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Elucidating the Endocrine Therapy Experiences of South Carolina Breast Cancer Survivors

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ELUCIDATING THE ENDOCRINE THERAPY EXPERIENCES OF SOUTH CAROLINA BREAST CANCER SURVIVORS

A Dissertation
Presented to
the Graduate School of
Clemson University

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy
Applied Health Research and Evaluation

by
Julie Summey Bedi
May 2018

Accepted by:
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ABSTRACT

The aims of this study were to 1) describe endocrine therapy (ET) non-initiation, non-adherence, and duration by age, race, and temporal trend; 2) identify demographic, clinical, and pharmaceutical factors that are associated with an individual’s ET usage; and 3) understand from the survivor perspective which modifiable factors could have the greatest impact on the likelihood of ET continuation.

This study utilized a convergent parallel mixed methods design. The sample included female South Carolina (SC) residents ages 18-64 at diagnosis with hormone receptor-positive breast cancer. SC Central Cancer Registry incidence data linked with South Carolina Medicaid data (N=3,830) were along with focus groups in four SC locations (N=22). Age, race, relative risk and median duration of ET use were compared. Temporal trends in ET non-initiation, non-adherence, and duration were observed using linear and logistic regression models, controlling for age and race. A series of multiple regression models were built to explore the association of demographic, clinical, and pharmaceutical factors with ET usage duration. Qualitative data analysis was completed by a three-member research team using an inductive narrative approach. Themes were examined by participant decision to continue or discontinue ET.

Fifty three percent of women in the sample did not initiate ET, with highest non-initiation rates among African Americans and survivors under age 50. Of those who did initiate ET, 42% were non-adherent with a median ET usage duration of 37 months. Twenty one percent of initiators continued taking ET for five years or more. There was no change in the odds of ET non-initiation from 2000 – 2004. The odds of ET non-
initiation decreased from 2005 – 2009 but then increased from 2010 – 2014. There was no change in the odds of ET non-adherence from 2000 – 2006, but from 2007 – 2012, the odds of ET non-adherence decreased each year. The average ET usage duration was increasing from 2000 – 2006 but decreasing from 2006 – 2012.

Multiple linear regression analysis showed that none of the demographic or clinical factors tested were significantly associated with ET usage duration. The type of ET taken as well as receipt of the prescriptions that could have been used to alleviate side effects were significantly associated. Participants’ feedback centered on a risk vs. benefit analysis unique to the individual survivor. Main themes included the importance of an open, honest patient/provider relationship and the need for personal information seeking and affirmation in the decision to take ET. There was clear support for the utility of multidisciplinary cancer care teams and incorporating integrative approaches.

This study provides a realistic picture of the challenges associated with ET usage among South Carolina Medicaid breast cancer patients. It particularly highlights more opportunity for improvement in ET initiation, adherence, and duration among younger women of lower socioeconomic status. Our study also highlights the potential value of concurrent prescriptions for improving ET usage duration, with an optimal intervention point before 14 months post ET initiation. Further research is needed to test pharmacologic interventions that may significantly increase ET duration as well as other non-pharmacologic strategies for side effect management. Research employing patient-centered perspectives is imperative. Novel and practical patient-centered interventions in
research exploring openness in the patient/provider relationship, survivor information seeking practices, multidisciplinary teams, and integrative approaches are needed.
DEDICATION

This dissertation work is dedicated to the beautiful participants in the Patient Engagement Studio and focus groups who told me they just want to live and live fully. Your joy amidst challenges and passion for life renewed my eagerness for this work. I am humbled that you trusted me to be your voice.
I would like to acknowledge the great contributions of my dissertation chair, Dr. Rachel Mayo. I am very thankful for her patience, graciousness, and guidance in my work over the past three years. I would also like to acknowledge the contributions of my dissertation committee members, Dr. Lori Dickes, Dr. Windsor Sherrill, Dr. Karyn Jones, and Dr. Liwei Chen, as well as Dr. Khoa Truong for his mentorship and the research opportunities he has provided me. The committee’s feedback has helped me grow and develop the “toolbox” of skills that I have today.

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I would also like to thank my parents, my brother Johnny, and my sister-in-law Rebecca for their love and encouragement during my studies. I appreciate them most for helping keep me grounded and reminding me what truly matters in life. Thank you for
always being there to do something fun; laugh, cry, and/or celebrate with me; or help me when I needed it. They are the best family I could ever dream of!

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Glory to God alone.
TABLE OF CONTENTS

Page

TITLE PAGE .............................................................................................................................................i
ABSTRACT .............................................................................................................................................ii
DEDICATION ..........................................................................................................................................v
ACKNOWLEDGMENTS .........................................................................................................................vi
LIST OF TABLES ....................................................................................................................................x
LIST OF FIGURES ...............................................................................................................................xi

CHAPTER

I. INTRODUCTION ..............................................................................................................................1
   Overview .........................................................................................................................................1
   Problem Statement .......................................................................................................................2
   Theoretical Framework ..............................................................................................................4

II. LITERATURE REVIEW ..................................................................................................................6
   Breast Cancer Epidemiology ........................................................................................................6
   Role and History of Endocrine Therapy in Breast Cancer Treatment ........................................9
   Problem of Endocrine Therapy Non-initiation, Non-adherence, and Discontinuation ................11
   Existing Interventions ..............................................................................................................15

III. METHODOLOGY ..........................................................................................................................20
   Research Questions ....................................................................................................................20
   Overall Research Design ..........................................................................................................22
   Quantitative Research Design ..................................................................................................24
   Qualitative Research Design .....................................................................................................30

