weak positive correlation was observed between Coping Appraisal and adherence (r = 0.453; p = 0.000). The correlations between adherence and Protection Motivation and Response Appraisal were significant at an alpha level of 0.05. There was a non-significant weak negative correlation observed between Threat Appraisal and adherence (r = -0.054; p = 0.300).

The correlations between the individual constructs were also significant at the 0.05 alpha level except for Perceived Severity and Perceived Vulnerability. Weak positive correlation was observed between Response Efficacy and adherence (r = 0.206; p = 0.021). Weak positive correlation was observed between Self Efficacy and adherence (r = 0.485; p = 0.000). Weak negative correlations were observed between Response Cost and adherence (r = -0.235; p = 0.011). Though not significant, weak negative correlation was observed between Perceived Severity and adherence (r = -0.090; p = 0.189) and between Perceived Vulnerability and adherence (r = 0.16; p = 0.437).

Interaction between the PMT Variables

Perceived Severity showed a significant weak positive correlation with Perceived Vulnerability (r = 0.210; p = 0.019) and Response Efficacy (r = 0.238; p = 0.009).
Response Efficacy showed a significant weak negative correlation with Response Cost ($r = -0.195; p = 0.027$). There was a weak negative correlation between Response Cost and Self Efficacy ($r = -0.262; p = 0.005$). Threat Appraisal showed a significant weak positive correlation with Response Efficacy ($r = 0.179; p = 0.039$) and with Response Cost ($r = 0.189; p = 0.033$).

Relationship between Non-PMT Variables and Adherence

One way ANOVA tests were used to determine if there were any statistically significant differences in the mean of the adherence scale across the following non-PMT variables:

1. Age
2. Education
3. Race
4. Income
5. Insurance
6. Type of Pharmacy
7. Comorbid Conditions
8. Number of Prescription
9. Stage of cancer
10. Recurrence of cancer
11. Years since diagnosis
12. Type of primary therapy received
13. Type of surgery
Results from the One-way ANOVA revealed that there were significant differences in rate of adherence with respect to age; marital status; annual income; insurance status and comorbid conditions. It was observed that the breast cancer survivors in the age group of 60-69 years were the most adherent, followed by those below 59 years of age. Survivors over the age of 70 years were least adherent to their prescribed hormonal therapy. Married women were found to be more adherent than women who were either single or widowed or separated. Women with lesser household income were less adherent to their therapy. The results also revealed that women who had an annual income between $45,000 and $84,999 were more adherent than women who had an annual income above $85,000 but the difference between the two categories is very small.

Significant differences were also observed in the rate of adherence with respect to the comorbid conditions. It was observed that patients with one comorbid condition had the highest adherence, followed by those with two comorbid conditions. Patients with no comorbid conditions had the third highest adherence while patients with three or more comorbid conditions had the least adherence. The relationship between the Side-Effects score and adherence was established using a Pearson correlation. A non-significant weak negative correlation was observed between the two variables \( r = -0.133; p = 0.073 \).
<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean (±S.D.)</th>
<th>F-value</th>
<th>Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less Than 59 years (n = 33)</td>
<td>6.88 (±1.62)</td>
<td>4.611</td>
<td>0.004*</td>
</tr>
<tr>
<td>60-69 years (n = 63)</td>
<td>7.13 (±1.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above 70 years (n = 35)</td>
<td>6.42 (± 2.42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Response (n = 1)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level of Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High School Graduate(GED) or less (n = 45)</td>
<td>6.83 (±1.95)</td>
<td>0.063</td>
<td>0.939</td>
</tr>
<tr>
<td>Some College (n = 54)</td>
<td>6.78 (±2.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>College Graduate (n = 33)</td>
<td>6.93 (±1.60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian (n = 120)</td>
<td>6.84 (±1.88)</td>
<td>0.015</td>
<td>0.902</td>
</tr>
<tr>
<td>Other (n = 12)</td>
<td>6.77 (±2.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married (n = 88)</td>
<td>7.10 (±1.48)</td>
<td>5.314</td>
<td>0.023*</td>
</tr>
<tr>
<td>Not Married (n = 44)</td>
<td>6.30 (±2.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Annual Household Income</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 44,900 (n = 48)</td>
<td>6.06 (±2.68)</td>
<td>4.933</td>
<td>0.003*</td>
</tr>
<tr>
<td>$45,000 - $84,999 (n = 43)</td>
<td>7.41 (±0.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than $85,000 (n = 30)</td>
<td>7.27 (±0.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no response (n = 10)</td>
<td>6.77 (±2.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insurance Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicare (n = 18)</td>
<td>7.40 (±0.59)</td>
<td>3.321</td>
<td>0.007*</td>
</tr>
<tr>
<td>Medicaid (n = 6)</td>
<td>5.29 (±3.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private Insurance (n = 64)</td>
<td>6.92 (±1.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Insurances (n= 41)</td>
<td>6.82 (±2.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uninsured (n = 2)</td>
<td>6.88 (±0.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (n = 1)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type of Pharmacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mail-order Pharmacy (n = 43)</td>
<td>7.10 (±1.39)</td>
<td>1.439</td>
<td>0.215</td>
</tr>
<tr>
<td>Community Pharmacy (n = 61)</td>
<td>6.63 (±2.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient Pharmacy (n = 8)</td>
<td>7.22 (±1.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Pharmacies (n = 17)</td>
<td>7.06 (±1.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (n = 1)</td>
<td>7.00 (±0.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no response (n = 2)</td>
<td>3.88 (±4.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variables</td>
<td>Mean (±S.D.)</td>
<td>F-Value</td>
<td>Significance (p-value)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------</td>
<td>---------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>Comorbid Conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No comorbidities (n = 49)</td>
<td>6.74 (±1.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only one comorbid condition (n = 26)</td>
<td>7.54 (±0.81)</td>
<td>4.007</td>
<td>0.004*</td>
</tr>
<tr>
<td>2 comorbid conditions (n = 30)</td>
<td>7.19 (±1.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 or more comorbid condition (n = 20)</td>
<td>5.51 (±2.81)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no response (n = 7)</td>
<td>7.11 (±1.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of Prescription Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 prescription medications (n = 58)</td>
<td>6.93 (±1.68)</td>
<td>0.467</td>
<td>0.628</td>
</tr>
<tr>
<td>4-6 prescription medications (n = 53)</td>
<td>6.65 (±2.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 or more prescription medications (n = 21)</td>
<td>7.05 (±1.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage of Cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer Free (n = 92)</td>
<td>6.94 (±1.71)</td>
<td>0.825</td>
<td>0.534</td>
</tr>
<tr>
<td>Stage 1 (n = 18)</td>
<td>6.76 (±2.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2 (n = 8)</td>
<td>6.97 (±0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 3 (n = 2)</td>
<td>6.88 (±1.59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 4 (n = 7)</td>
<td>6.64 (±2.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no response (n = 5)</td>
<td>5.20 (±3.83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cancer Recurrence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 113)</td>
<td>6.76 (±1.93)</td>
<td>0.804</td>
<td>0.450</td>
</tr>
<tr>
<td>No (n = 16)</td>
<td>7.16 (±1.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no response (n = 3)</td>
<td>7.92 (±0.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Year Since Diagnosis</strong></td>
<td></td>
<td>1.197</td>
<td>0.314</td>
</tr>
<tr>
<td>less than one year (n = 3)</td>
<td>7.17 (±1.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>more than 1 year but less than 2 years (n = 33)</td>
<td>7.23 (±1.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>more than 2 year but less than 3 years (n = 33)</td>
<td>6.96 (±1.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>more than 3 year but less than 4 years (n = 25)</td>
<td>7.04 (±1.44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>more than 4 year but less than 5 years (n = 23)</td>
<td>6.18 (±2.57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>more than 5 year but less than 6 years (n = 15)</td>
<td>6.28 (±2.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary Therapy Received</strong></td>
<td></td>
<td>0.519</td>
<td>0.670</td>
</tr>
<tr>
<td>both surgery and non-surgical therapy (n = 92)</td>
<td>6.93 (±1.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>surgery only (n = 27)</td>
<td>6.75 (±2.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-surgical primary therapy (n = 12)</td>
<td>6.25 (±2.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no primary therapy (n = 2)</td>
<td>7.38 (±0.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type of surgery</strong></td>
<td></td>
<td>0.593</td>
<td>0.621</td>
</tr>
<tr>
<td>No surgery (n = 14)</td>
<td>6.41 (±2.39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lumpectomy only (n = 67)</td>
<td>6.82 (±1.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy (n = 43)</td>
<td>6.86 (±1.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>both Mastectomy and Lumpectomy (n = 8)</td>
<td>7.53 (±0.65)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Represents results which were significant at 0.05 α level
Predictors of Adherence