IV. PAPER 1: “ENDOCRINE THERAPY USE IN THE 21ST CENTURY: TEMPORAL TRENDS ILLUSTRATE OPPORTUNITIES FOR IMPROVEMENT FOR SOUTH CAROLINA MEDICAID WOMEN” .........................................................................39
   Abstract .......................................................................................................................................39
Table of Contents (Continued)

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>40</td>
</tr>
<tr>
<td>Methods</td>
<td>41</td>
</tr>
<tr>
<td>Results</td>
<td>45</td>
</tr>
<tr>
<td>Conclusion</td>
<td>47</td>
</tr>
<tr>
<td>References</td>
<td>49</td>
</tr>
<tr>
<td>Figures</td>
<td>52</td>
</tr>
<tr>
<td>Tables</td>
<td>53</td>
</tr>
</tbody>
</table>

V. PAPER 2: “FACTORS ASSOCIATED WITH LONGER ENDOCRINE THERAPY USE BY SOUTH CAROLINA MEDICAID-INSURED BREAST CANCER SURVIVORS” .......................................................... 56

Abstract........................................................................................................ 56
Introduction................................................................................................. 57
Methods......................................................................................................... 59
Results.......................................................................................................... 61
Conclusion..................................................................................................... 63
References...................................................................................................... 67
Tables............................................................................................................ 71

VI. PAPER 3: “‘WALK A MILE IN MY SHOES’ – BREAST CANCER SURVIVORS’ PERSPECTIVES ON THE ENDOCRINE THERAPY EXPERIENCE” ................................................................. 73

Abstract........................................................................................................ 73
Introduction................................................................................................. 74
Methods......................................................................................................... 75
Results.......................................................................................................... 77
Conclusion..................................................................................................... 83
References...................................................................................................... 88
Figures............................................................................................................ 92
Tables............................................................................................................ 93

VII. DISCUSSION ............................................................................................. 95

Overview of Study Findings and Strengths ............................................. 95
Limitations..................................................................................................... 100
Future Work .................................................................................................. 101
Table of Contents (Continued)

APPENDICES .......................................................................................................................... 106

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Health Belief Model for Endocrine Therapy Usage to Reduce Risk of Recurrence among South Carolina Breast Cancer Survivors Ages 18-64 at Diagnosis</td>
<td>107</td>
</tr>
<tr>
<td>B</td>
<td>Table of Variables</td>
<td>108</td>
</tr>
<tr>
<td>C</td>
<td>Recruitment Flyer</td>
<td>109</td>
</tr>
<tr>
<td>D</td>
<td>Screening Questions</td>
<td>110</td>
</tr>
<tr>
<td>E</td>
<td>Focus Group Guide</td>
<td>112</td>
</tr>
<tr>
<td>F</td>
<td>Participant Survey</td>
<td>116</td>
</tr>
</tbody>
</table>

REFERENCES ............................................................................................................................ 118
<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>Demographic characteristics of South Carolina Medicaid breast cancer survivor endocrine therapy initiators and non-initiators, 2000 – 2014</td>
<td>53</td>
</tr>
<tr>
<td>4.2</td>
<td>Endocrine therapy non-initiation rates (%) and relative ratios (95% CI) by age and race subgroups of South Carolina Medicaid breast cancer survivors</td>
<td>53</td>
</tr>
<tr>
<td>4.3</td>
<td>Endocrine therapy non-adherence rates (%) and relative ratios (95% CI) by age and race subgroups of South Carolina Medicaid breast cancer survivors</td>
<td>53</td>
</tr>
<tr>
<td>4.4</td>
<td>Endocrine therapy non-initiation rates among South Carolina Medicaid breast cancer survivors by year of diagnosis, 2000 – 2014</td>
<td>54</td>
</tr>
<tr>
<td>4.5</td>
<td>Demographics and endocrine therapy usage non-adherence and duration patterns in South Carolina Medicaid breast cancer survivors by year of diagnosis, 2000 – 2014</td>
<td>55</td>
</tr>
<tr>
<td>5.1</td>
<td>Multiple regression results for variables associated with endocrine therapy usage duration for the South Carolina Medicaid population, 2000 - 2012 (models A – H)</td>
<td>71</td>
</tr>
<tr>
<td>5.2</td>
<td>Multiple regression results for variables associated with endocrine therapy usage duration for the South Carolina Medicaid population, 2000 - 2012 (final model)</td>
<td>72</td>
</tr>
<tr>
<td>6.1</td>
<td>Participant endocrine therapy usage characteristics (N=22)</td>
<td>93</td>
</tr>
<tr>
<td>6.2</td>
<td>Sample quotes exemplifying participant perceptions regarding susceptibility and severity of breast cancer recurrence and motivation for continuing or discontinuing endocrine therapy</td>
<td>94</td>
</tr>
<tr>
<td>7.1</td>
<td>Summary of research aims, questions, hypotheses, and results</td>
<td>95</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>Cohort selection criteria</td>
<td>52</td>
</tr>
<tr>
<td>4.2</td>
<td>Adjusted trends in South Carolina Medicaid breast cancer survivors’ endocrine therapy non-initiation, non-adherence, and duration by year of breast cancer diagnosis</td>
<td>52</td>
</tr>
<tr>
<td>6.1</td>
<td>Health belief model for endocrine therapy usage to reduce risk of breast cancer recurrence among low income South Carolina breast cancer survivors ages 18-64</td>
<td>92</td>
</tr>
</tbody>
</table>
CHAPTER ONE

INTRODUCTION

Overview

It is well known that breast cancer is the most common type of cancer in the United States, accounting for almost 15% of all new cancer cases and 6.8% of all cancer deaths in 2016 (“Cancer Among Women,” 2016; “Cancer of the Breast,” 2016). Following surgery, radiation therapy, and/or chemotherapy, a woman with Stage 0-III hormone receptor-positive breast cancer is typically prescribed endocrine therapy (ET) for five years or longer as part of initial treatment (“Hormonal Therapy,” 2016; “Ten Years,” 2014). The purpose of ET is to reduce a woman’s risk of breast cancer recurrence. Taking ET (Tamoxifen or an aromatase inhibitor) as prescribed for five years can reduce the risk of recurrence by 40% and death by one-third (Early Breast Cancer Trialists' Collaborative Group [EBCTCG], 2005).