A multiple regression was performed with adherence (measured as Morisky Scale) as a dependent variable and the independent variables: Perceived Vulnerability, Perceived Severity, Response Efficacy, Response Cost, and Self-Efficacy using the enter method. The results indicated that the model used was statistically significant in predicting adherence ($R^2 = 0.258; F (10,122) = 6.536; p<0.001$). The variables used in the model predicted 25.8% of the variance in the Morisky Scale. The significant factor predicting the adherence was Self Efficacy ($\beta = 0.429; p<0.001$). A second multiple regression was performed to use the Threat Appraisal and the Coping Appraisal to predict the adherence to Aromatase Inhibitors ($R^2 = 0.437; F (2, 97) = 11.437; p<0.001$). Of the two predictors, coping appraisal was a stronger predictor of adherence ($\beta = 0.437; p<0.001$) while threat appraisal was not a significant predictor.
CHAPTER 5: DISCUSSION

This chapter provides a thorough discussion of the results of the study presented in the previous chapter along with the strengths and limitations of the study and some potential implication for practice and future research.

Discussion

The primary aim of the present study was to assess and explain adherence to aromatase inhibitor therapy in breast cancer patients. The Protection Motivation theory (PMT) developed by Rogers et.al. was used along with a few socio-demographic characteristics. According to this theory, a patients’ behavior could be predicted by her motivation to protect herself from a perceived risk by performing recommended health behaviors. Threat appraisal is defined as the patients perceptions, beliefs and attitudes towards the threat posed by the disease condition and comprises of two constructs, the Perceived Vulnerability to the disease and the Perceived Severity of the disease. The Coping Appraisal could be defined as the perceptions, attitudes and beliefs of the patients regarding the coping behavior. The Coping Appraisal comprises of the constructs Response Efficacy minus Response Cost or the patients beliefs about the efficacy over the cost of carrying out the behavior and Self-Efficacy of being able to comply with the coping behavior. Based on the theory, we hypothesized that in order for the patients to be
adherent to their Aromatase Inhibitor regimen, the patient should have a high threat appraisal regarding the threat of a recurrence of the cancer and a high coping appraisal regarding taking the Aromatase Inhibitor regimen.

Our sample was characterized by 38% of the population being classified as non-adherent to their Aromatase Inhibitor regimen using the mean of the Morisky Scale as a cut off. In fact, 6 of these patients had discontinued their medications for reasons other than doctor’s orders. The results from the data collected through this project revealed that the level of protection motivation was a significant predictor of adherence. The constructs of the theory that was a major factor attributed to low adherence in the population was a low coping appraisal. Threat appraisal was not found to be a significant factor. Other socio-demographic characteristics that were found to have a significant effect on adherence were age, marital status, income, insurance status and comorbid condition.