Research and clinical practice confirm that rates of ET initiation (i.e. filling the first prescription), adherence (i.e. following the provider’s recommendations day-to-day regarding the timing, dosage, and frequency of the ET), and continuation (i.e. the act of continuing ET for the prescribed duration) are quite low (Cramer et al., 2008; Hershman et al., 2011; Partridge, Wang, Winer, & Avorn, 2003; Wheeler et al., 2014). Studies conducted in the North Carolina and New York Medicaid populations showed non-initiation rates around 50% without intervention (Wagner et al., 2016; Wheeler et al., 2014). A systematic review by Murphy et al. (2012) showed that adherence ranged from
41–72% and discontinuation ranged from 31–73%, measured at the end of 5 years of treatment.

Knowledge of the population affected by ET non-initiation, non-adherence, and early discontinuation in South Carolina is limited, as is knowledge of how to improve the ET experience for patients, both in South Carolina and across the nation. The few studies that have addressed interventions showed little to no improvement over usual care (Hurtado-de-Mendoza, Cabling, Lobo, Dash, & Sheppard, 2016; Ekinci et al., 2018). The overall aim of this research is to inform the development of future interventions by 1) describing ET non-initiation, non-adherence, and duration by age, race, and temporal trend and 2) identifying demographic, clinical, and pharmaceutical factors that are associated with an individual’s ET usage duration for South Carolina Medicaid-enrolled women who had hormone receptor-positive breast cancer diagnosed between 2000 and 2014. This third aim of this research is to inform future interventions by understanding, from the survivor perspective, which modifiable factors could have the greatest impact on the likelihood of ET continuation.

Problem Statement

ET discontinuation and non-adherence rates remain high despite the use of ET for decades as the primary means of reducing the risk of breast cancer recurrence in women with hormone receptor-positive Stage 0-III disease (EBCTCG, 2005; Reynolds & Higgins, 2013). The only known published research regarding ET usage among South Carolina women was conducted among Medicaid enrollees by Wu and Lu (2013) and
Felder et al. (2016). Wu and Lu examined the association between adherence to hormone therapy and healthcare costs from 2000-2008 and found no significant difference in total healthcare costs between the adherent and non-adherent women. Felder et al. (2016) studied racial differences in the receipt of ET among patients in one health care system and found no significant differences by race but overall low usage rates.

The purpose of the proposed study is to further expand on the work of Wu and Lu (2013) and Felder et al. (2016) to examine the ET non-initiation, non-adherence, and duration of SC women recipients diagnosed with hormone receptor-positive breast cancer after 2000 and to ultimately inform a patient-centered intervention to improve ET usage. Specifically, the aims of this study are 1) to describe ET non-initiation, non-adherence, and duration by age, race, and temporal trend and 2) to identify demographic, clinical, and pharmaceutical factors that are associated with an individual’s ET usage duration for South Carolina Medicaid-enrolled women who had hormone receptor-positive breast cancer diagnosed between 2000 and 2014; and 3) to understand from the survivor perspective which modifiable factors could have the greatest impact on the likelihood of ET continuation. It is imperative that research be conducted that employs a patient-centered perspective. The knowledge gained through further study can be integrated in developing future patient-centered interventions to enhance the ET experience for breast cancer survivors.
Theoretical Framework

The Health Belief Model was used as the theoretical framework to explain what is currently known about ET usage and informed the study design. The Health Belief Model was developed in the 1950s by Hochbaum, Rosenstock, and Kegels of the U.S. Public Health Services (“Health Belief Model,” n.d.). Since then, it has been widely used to study various preventive health and clinic use behaviors among many populations (Baghianimoghadam et al., 2013; Farma, Jalili, Zareban, Pour, 2014; Holwerda, 2000; VanDyke & Shell, 2016; Wang et al., 2014).

The study used the original Health Belief Model, which consists of six major constructs: perceived susceptibility, perceived seriousness, perceived benefits, perceived barriers, modifying variables, and cues to action. In the study context, these constructs were briefly defined as follows (Hayden, 2013; “Health Belief Model,” n.d.):

- **Perceived susceptibility**: A woman’s assessment of the chances of breast cancer recurrence
- **Perceived seriousness**: A woman’s assessment of the severity of breast cancer recurrence
- **Perceived benefits**: A woman’s degree of belief in the efficacy of ET in reducing breast cancer recurrence
- **Perceived barriers**: A woman’s assessment of the costs of ET continuation and adherence
- **Modifying variables**: Personal factors that affect ET usage
- **Cues to action**: Factors that help “activate readiness” in a woman taking ET
See Appendix A for a detailed diagram of the Health Belief Model applied to this study on ET usage among South Carolina breast cancer survivors.