A systematic review of the studies assessing adherence to adjuvant therapy reported that adherence rates in breast cancer patients using aromatase inhibitors range from 50-91%. In a study conducted in Germany using a self-reported measure of adherence to adjuvant hormonal therapy, the researchers found a proportion of 33% of their study population was non-adherent to the medications. Most of the studies that analyzed long term adherence to aromatase inhibitors found that adherence decreased as the length of the therapy increased. This was consistent with the findings in the present study. In our data, we found a trend of decrease in the percentage of women who were adherent to the medication as the years since initial diagnosis increased. This may be explained by the fact that patients who have had the disease for a long time may have decreased frequency of visits with the physicians than patients in their initial stage of...
diagnosis. The decreased interaction with physicians maybe a reason for poor adherence in women who have had the disease for long. This is where other healthcare professionals can step in. A majority of the patients obtain their medications through community pharmacies. The pharmacists can check the refill rates of the patient to determine the patients who are not adherent and carry out interventions to improve adherence in these patients. Most of the breast cancer survivors belong to support groups and associations like the Susan G. Komen (national organization) or the Victory Center (local organization) which help them cope with their disease. A secondary focus of these support groups can be to improve adherence to medication in these cancer survivors.

This study is unique as it is the first one that utilizes a behavioral theory to explain the causes of poor adherence in patients with breast cancer. Behavioral theories like the Health Belief Model, Theory of Planned Behavior, Trans-theoretical model and Medication Adherence Model which have been explained in the literature review section has been used previously to study this behavior in other disease conditions. This is in fact the first ever study that has utilized the Protection Motivation Theory to study the factors affecting adherence to medication. The theory had been previously used successfully to explain motivation to adopt healthy behavior in cancer patients. Rogers et. al., Helmes et.al. and Milne et.al. in their respective studies, have successfully used the theory to explain motivation to undergo breast cancer screenings in women at a high risk.90-92

The results of the correlations and the multiple regression shows that the theory was somewhat applicable to study the factors affecting adherence to Aromatase Inhibitor therapy in breast cancer patients. Our study was characterized by significant correlations between the coping appraisal variables and the behavior. This is in accordance with
Rogers’ theory that in the absence of a coping method to counteract the threat posed by a health risk the patient tends to go into a maladaptive fear control process. However, contrary to the PMT, the correlation between the threat appraisal variables and behavior were not significant. This non-significant correlation may be due to the small sample size. Due to missing data, the final regression model was able to use data from 100 respondents who completed the entire survey.

In general, the sample in our study exhibited a lower perceived severity, perceived vulnerability and threat appraisal. This may be attributed to the fact that the majority of the respondents reported themselves to be cancer free. There were some interaction effect that was noted between the threat appraisal variable and response cost and response efficacy as well which might explain the non-significant relationship between adherence and threat appraisal. It was found that patients who had a higher threat appraisal had higher perceptions about taking the medications and lower perceptions about the cost and inconvenience of taking the medication. This shows that even in the presence of low threat appraisal, if the patients have a higher coping appraisal, they can be motivated to take the medications.

A positive correlation was observed between the response efficacy and adherence while the correlation between the response cost and adherence was a negative one. This finding indicated that a patient who believed in the efficacy of the medication and had a low perception about the psychological costs and inconvenience of taking the medication would be more likely to be more adherent to their Aromatase Inhibitor regimen. Beliefs about medications play an important role in the patients’ decision to be adherent or not as suggested in the adherence report published by WHO and replicated in many studies.
conducted by various researchers.\textsuperscript{93,94} As expected, it was seen that patients with a higher perceived response efficacy showed a higher adherence while patients with lower perceived response cost showed higher adherence. It was observed in our sample population that a positive belief about the efficacy of the medications is a predictor for improved adherence. This concept is reiterated by Procheska’s concept of decisional balance according to which a person makes a decision regarding adopting a new behavior after carefully weighing the pros and cons of adopting the new behavior.\textsuperscript{95}

Healthcare interventions and messages designed to empower the patients with appropriate knowledge about their medications can serve as an important step towards improved medication adherence. Patients should be encouraged to express their doubts or concern about their medications to their healthcare providers. Healthcare providers in turn should be able to mitigate the doubts and concerns of the patients by imparting appropriate knowledge and resources. The cost versus benefit of taking the medications should be explicitly explained to the patients so that they can make informed decisions.

Of the coping appraisal variables, self-efficacy has shown the strongest positive correlation with medication adherence with an effect size of 18.04\%. This shows that the patient is able to obtain their medication on time, follow the instructions, remember to take the medication on time and take the medication in spite of side-effects, they are more likely to be adherent to their medications. Bandura in his social cognitive theory emphasizes the role of self-efficacy to improve behavior modification and identified ways to improve self-efficacy.\textsuperscript{96} In our particular scenario, self-efficacy in the patients can be improved by making sure the patient is able to obtain her medications on time and helping them to understand the instructions. Another way to improve self-efficacy may
be to tell the patients the benefits of taking the medication in spite of the costs, side-effects and other barriers. Our results indicated that there was a negative correlation between self-efficacy and response cost. Hence decreasing the patients’ perceptions about the costs and barriers of taking the medication may spontaneously improve their self-efficacy. Helping the patients cope with their side-effects by prescribing palliative therapy may be another way to improve their self-efficacy.

Adherence to the medications varied significantly with age, marital status, income, insurance and comorbid conditions. The study shows that patients in the age group of 60-69 years have highest adherence followed by patients who are younger than 50 years and adherence to Aromatase Inhibitor was lowest in patients older than 70 years. Similar results were reported by Partridge et.al and Hershman et.al. in their studies where they found that older and younger age was associated with lower adherence.21,97 Several studies have shown that elderly patients are more prone to low levels of adherence98-100 In a systematic review to find the barriers associated with adherence to medications in elderly populations, the researchers classified the factors into patient-related factors, drug-related factors and other factors. Some of the patient-related factors included psychosocial profile, and health beliefs. Depression has been often cited as a major reason for non-adherence. Health literacy, especially about the benefits of taking the medication is another reason cited by the article.100

Since most of the breast cancer patients belong to this age group, it is of utmost importance that this issue receives more attention. Older patients find it difficult to remember to take medications on time and are prone to forgetting to take their medications. They may also have a complex medication regimen which makes it difficult
for them to remember to take their medications. Various tools like pill boxes and pill cards are available to help aid adherence and have been proven to be efficacious. Healthcare professionals should take the time to introduce these methods to the patients who have difficulty remembering to take their medications.

It was also observed that adherence differed significantly by marital status with married women showing higher adherence rates than unmarried women. Similar results were found by Hershman et.al. and in their study.\textsuperscript{97,101} The low adherence in unmarried women may be attributed to the lack of a social support at home.\textsuperscript{1} Married women experience better adherence due to the support that they gain from their spouse.\textsuperscript{102} Another significant predictor of adherence was insurance with patients on medicare and multiple insurance sources reporting higher adherence rates than patients on Medicaid or without insurance. This trend may be explained due to the fact that Medicaid caters to patients with a lower economic background. This can be further explained by the fact that our study showed that patients with a lower income were less adherent that patients with a higher income. These findings are supported by the report on adherence to long term therapy published by WHO.\textsuperscript{1} Patients with lower income usually find cost as a huge barrier to taking medications. Alternative methods to obtain medications at a cheaper rate should be mentioned to such people like patient assistance programs.

**Strengths and Limitations and Future Implications**

In this study, about 89% of the survey respondents were white compared to only 6% black. This may be explained by the fact that incidence of breast cancer is higher in white Caucasians compared to other races. According to the SEER data, approximately
85% of the breast cancer cases diagnosed during 2005-2009 were white Caucasian females compared to 11% who were black. Analysis of the cancer incidence trend in Lucas County revealed similar trends. Approximately 83% of the reported cases were white compared to 13% blacks. A site analysis conducted on the UTMC cancer registry revealed that approximately 84% of the breast cancer cases were white, compared to 13% who were black.

Most of the survey respondents in our study belonged to the age group of 50-79 years. Aromatase inhibitors are usually prescribed to post-menopausal women with estrogen receptor positive tumors. The average age for menopause among women is 51 years. Additionally, the site analysis of the UTMC showed that in 2008, majority of the breast cancer patients belonged to this age group. It was observed that out of the 186 diagnosed cases of breast cancer, approximately, 56% were in the age group of 50-70 years while 26% were below 50 years of age. Nationally, an older age was associated with a higher incidence of the disease.

The older population also explains the distribution of comorbidity, number of prescription medications and the insurance status. Citizens over the age of 65 years are eligible to receive their healthcare coverage through Medicare. This explains that approximately 44% of the study population cited Medicare as one of the sources of healthcare coverage. Additionally, older age has been generally associated with higher number of co-morbid condition and higher number of prescription medications, which explains the higher number of comorbid conditions and the higher number of prescription medications.
The majority of the respondents of the study were cancer free. This may be explained due to the fact that Aromatase inhibitors are usually prescribed to patients as adjuvant therapy to control the recurrence of cancer.13 Hence most of these women have undergone some primary therapy and hence must be currently cancer free. This is also reflected in the fact that majority of our population has received a primary therapy like radiation, chemotherapy and surgery. Further analysis of the types of primary therapy received show that our study population is representative of the population treated at the UTMC. The site analysis revealed that majority of the patients had undergone surgery as a primary therapy. Of those who had undergone surgery, majority had undergone a lumpectomy, followed by mastectomy.105 These distributions were similar to the distribution seen in the survey respondents.

Looking at the above evidence, we can say that the sample population in this study was representative of the study population at UTMC. Hence the conclusions can be safely generalized to the study population. Furthermore, the site analysis reported by the medical center revealed that the population of the breast cancer patients treated at the center was a representative population of the national breast cancer population.105 Hence, our study population can be considered as a good representation of national breast cancer population. However due to the small number of participants, caution should be exerted while making generalizations to the national population.

One of the other strengths of the study was the moderately high response rate. A high response rate is beneficial as it removes chances of error due to bias. The high response rate for the study could be attributed to the use of incentives and other tried and tested methods as described earlier. It has been proven through a randomized trial that
use of small monetary incentives significantly improves the response rate of a mail survey. Since the incentive is only nominal, it does not inappropriately influence the patients’ performance on the survey thereby proving to be a harmless and cost-effective way to improve the response rate.\textsuperscript{106} This hypothesis has also been tested in a group of breast cancer patients with the same results.\textsuperscript{107} The other factors attributable to the high response rate maybe the use of three wave reminder mailing, use of personalized cover letters and the pre-paid return envelope included in the mailing.\textsuperscript{108}

The validity and the reliability tests confirmed that the survey was a strong one and could be used in the future for other studies. The items of the survey can be modified to conduct similar research in patients with other types of cancer receiving chronic oral therapy like prostate cancer, chronic myeloid leukemia, lung cancer and others. The major limitation of the study was the small study population and sample population. As a result, there was not a wide variation in the subjects in terms of race. The results should be generalized to the entire breast cancer population with caution. Nonetheless, the study deserves merit due to the uniqueness of the research questions and the utility of the study as a pilot for a future larger population.
REFERENCES