The study also employed grounded theory in interpreting its qualitative findings. This theory was first published by Glaser & Strauss in 1967 (Cohen & Crabtree, 2006). Grounded theory is an empirical, inductive, systematic process in which theoretical insights are generated from the data collected and are not established prior to the study; however, it is possible that the findings may reveal that an established theory is the most fitting for their interpretation (Chapman, Hadfield, & Chapman, 2014; Cohen & Crabtree, 2006; Hussein, Hirst, Salyers, & Osuji, 2014). For example, it was hypothesized that based on cancer survivorship and medication adherence literature, Michel’s Uncertainty in Illness Theory, Theory of Planned Behavior, a quality of life theory, or a stress and coping theory may be suited to the findings. Nevertheless, in keeping with the principles of grounded theory, this was not assumed nor determined until data analysis (Hussein, Hirst, Salyers, & Osuji, 2014). As pointed out by Achora and Matua (2016), although grounded theory was employed, the research questions, data collection methods, and coding processes were clearly specified and explained prior to data collection.
CHAPTER TWO

LITERATURE REVIEW

To provide background and context for the study, several pertinent topics were surveyed in the literature including breast cancer epidemiology; the role and history of ET in breast cancer treatment; the problem of ET non-initiation, non-adherence, and discontinuation; and existing interventions.

Breast Cancer Epidemiology

The human body is composed of trillions of cells that grow and divide to form new cells that take the place of old or damaged cells as they die (“What is Cancer?,” 2015). “Cancer” is a broad term describing a condition in which genetic changes cause cells to grow and divide endlessly, even though not needed by the body (“What is Cancer?,” 2015). These additional cells can form tumors that are usually named for the part of the body where they originate (“Breast Cancer Facts,” 2015). For example, breast cancers begin in parts of the breast, usually the ducts or lobules (“Breast Cancer Facts,” 2015).

Female breast cancer is currently the most common type of cancer in the United States, followed by lung and bronchus cancer, prostate cancer, colon and rectum cancer, and bladder cancer. In 2016, there were approximately 246,660 new cases of female breast cancer, which accounted for 14.6% of all new cancer cases, and there were 40,450 estimated deaths from female breast cancer, which accounted for 6.8% of all cancer deaths (“Cancer of the breast,” 2016). From 2006-2012, 89.7% of persons with female
breast cancer survived five years or more post-diagnosis (“Cancer of the breast,” 2016). From 2009-2013, female breast cancer was most commonly diagnosed among women ages 55-64 (25.7%), and women ages 45-74 accounted for almost 70% of all new breast cancer cases (“Cancer of the breast,” 2016). The female breast cancer incidence rate from 2009-2013 was highest among white women (128.0 per 100,000), followed closely by black women (125.2 per 100,000); however, the number of deaths was higher for black women (29.6 per 100,000) compared to white women (21.0 per 100,000) (“Cancer of the Breast,” 2016).


South Carolina has a higher female breast cancer mortality rate (2009-2013) compared to the U.S., ranking 14th when compared to the rest of the nation’s states (22.4 per 100,000 versus 21.5 per 100,000) (“Breast Cancer in South Carolina,” 2016). Similar to national trends, the breast cancer mortality rate is higher for South Carolina black women compared to white women (28.7 per 100,000 versus 20.3 per 100,000) (“Breast Cancer in South Carolina,” 2016).
With advances in breast cancer screening and treatment, the population of female breast cancer survivors in the United States continues to grow and was estimated at 3,560,570 as of January 2016 (“Cancer Treatment & Survivorship,” 2016). This population is expected to total 4,571,210 by 2026 (“Cancer Treatment & Survivorship,” 2016). Female breast cancer survivors can experience long-term effects from their surgical, radiation, or chemotherapy treatments, including numbness, tingling, or tightness in the chest wall, arms, or shoulders; persistent nerve pain in the chest wall, armpit, and/or arm after surgery; or other types of chronic pain (“Cancer Treatment & Survivorship,” 2016). In addition, breast cancer treatments can affect a woman’s fertility and menopausal status and put a woman at an increased risk for osteoporosis (“Cancer Treatment & Survivorship,” 2016).

An important issue for breast cancer survivors is the risk of cancer recurrence. Once the initial cancer is treated, there remains the risk of the cancer recurring either locally in the breast or metastasizing (i.e. spreading to other parts of the body). The amount of risk for secondary cancers depends on many different factors related to the original cancer and the initial treatment. Some of these factors can include the hormone receptor status, human epidermal growth factor receptor 2 (HER2), whether the tumor margins and lymph nodes contain cancer cells, whether a woman had a lumpectomy (i.e. breast conserving surgery) and radiation therapy versus a mastectomy, and whether a woman had chemotherapy (“What are the risks,” 2016). For instance, for women who have a lumpectomy and complete radiation therapy, the risk of local recurrence within ten years is between three to fifteen percent (Arvold et al., 2011). For women who have a
mastectomy and whose lymph nodes do not contain cancer, the chance of local recurrence in five years is approximately six percent (Celik, Aydoğan, Yılmaz, Yaşar, & Müslümanoğlu, 2016).

Role and History of Endocrine Therapy in Breast Cancer Treatment

During a biopsy or surgery, cancer cells are tested to determine if they have estrogen or progesterone receptors ("Breast Cancer Hormone Receptor," 2016). Sixty to seventy-five percent of cancers are hormone receptor-positive, meaning that the cells test positive for estrogen ("Breast Cancer Hormone Receptor," 2016; Burstein et al., 2014). Knowing this status is important in determining the treatment options because after the initial chemotherapy, radiation, and/or surgery, if the cancer is hormone receptor-positive, a woman can be prescribed ET to reduce her risk of breast cancer recurrence.