100


APPENDIX

Appendix 1: Morisky’s 4-item questionnaire

1. Do you ever forget to take your medications?
   - Yes
   - No

2. Are you careless at times about taking your medications?
   - Yes
   - No

3. When you feel better, do you sometimes stop taking your medications?
   - Yes
   - No

4. Sometimes if you feel worse when you take your medications, do you stop taking them?
   - Yes
   - No

Appendix 2: Morisky’s 8-item questionnaire

1. Do you sometimes forget to take your [health concern] pills?
a. Yes
b. No

2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your [health concern] medicine?
   a. Yes
   b. No

3. Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?
   a. Yes
   b. No

4. When you travel or leave home, do you sometimes forget to bring along your [health concern] medication?
   a. Yes
   b. No
5. Did you take your [health concern] medicine yesterday?
   a. Yes
   b. No

6. When you feel like your [health concern] is under control, do you sometimes stop
   taking your medicine?
   a. Yes
   b. No

7. Taking medication everyday is a real inconvenience for some people. Do you ever
   feel hassled about sticking to your blood pressure treatment plan?
   a. Yes
   b. No

8. How often do you have difficulty remembering to take all your medications?
   (Please circle the correct number)
   a. Never/Rarely
   b. Once in a while
   c. Sometimes
   d. Usually
   e. All the time
Appendix 3: IRB Approval Letter

The University of Toledo
Department for Human Research Protections
Biomedical Institutional Review Board
Center for Creative Education Building – Room 0106
3025 Arlington Avenue, Toledo, Ohio 43614-2570
Phone: 419-383-6796 Fax: 419-383-3248
FWA00010686

TO: Sharrel Pinto, Ph.D. - Faculty Advisor
Monita Karmakar - Student Investigator
UT Department of Pharmacy Practice

FROM: Deepak Malhotra, M.D., Vice Chair
Gregory Siegel, R.Ph., J.D., Chair Designee
UT Biomedical Institutional Review Board

SIGNED: ___________________________ DATE 7/13/12

SUBJECT: IRB # 107898
TITLE: Retrospective Study Comparing Different Chemotherapy Regimens Applied in the Treatment for Follicular and Other Low Grade Lymphomas

The above research was reviewed and approved by the Chair of the Biomedical Institutional Review Board as an expedited review (category #7). The requirement to obtain a signed consent/authorization for use and disclosure of protected health information form has been waived as this research is determined to be minimal risk and a signed consent/authorization document would be the only record linking the subject to the data. It was determined that this waiver for signed consent/authorization for use and disclosure of protected health information form will not adversely affect the rights or welfare of the participants. The Principal Investigator must provide a copy of the cover letter referenced below to all participants prior to participation. This action will be reported to the committee at its meeting on 07/19/2012.

Items Available for Review:
• IRB Application Requesting Initial Review of Expedited Research
• Protocol/Literature Review with List of Sources (assigned version date 07/11/2012)
• Questionnaire – Beliefs About Breast Cancer Hormone Medications (assigned version date 07/11/2012)
• Research Subject Information and Consent Form (assigned version date 07/11/2012)
• Cover Letter – Request for Survey – Research Project on Breast Cancer Medication (Request #1, #2, and #3)(assigned version date 07/11/2012)
• Signed Letter of Support from Iman Mohamed, M.D. (dated May 2, 2012)
• Request for Waiver of Individual Authorization For Use and Disclosure of Protected Health Information (PHI) for Purposes of Research

This research is approved until the expiration date listed below, unless the IRB notifies you otherwise.

You are approved to enroll up to 200 participants in this study.

APPROVAL DATE: 07/11/2012 EXPIRATION DATE: 07/10/2013

Please read the following attachment detailing Principal Investigator responsibilities.
Appendix 4: Survey Questionnaire

Beliefs About Breast Cancer Hormone Medications

**Directions:** Please answer the following questions to the best of your knowledge. There is no right or wrong answer. Please answer each question based on your personal experience with breast cancer. Do not put your name or any identifying marks on this survey. Thank you!

| Your Anti-Hormone Medication: Please circle the answer that best matches you. |
|---|---|---|
| 1. Do you sometimes forget to take your anti-hormone pills? | Yes | No |
| 2. Do you sometimes **NOT** take your anti-hormone pills due to reasons other than forgetting? | Yes | No |
| 3. Have you ever cut back or stopped taking your anti-hormone pills without telling your doctor? | Yes | No |
| 4. When you travel or leave home, do you sometimes forget to bring along your anti-hormone pills? | Yes | No |
| 5. Did you take your anti-hormone pills yesterday? | Yes | No |
| 6. When you feel like your breast cancer is under control, do you sometimes stop taking your anti-hormone pills? | Yes | No |
| 7. Taking medication everyday is a real inconvenience for some people. Do you ever feel hassled about taking your anti-hormone pills? | Yes | No |

8. **How often do you have difficulty remembering to take your anti-hormone pills? (circle one below)**
   - Never
   - Rarely
   - Sometimes
   - Usually
   - All the Time

9. **Do you still take your anti-hormone pills as recommended by your doctor? (select only one below)**
   - Yes
   - No, I have discontinued taking my medicines

   If you answered “NO” to number 9 above, **why** have you discontinued taking your medication? (Select all that apply)
   - My doctor told me to discontinue
   - Because of side effects
   - I could not afford the costs of the medicines
   - Other (Please specify)
### Perceptions About Medications

Please circle the answer that best describes your level of agreement with the following statements regarding your experience with your anti-hormone medications.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. Without my anti-hormone pills, I would probably get breast cancer again.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>11. Obtaining my anti-hormone pills puts a financial burden on me and my family.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>12. My anti-hormone pills protect me from getting breast cancer again.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>13. I worry about the long-term effects of my anti-hormone pills.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>14. Taking my anti-hormone pills disrupts my lifestyle.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>15. It is difficult for me to take my anti-hormone pills in exactly the way my doctor told me.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>16. My anti-hormone pills do me more harm than good.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>17. My anti-hormone pills are very effective at lowering my risk of having breast cancer again.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>18. Having to take my anti-hormone pills worries me.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>19. My anti-hormone pills have too many negative side effects.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>20. My anti-hormone pills work only if they are taken regularly.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
</tbody>
</table>

### Level of Confidence

Please circle the answer that best describes your confidence level:

<table>
<thead>
<tr>
<th>How confident are you to . . .</th>
<th>Very Confident</th>
<th>Confident</th>
<th>Little Confidence</th>
<th>No Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>21. Remember to take your anti-hormone pills every day.</td>
<td>VC</td>
<td>C</td>
<td>LC</td>
<td>NC</td>
</tr>
<tr>
<td>22. Obtain your anti-hormone pills when your doctor prescribes them.</td>
<td>VC</td>
<td>C</td>
<td>LC</td>
<td>NC</td>
</tr>
<tr>
<td>23. Follow your doctor’s orders for taking your anti-hormone pills.</td>
<td>VC</td>
<td>C</td>
<td>LC</td>
<td>NC</td>
</tr>
<tr>
<td>24. Take your anti-hormone pills even though it may disrupt your lifestyle.</td>
<td>VC</td>
<td>C</td>
<td>LC</td>
<td>NC</td>
</tr>
<tr>
<td>25. Take my anti-hormone pills even though you may experience negative side effects.</td>
<td>VC</td>
<td>C</td>
<td>LC</td>
<td>NC</td>
</tr>
<tr>
<td>26. Obtain your anti-hormone pills even though they may be expensive.</td>
<td>VC</td>
<td>C</td>
<td>LC</td>
<td>NC</td>
</tr>
<tr>
<td>27. Take your anti-hormone pills even though you may be taking additional medications.</td>
<td>VC</td>
<td>C</td>
<td>LC</td>
<td>NC</td>
</tr>
</tbody>
</table>
**SIDE EFFECTS:** Listed below are some common side effects of anti-hormone pills. For each side effect, please rate how much of a problem it has been for you. Please circle only one answer for each side effect.

<table>
<thead>
<tr>
<th>How much of a problem has each side effect been for you?</th>
<th>Major Problem</th>
<th>Moderate Problem</th>
<th>Slight Problem</th>
<th>No Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>28. Hot Flashes</td>
<td>Major</td>
<td>Moderate</td>
<td>Slight</td>
<td>No</td>
</tr>
<tr>
<td>29. Fatigue/Tiredness</td>
<td>Major</td>
<td>Moderate</td>
<td>Slight</td>
<td>No</td>
</tr>
<tr>
<td>30. Joint Pain</td>
<td>Major</td>
<td>Moderate</td>
<td>Slight</td>
<td>No</td>
</tr>
<tr>
<td>31. Vaginal Dryness/ Bleeding</td>
<td>Major</td>
<td>Moderate</td>
<td>Slight</td>
<td>No</td>
</tr>
<tr>
<td>32. Decreased sex drive</td>
<td>Major</td>
<td>Moderate</td>
<td>Slight</td>
<td>No</td>
</tr>
<tr>
<td>33. Nausea/vomiting</td>
<td>Major</td>
<td>Moderate</td>
<td>Slight</td>
<td>No</td>
</tr>
<tr>
<td>34. Mood changes</td>
<td>Major</td>
<td>Moderate</td>
<td>Slight</td>
<td>No</td>
</tr>
<tr>
<td>35. Flushing (face feeling red and hot)</td>
<td>Major</td>
<td>Moderate</td>
<td>Slight</td>
<td>No</td>
</tr>
<tr>
<td>36. Loss of appetite/ change in weight</td>
<td>Major</td>
<td>Moderate</td>
<td>Slight</td>
<td>No</td>
</tr>
</tbody>
</table>

**Perceptions About Breast Cancer:** Please circle the answer that best describes your level of agreement with the following statements:

<table>
<thead>
<tr>
<th>Do you agree or disagree?</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>37. If I were to have breast cancer again, it would hurt me financially.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>38. Having a return of breast cancer would create severe problems for my loved ones.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>39. Compared to other breast cancer survivors, my odds of having a return of breast cancer are low.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>40. I feel vulnerable to a return of breast cancer at some point in life.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>41. My chances of having a return of breast cancer are high.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>42. My gut feelings tell me that I will NOT have a return of breast cancer.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>43. There is a good chance that breast cancer may be developing again within my body.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>44. Having another case of breast cancer would be life threatening for me.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>45. If I were to have breast cancer again, the health consequences would be severe.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>46. Developing breast cancer would be the worst thing that could happen to me.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
<tr>
<td>47. Having a return of breast cancer would have a bad effect on my quality of life.</td>
<td>SA</td>
<td>A</td>
<td>D</td>
<td>SD</td>
</tr>
</tbody>
</table>

*Please turn the page and finish the survey. Thanks!*
Facts about you: These responses are being collected purely for classification purposes. Please put an X before the appropriate response.