Two types of ET that can be used to reduce the risk of breast cancer recurrence for women with hormone receptor-positive cancer are Tamoxifen and aromatase inhibitors. Tamoxifen is a selective estrogen receptor modulator and blocks estrogen receptors in breast cancer cells ("Hormone Therapy," 2016) and is typically prescribed for pre-menopausal women. Aromatase inhibitors (Letrozole/Femara, Anastrozole/Arimidex, and Exemestane/Aromasin) are given to women whose ovaries no longer produce estrogen (i.e. usually post-menopausal women or women receiving ovarian ablation). Aromatase inhibitors block aromatase, an enzyme in fat tissue, from making estrogen ("Hormone Therapy," 2016).
The beginnings of understanding the role that estrogen plays in breast cancer can historically be traced back to the late 1800s (“Evolution of Cancer,” 2014; Jones & Buzdar, 2004). Tamoxifen was originally introduced in 1967 as an antifertility agent in rats and was proposed for long term adjuvant therapy ten years later (Jordan, 2006; Maximov, Lee, & Jordan, 2013). In 1977, research targeting the aromatase enzyme also began (Maximov, Lee, & Jordan, 2013). Selective aromatase inhibitors were first reported in 1973 and began testing in clinical trials in the 1990’s (Jordan & Brodie, 2007).

For decades, Tamoxifen was prescribed for five years as standard treatment. In 2014, the American Society of Clinical Oncology (ASCO) convened a committee to conduct a systematic review to examine evidence from 2009 through 2013 trials regarding extending the duration of Tamoxifen from five to ten years (Burstein et al., 2014). The results of the MA.17R trial were also released in 2016 and showed benefits of taking aromatase inhibitors for up to ten years over five years (Goss et al., 2016). As of 2016, ASCO and the National Comprehensive Cancer Network generally recommend the following regimens for women with Stage I-III breast cancer (“Hormonal Therapy for Early-Stage,” 2016; NCCN Guidelines, 2014; NCCN Guidelines, 2016):

- Premenopausal women should take Tamoxifen for five years possibly combined with ovarian suppression or ablation. At the end of five years, if the woman is still premenopausal, she should consider taking Tamoxifen for another five years or stop taking ET. At the end of the first five years, if the woman is postmenopausal,
the woman could take aromatase inhibitors for five years or consider taking Tamoxifen for another five years.

- An alternate to Tamoxifen as initial treatment for premenopausal women is to take an aromatase inhibitor for five years with ovarian suppression or ablation.

- Postmenopausal women have the option to take an aromatase inhibitor for five years, consider Tamoxifen for ten years if aromatase inhibitors are not an option, or take Tamoxifen for a period of time, followed by an aromatase inhibitor until five or ten years of ET duration is reached.

**Problem of Endocrine Therapy Non-initiation, Non-adherence, and Discontinuation**

Numerous studies have been conducted to examine the problem of ET non-initiation, non-adherence, and discontinuation. These studies estimate the percentage of patients who do not initiate, are non-adherent, or discontinue as well as identify risk factors for non-initiation, non-adherence, or discontinuation. Studies conducted in Medicaid populations in New York and North Carolina showed non-initiation rates around 50% without intervention (Wagner et al., 2016; Wheeler et al., 2014). The results of four major systematic reviews will be presented.

Gotay and Dunn (2011) conducted a systematic review of studies published between 2007 and 2011 examining ET use in clinical practice with a sample size of at least 100. Fourteen studies met the inclusion criteria. The review showed that adherence rates after one year of ET usage ranged from 77–88%, and adherence rates in years four and five ranged from 27–49%. Middle-aged women (e.g. 50–69 years) appeared to be
most adherent. Low social support was negatively associated with adherence. Being married produced mixed results. Greater comorbidity and drug cost were also negatively associated with adherence. Side effects such as hot flashes, mood disturbances, and muscle aches largely contributed to patients not taking ET as did lack of communication from their providers regarding the importance of taking ET. Studies that examined use of both Tamoxifen and aromatase inhibitors reported better adherence to aromatase inhibitors, although the groups were different based on important factors such as age.

Murphy et al. (2012) conducted a systematic review to examine literature from 1998-2012 related to ET adherence and continuation in routine clinical settings, excluding clinical trials. Twenty-nine studies met the review inclusion criteria. The review showed that the prevalence of adherence ranged from 41–88% among Tamoxifen users and 50–91% for aromatase inhibitor users (Murphy et al., 2012). The percentage of Tamoxifen users who discontinued treatment ranged from 15–20% in the first year of therapy to 31–60% at the end of five years. The percentage of aromatase inhibitor users who discontinued treatment ranged from 5–25% during the first two years of therapy. Studies that examined users of both Tamoxifen and aromatase inhibitors aggregately showed discontinuation rates that ranged from 32–73% at the end of five years. Prospective studies describing Tamoxifen discontinuation revealed rates of 21%, 15%, and 31% at the end of 27, 33, and 63 month study periods, respectively. The systematic review also showed that women who originally took Tamoxifen and switched to an aromatase inhibitor after two to three years were less likely to adhere to treatment. The following factors were found to be negatively associated with adherence: Extremes of age
(i.e., older or younger), increasing out-of-pocket costs, follow-up care with a general practitioner (vs. cancer specialist), and treatment side effects. The following factors were found to be positively associated with adherence: taking more medications at baseline, referral to an oncologist, and earlier year at diagnosis. Low social support was found to be negatively associated with continuation.

Chlebowski, Kim, and Haque (2014) conducted a comprehensive literature review that showed the following factors were associated with ET discontinuation: side effects, higher comorbidity, financial considerations or low socioeconomic status, very young or older age, lack of provider recommendation, perception of low risk of recurrence, lack of social support, follow-up care with general practitioner vs. oncologist, African American race/ethnicity, cigarette smoking, and alcohol use. The presence of anxiety/depression was linked to better adherence. Findings regarding adherence stratified by race/ethnicity were mixed.