48. What is your age? (Check only one below)
   ____ Less than 40 years  ____ 50-59 years  ____ 70-79 years
   ____ 40-49 years  ____ 60-69 years  ____ Above 80 years

49. What is your highest level of education? (Check only one below)
   ____ Less than high school graduate  ____ Some college
   ____ High School graduate or GED  ____ College graduate (4 years or more)

50. What is your race/ethnicity? (Check only one below)
   ____ White/Caucasian  ____ Bi-racial
   ____ Black/African American  ____ Other (please specify)
   ____ Hispanic/Latino
   ____ Asian

51. Marital status: (Check only one below)
   ____ Married  ____ Divorced  ____ Widow
   ____ Single (never married)  ____ Separated

52. Total household income last year before taxes:
   ____ Less than $14,999  ____ $45,000 - $54,999  ____ $85,000 - $94,999
   ____ $15,000 - $24,999  ____ $55,000 - $64,999  ____ More than $95,000
   ____ $25,000 - $34,999  ____ $65,000 - $74,999
   ____ $35,000 - $44,999  ____ $75,000 - $84,999

53. What type of health insurance do you have? (Check all that apply)
   ____ Medicare  ____ Private insurance  ____ Other ______
   ____ Medicaid  ____ Uninsured

54. Where do you usually get your medicines? (Check all that apply)
   ____ Mail Order  ____ Pharmacy  ____ Community Pharmacy  ____ Outpatient Pharmacy

55. Have you ever had a remission of cancer? ______ Yes ______ No

56. What is the stage of your breast cancer? (Check only one that apply)
   ____ Stage 1  ____ Stage 2  ____ Stage 3  ____ Stage 4

57. Which kind of primary therapy did you receive? (Check all that apply)
   ____ Radiation  ____ Lymphectomy  ____ Single Breast Mastectomy  ____ Double Breast Mastectomy
   ____ Chemotherapy  ____ None

58. How many medicines are you currently taking for breast cancer and/or other diseases? (Check only one)

   1  2  3  4  5  6  7  8  9  10  More than 10

59. Are you diagnosed of any other disease than breast cancer? (Check only one)
   ____ Yes
   ____ No
Appendix 5: Cover letter – 1st wave

August 7, 2012

First Name Last Name
Address line 1
City, State Zip

Re: Request for Survey – Research Project on Breast Cancer Medication

Dear Mrs. or Ms. Last Name

Breast cancer affects numerous women in United States and research on this topic is of great importance. Such research can help cancer patients enjoy a higher quality of life. You have been selected to participate in a research study conducted jointly by the Rupert Health Center and the College of Pharmacy and Pharmaceutical Sciences.

We need your help in a research study regarding breast cancer patients like you and their medications. This study will focus on aromatase inhibitors – a type of hormonal therapy for breast cancer. The results of this study will be used to help patients and physicians better understand factors that contribute to how and why patients take their medications.

To participate in the study please complete the attached survey. The survey will take approximately **15 minutes** to complete. Participation in the survey is voluntary. Choosing not to participate will not affect your relationship with your physician, the nurses, or the medical staff. If you have already participated in the survey in the clinic, please disregard this survey. To show our appreciation to you for your time, we have included a dollar bill along with this mailing. Feel free to use this dollar to purchase a cold drink or a cup of coffee “on us”

Your answers to the survey questions will be confidential and patient IDs will not be revealed at anytime. Your responses will not be shared with your doctor. All the completed surveys will be combined together and all patients’ answers will be analyzed as a group. Please return your completed questionnaire in the enclosed postage paid return envelope by **3rd August 2012**.

If you have any further questions, comments or suggestions, please feel free to contact me, Monita Karmakar via e-mail: monita.karmakar@rockets.utoledo.edu or by phone at (419)383-1969. Alternatively, you may contact Dr. Sharrel Pinto via email at sharrel.pinto@utoledo.edu.

Thank you very much for your co-operation. Your help is greatly appreciated.

Cordially,

Monita Karmakar
MS (Candidate) Pharmacy Health Care Administration

Dr. Sharrel Pinto
Major Adviser
Appendix 6: Cover letter – 2nd wave

August 27, 2012

First Name Last Name  
Address line 1  
City, State Zip

Re: Second Request for Survey – Research Project on Breast Cancer Medication

Dear First Name

Two weeks back we had written to you about the enclosed questionnaire. You have been selected to participate in a research study conducted jointly by the Rupert Health Center and the College of Pharmacy and Pharmaceutical Sciences.

Completing the enclosed questionnaire will take about 15 minutes, but the information from this survey will help patients and physicians better understand factors that contribute to how and why patients take their medications. This study will focus on aromatase inhibitors – a type of hormonal therapy for breast cancer.

You are part of a chosen sample of breast cancer patients. For the survey to be successful, we need to hear from all the chosen patients. Your views about your medications and the disease are important to us as they represent the views of other patients like you. Participation in the survey is voluntary. Choosing not to participate will not affect your relationship with your physician, the nurses, or the medical staff. If you have already participated in the survey in the clinic or have replied to our earlier mail, please accept our thanks and disregard this survey.

Your answers to the survey questions will be confidential and patient IDs will not be revealed at anytime. Your responses will not be shared with your doctor. All the completed surveys will be combined together and all patients’ answers will be analyzed as a group. Please return your completed questionnaire in the enclosed postage paid return envelope by [enter date].

If you have any further questions, comments or suggestions, please feel free to contact me, Monita Karmakar via e-mail: monita.karmakar@rockets.utoledo.edu or by phone at 419 383 1969. Alternatively, you may contact Dr. Sharrel Pinto via email at sharrel.pinto@utoledo.edu.

Thank you very much for your co-operation. Your help is greatly appreciated.