Roberts, Wheeler, and Reeder-Hayes (2015) conducted a systematic review of literature to determine racial/ethnic and socioeconomic disparities in ET adherence. The literature search included studies from 1978-2014. Fourteen articles met the inclusion criteria. Half of the articles showed there was significant racial/ethnic variation in ET usage, with four of the studies showing that Black women were less likely to initiate or adhere to ET than women of other racial/ethnic groups. Half of the articles showed there was no effect of race/ethnicity on ET use. Across racial/ethnic groups, side effects were among the top reported barriers to ET use. The relationship between cost and ET use is unclear, as results varied widely among studies. Referral to a medical oncologist was
positively associated with ET use. Among low-income women, higher perceived efficacy of patient-physician interactions and the quality of patient-provider communication was associated with increased ET continuation. Social support was not strongly associated with ET use.

Though the systematic reviews included qualitative studies, a two pertinent qualitative studies will be highlighted individually that are especially relevant to the proposed study. J Van Londen et al. (2015) conducted focus groups with fourteen breast cancer survivors taking adjuvant ET at the University of Pittsburgh. Results showed that initially, the women did not view taking ET as a decision but felt it something necessary for their future health. Once unanticipated symptoms occurred (including vasomotor symptoms, sexual dysfunction, insomnia, fatigue, cognitive dysfunction, pain, functional limitations, mood disturbance, and anxiety), women were uncertain about the cause of their symptoms, felt their friends and families could not relate, and felt that talking with their providers about the symptoms was difficult and could be seen as a sign of emotional/psychological problems. Frustration ensued, and women expressed dissatisfaction with the symptom management information from healthcare providers and found few effective and tolerable symptom management strategies. These issues caused the women to rethink their decision to take ET and to reweigh the pros and cons of whether the reduced risk of recurrence was worth losing their current quality of life.

Pellegrini et al. (2010) conducted semi-structured interviews with 34 women aged 35-65 at two French cancer centers. All participants were breast cancer patients and had been prescribed Tamoxifen. Findings showed that women confused the hormonal/anti-
hormonal effects of Tamoxifen and how it was related to contraceptive pills and hormone replacement therapy. Many women admitted lacking knowledge about Tamoxifen’s action and expressed doubts as to its necessity. A common theme women expressed was a dislike of drugs and a fear that Tamoxifen could cause other types of cancer. Women also expressed concern for the lack of treatment options for side effects, especially hot flashes and tiredness, and the need for clarification about the causes of perceived menopausal symptoms. Women said they received conflicting messages from their oncologist, other patients, and the internet. Women shared the distress and tension they felt while taking Tamoxifen because of the paradoxical situation that the drug’s purpose was to save life but it was causing their youthful looks and femininity to diminish.

Research is needed on modifiable factors associated with ET use as well as the development of behavioral and educational interventions intended to improve initiation, adherence, and continuation (Chlebowski, Kim, & Haque, 2014; Murphy et al., 2012).

**Existing Interventions**

Hurtado-de-Mendoza et al. (2016) published what the authors describe as the first systematic literature review examining behavioral interventions aimed at improving hormone therapy adherence. Five articles met the study inclusion criteria. The Patient’s Anastrozole Compliance to Therapy (PACT) was used in three of the studies. PACT employed educational materials (i.e. nine pamphlets and ten personal letters) about breast cancer, treatments, medication side effects, strategies for enhancing adherence, and information about diet and physical exercise as well as monthly reminders about
medication adherence. Variations of PACT were tested in three of the five studies, which were conducted in Germany, eighteen countries, and China, respectively. Another study consisted of a three-arm randomized controlled trial. Participants in one arm received personalized motivational reminder letters containing information including the importance and impact of disease, effects of AIs, and nurse contacts to answer questions as well as a breast cancer leaflet. Those assigned to the second arm received telephone calls from a nurse who conducted motivational interviewing and provided motivation, reminders, and individualized information regarding the patient’s specific problems. Finally, a third intervention used a two-arm randomized trial design to assign patients to an enhanced standard of care arm with written resource patient navigation information or to a written information plus one structured phone interview by a patient navigator. None of the interventions tested in the five studies significantly improved adherence or continuation when compared to usual care.

Studies have also tested novel communication strategies for patients and providers. Epstein et al. (2015) developed and tested a bi-directional text messaging application that simultaneously assesses patient adherence to ET and provides real-time feedback to the provider. The pilot study of 62 patients showed found the application helpful, easy to use, and not time consuming, with none of the patients discontinuing ET compared to nine percent of historical controls.

Another e-Health intervention is currently taking place in Montreal, Canada with results expected by June of 2018 (Meguerditchian et al., 2016). This e-Health tool integrates real-time analysis of health administrative claims data to provide point-of-care
decision support for clinicians. The purpose of the study is to determine the effectiveness of the intervention in reducing rates of ET discontinuation, to understand patient-level factors related to ET discontinuation, and to assess the integration of e-Health alerts regarding deviations from best practices in ET administration by cancer care teams.

Some interventions focus on relieving side effect symptoms and increasing quality of life through various means including exercise, sleep aids, and mindfulness. These studies typically have not measured whether the improvement in side effect symptoms or quality of life actually has improved ET usage. Hojlan, Molinska-Glura, and Milecki (2012) studied the results of an aerobic exercise program for a sample of forty-one premenopausal women. The program began six months after ET initiation. The program took place at the Rehabilitation Ward in the Greater Poland Cancer Centre. Body composition, body physique, and Quality of Life were evaluated before and after six, 12, and 18 months of ET using dual-energy x-ray absorptiometry (DXA) scans, anthropometric measurement techniques, and questionnaires from the European Organization for Research and Treatment of Cancer, respectively. In the eighteenth month of the study, results showed a significant increase in overall quality of life and functioning levels, improved positive body image, and a reduction in symptom levels.

The Yale Fitness Intervention Trial sought to determine the effects of a twelve-month aerobic-resistance exercise intervention compared to a home-based physical activity group (Knobf et al., 2016). Seventy-six patients were randomized to the exercise intervention, and 78 were randomized to the home group. When compared at one year, participants on Tamoxifen or no ET did not lose a significant amount of bone mineral
density except in the femoral neck, but participants on aromatase inhibitors had significant bone mineral density loss at all sites. Thus, the intervention proved ineffective for patients taking aromatase inhibitors.

Marshall-McKenna et al. (2015) studied the effect of a cool pad pillow topper versus standard care for women taking ET suffering from hot flushes and insomnia. Thirty-seven women were randomized to the intervention arm, and thirty-eight were randomized to the control arm. Sleep efficiency score increased twice as much in the intervention arm between two to four weeks of the intervention. There was also significantly greater reductions in hot flushes and the depression score for the intervention arm.

Mebis et al. (2016) reported on an eight-week Mindfulness-Based Stress Reduction (MBSR) intervention provided to twenty newly diagnosed breast cancer patients taking Tamoxifen. MBSR is a structured group intervention that is based on meditation and its daily life application. MBSR has proven effective when used to help cancer patients but had not yet been tested specifically with ET patients. Mebis et al. (2016) found that after receiving the MBSR intervention, the depression anxiety stress scale scores of the twenty patient cohort significantly decreased; however, the quality of life scale scores also decreased during the intervention but were improved over baseline six months post-intervention.

Future research should test these interventions’ impact on ET usage. Other approaches for improving ET adherence and continuation have been suggested such as enhancing nurse-patient communication regarding ET; clinical approaches to early
recognition and treatment of genitourinary side effects of ET; and utilizing patient support groups, and online communities and blogs; but these have yet to be tested. (Gotay & Dunn, 2011; Miaskowski, Shockney, & Chlebowski, 2008; Sousa et al., 2017).

Although the results of systematics reviews show little to no improvement in ET usage, there are certainly elements of interventions that have proven successful in decreasing side effects or increasing quality of life that have potential to improve ET usage. More research is needed to better understand how and when to intervene to improve ET usage among South Carolina women. More information is required to inform future practice and intervention, including which populations are most in need, how ET usage has changed over time, factors that are associated with longer ET usage, and which modifiable elements patients say could be the most useful.
CHAPTER THREE

METHODOLOGY

Research Questions

This dissertation research focused on female, South Carolina residents diagnosed with stage 0-III or unstaged hormone receptor-positive breast cancer and who were age 18-64 at diagnosis. This research was guided by six primary research questions:

AIM 1: To describe ET non-initiation, non-adherence, and duration by age, race, and temporal trend

Question 1: How do rates of ET non-initiation, non-adherence, and duration vary by age and race?

Hypothesis 1: ET non-initiation, non-adherence, and duration rates are worse among younger women and women of African American race.

Question 2: How have rates of ET non-initiation, non-adherence, and duration changed during the study period?

Hypothesis 2: There has been no change over the study period in ET non-initiation, non-adherence, and duration.

AIM 2: To identify demographic, clinical, and pharmaceutical factors that are associated with an individual’s ET usage duration

Question 3: Which demographic, clinical, and pharmaceutical factors are associated with an individual’s ET usage duration?
Demographic: race (white, African American, or other), age at diagnosis, marital status (married/unmarried), and rural/urban residency status (2013 Rural-Urban Continuum Codes)

Clinical: SEER summary breast cancer stage, receipt of chemotherapy (yes/no), and receipt of radiation therapy (yes/no)

Pharmaceutical: Type of endocrine therapy (Tamoxifen, Anastrozole/Arimidex, Exemestane/Aromasin, Letrozole/Femara, switched between aromatase inhibitors, switched between Tamoxifen and aromatase inhibitors), and filled alpha-agonist hypertensives prescription (yes/no), filled antidepressants prescription (yes/no), filled anticonvulsants prescription (yes/no), filled adrenals prescription (yes/no), filled nonsteroidal anti-inflammatory agents prescription (yes/no), filled anti-inflammatory agents prescription (yes/no), and filled vitamins prescription (B, C, D, K, and/or multivitamin) (yes/no).

**Hypothesis 3:** Women taking Tamoxifen will have lower ET usage duration than women taking aromatase inhibitors. Filling prescriptions for drugs known to alleviate side effects will be associated with increased ET usage duration.

**AIM 3:** To understand from the survivor perspective which modifiable factors could have the greatest impact on the likelihood of ET continuation.

**Question 4:** What are women’s’ perceptions regarding susceptibility/severity of breast cancer recurrence?
**Hypothesis 4:** Women’s susceptibility to breast cancer recurrence will be influenced by provider-patient communication. Women will perceive recurrence as severe but also be influenced by short-term quality of life preferences.

**Question 5:** What are the perceived benefits/barriers to ET continuation?

**Hypothesis 5:** Side effects will emerge as a major perceived barrier to ET continuation.

**Question 6:** What are the cues to action that encourage and support ET continuation?

**Hypothesis 6:** Provider-patient communication will play a key role in supporting ET continuation.

**Overall Research Design**

This study utilized a convergent parallel mixed methods design. A mixed methods design was chosen because the quantitative and qualitative approaches were structured to answer different but complementary questions. By choosing the convergent parallel design, the quantitative and qualitative data collection and analyses were able to take place simultaneously (Creswell & Clark, 2007). Their results were combined to provide a richer multidimensional understanding of the problem of ET non-initiation, non-adherence, and discontinuation than one approach alone (Curry & Nunez-Smith, 2014). Figure 3.1 illustrates the mixed methods design of the proposed study.
The methodology for the quantitative and qualitative branches of the study are described separately in the following sections. Both branches of the study include female South Carolina residents ages 18-64 at diagnosis with stage 0-III or unstaged hormone receptor-positive breast cancer; however, the individual women sampled in the qualitative study may or may not have been included in the quantitative study. See Appendix B for a table of variables that were used in the study.