Cordially,

Monita Karmakar  
MS (Candidate) Pharmacy Health Care Administration

Dr. Sharrel Pinto  
Major Adviser
Appendix 7: Cover letter – 3rd wave

September 16, 2012

First Name Last Name
Address line 1
City, State Zip

Re: Third Request for Survey – Research Project on Breast Cancer Medication

Dear First Name

We need your help! Over the past month, we have attempted to contact you by mail on two previous occasions. The previous mailings included a survey about breast cancer medications (on pink paper) and a postage paid return envelope. Unfortunately, we have not yet received your completed survey.

Your views and opinions are very important to us! To ensure that we hear from as many breast cancer patients as possible, we are sending the survey to you a third time. If you have already completed the survey at your cancer doctor’s office or have replied to one of our previous mailings, please accept our thanks and disregard this letter.

It is not too late to complete and return the survey to us. The survey takes about 15 minutes to complete. Please return the survey in the postage paid envelope.

If you have any further questions, comments or suggestions, please feel free to contact me, Monita Karmakar via e-mail: monita.karmakar@rockets.utoledo.edu or by phone at 419-383-1969. You may also contact Dr. Sharrel Pinto via email at sharrel.pinto@utoledo.edu.

Thank you very much for your co-operation. Your help is greatly appreciated.

Cordially,

Monita Karmakar
MS (Candidate) Pharmacy Health Care Administration

Dr. Sharrel Pinto
Major Adviser
Appendix 8: Cover letter – test retest

September 3, 2012

First Name Last Name
Address line 1
City, State Zip

Dear First name:

Greetings from the University of Toledo! If you recall, about three weeks ago you received a cover letter, a dollar bill, and a survey printed on pink paper. The survey was about your breast cancer medications. Thanks for completing the survey and returning it to us! We truly appreciate your help!

We need to ask you for one more small favor. For research purposes, we need to test the reliability of the survey questions by having 50 people complete the survey twice. You have already completed it once. Would you be kind enough to complete the survey one more time so we can compare your answers on your first survey to your second survey?

Having two surveys from you will help us measure the reliability of the survey questions. Your cooperation will help us prove that this research study meets the standards required for professional research in medicine.

Please complete the survey again and return it to us in the postage paid envelope. Enclosed is the 2nd copy of the survey and another $1 bill as a token of our appreciation. Completing the survey a second time will take approximately 15 minutes.

As before, your survey responses are confidential and protected. Please do not write your name or any other personal identifying information on the survey. We do not want to know your identity. We are using the results of your two surveys for testing purposes only.

If you have any questions, please feel free to contact me, Monita Karmakar via e-mail: monita.karmakar@rockets.utoledo.edu or by phone at 419-383-1969. You may also contact Dr. Sharrel Pinto via email at sharrel.pinto@utoledo.edu.

Thank you very much for your cooperation!
Cordially,

Monita Karmakar
MS (Candidate) Pharmacy Health Care Administration

Dr. Sharrel Pinto
Major Adviser

Monita Karmakar
Dr. Sharrel Pinto
Appendix 9: Informed Consent

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

Predicting Adherence to Aromatase Inhibitor Therapy in Patients with Breast Cancer Using Protection Motivation Theory

Principal Investigator: Sharrel Pinto, B.S.Pharm, D.M.M., M.S., Ph.D
Student Investigator: Monita Karmakar, B.S. Pharm, M.S. Candidate
Contact Phone number: 419-383-1967

Dear Patient:
You are invited to participate in the research project entitled, “Predicting Adherence to Aromatase Inhibitor Therapy in Patients with Breast Cancer Using Protection Motivation Theory”, which is being conducted at the University of Toledo, College of Pharmacy in collaboration with Dr. Iman Mohamed’s Practice at the University of Toledo, Medical Center under the direction of Dr. Sharrel Pinto and Miss Monita Karmakar. This form provides you with information regarding the purpose, potential risks, and potential benefits of participating in this research study. You may keep this form.

Purpose of the Study:
The purpose of this study is to identify the factors that affect patients’ adherence to their medication regimen and their perceptions about breast cancer and the medications.

Description of Procedure:
The study will use a survey questionnaire that was developed by the researchers at the University. This survey will be mailed to nearly 300 patients - breast cancer survivors like you. When you receive the survey, you will be invited to complete it and return it via postal mail using the self-addressed stamped envelope provided for you.

Potential Risks and Benefits:
There are no risks involved in completing the survey. Your identity will always be hidden from the researchers and from your doctor(s). Your doctor will never see your answers to this survey. The researchers will never be able to link your identity to your completed survey. The benefits of participating are knowing that you help medical researchers find ways to better help patients adhere to their medication regimen.

Voluntary Participation:
You may choose not to participate in this research by simply not choosing to fill out the survey. Taking part in this study is voluntary. You may refuse to participate or discontinue participation at any time without penalty or a loss of benefits to which you are otherwise entitled. If you decide not to participate or to discontinue participation, your decision will not affect your future relations with the University of Toledo or The University of Toledo Medical Center. Even if you choose not to participate, you may keep the $1 bill that was included in the mailing. Should you choose to participate, returning the completed survey via postal mail will be interpreted as your informed consent.
Confidentiality:
Your answers to the survey questions will be confidential and patient identification will not be revealed at any time. Your responses will not be shared with your doctor. The researchers will not be able to link your completed survey to your identify. Only group results from all patients will be analyzed.

We thank you very much for your time and consideration. Please feel free to contact us anytime should you have any further questions.

Offer To Answer Questions
Before you sign this form, please ask any questions on any aspect of this study that is unclear to you. You may take as much time as necessary to think it over. You can take this form with you so that you have important information about the research. If you have questions regarding the research at any time before, during or after the study, you may contact Sharrel Pinto at 419-383-1967.

If you have questions beyond those answered by the research team or your rights as a research subject or research-related injuries, please feel free to contact the Chairperson of the University of Toledo Biomedical Institutional Review Board at 419-383-6796.