The results of the quantitative and qualitative studies were used in conjunction to better inform emerging interventions. By highlighting how ET usage rates have changed since 2000 and which subgroups are in need of particular attention, interventions can glean from past improvements and use resources more effectively. Demographic, clinical, and pharmaceutical factors that are associated with longer ET usage duration can be
highlighted and tested in interventions. The results generated from the quantitative studies can be better validated and further explained by the qualitative study. Understanding from the survivor perspective which modifiable factors could have the greatest impact on the likelihood of ET continuation will be key to successful future interventions.

**Quantitative Research Design**

The aim of the quantitative study is 1) to describe ET non-initiation, non-adherence, and duration by age, race, and temporal trend and 2) identify demographic, clinical, and pharmaceutical factors that are associated with an individual’s ET usage duration.

**Data**

South Carolina Central Cancer Registry (SCCCR) incidence data from 2000-2014 was used to identify the study sample and then linked with South Carolina Medicaid prescription claims and administrative data from 2000 through September 2016. Variables were obtained from the SCCCR data and Medicaid prescription claims and administrative data as indicated in Appendix B. Non-initiation, non-adherence, and duration outcomes were studied through the Medicaid prescription claims data.

The data were linked by South Carolina Department of Revenue and Fiscal Affairs using probabilistic match by patient first name, last name, social security number, and date of birth. Data was de-identified prior to release to the researchers. Clemson
University (IRB2017-133) and South Carolina Department of Health and Environmental Control Institutional Review Boards approved the study.

Sample

This retrospective cohort study included SC women ages 18-64 at diagnosis with Stage 0-III or unstaged hormone receptor-positive breast cancer diagnosed between 2000 and 2014 (N=34,791). Breast cancer survivors who had SEER summary stage 7 cancer (N=1,531), who did not have estrogen receptor-positive cancer (N=5,183), who had prior cancer diagnoses (N=3,016), or whose cancer was identified through autopsy or death certificate (N=72) were excluded. After linking with SC Medicaid prescription data, breast cancer survivors who did not meet Medicaid eligibility inclusion criteria (i.e. no prescription data; N=18,762 or dually enrolled in Medicare; N=2,397) were also excluded. Those who were dually enrolled in Medicare were excluded because Medicare prescription claims were not available and therefore, ET usage could not be reliably tracked. After exclusions, there were 3,830 breast cancer survivors included in this study.

Dependent Variables

ET was defined as Tamoxifen or one of the following aromatase inhibitors: Anastrozole/Arimidex, Letrozole/Femara, or Exemestane/Aromasin, which were identified using National Drug Codes from the Medicaid prescription claims. Non-initiation was defined as not having any Medicaid prescription claims in the entire study period (from 2000-2016). The non-initiation rate was calculated by dividing the number of women who were ET non-initiators by the total number of eligible women (N=3,830). Non-adherence was defined as an ET medication possession ratio of less than 80 percent,
meaning that the pill supply covered less than 80 percent of the days from the first ET prescription dispense date through the last (Hershman et al., 2010). Duration of ET usage was calculated as the number of months between the first and last ET prescription dispense date. The proportion of women taking ET for at least 5 years was calculated by dividing the total number of women taking ET for at least 5 years by the total number of women initiating ET. Non-adherence and duration were calculated using the date dispensed and days supplied variables from the South Carolina Medicaid pharmacy claims file.

Independent Variables

For Research Questions 1-2 (Aim 1), the independent variables were year of breast cancer diagnosis, age at diagnosis (centered at mean), and race (0 = White, 1 = African American).

For Research Question 3 (Aim 2), independent variables included the factors hypothesized to be associated with ET usage duration based on literature review. The following demographic, clinical, and pharmaceutical factors were examined:

- Demographic: race (White, African American, or other), age at diagnosis, marital status (married/unmarried), and rural/urban residency status (2013 Rural-Urban Continuum Codes)
- Clinical: SEER summary breast cancer stage, receipt of chemotherapy (yes/no), and receipt of radiation therapy (yes/no)
- Pharmaceutical: Type of endocrine therapy (Tamoxifen, Anastrozole/Arimidex, Exemestane/Aromasin, Letrozole/Femara, switched between aromatase inhibitors,
switched between Tamoxifen and aromatase inhibitors), and filled alpha-agonist hypertensives prescription (yes/no), filled antidepressants prescription (yes/no), filled anticonvulsants prescription (yes/no), filled adrenals prescription (yes/no), filled nonsteroidal anti-inflammatory agents prescription (yes/no), filled anti-inflammatory agents prescription (yes/no), and filled vitamins prescription (B, C, D, K, and/or multivitamin) (yes/no). The prescriptions were identified by therapeutic class code and measured as ever having filled prescription during the study period as evidenced by Medicaid claims.

Provider specialty data had a high number of missing values and therefore was not included in the study.

Statistical Analysis: Aim 1

Demographic characteristics were compared between ET initiators and non-initiators using Chi-square tests. Relative risk was calculated for ET non-initiation for each of the age/race subgroups, with white/age ≥ 50 years as the reference group.

ET non-adherence and usage duration analyses were conducted among women who had filed at least one ET prescription claim through South Carolina Medicaid and who were diagnosed between 2000 – 2012 (N=1,366). Women diagnosed in 2013 and 2014 were excluded due to the shortened follow-up time since prescription records were only available through 2016. Chi-square tests were used to test for a difference in non-adherence rates among age/race subgroups (i.e. White/age < 50 years, African American/age < 50 years, White/age ≥ 50 years, African American/age ≥ 50 years).

Relative risk of ET non-adherence was calculated for each of the age/race subgroups,
with White/age ≥ 50 years as the reference group. Kruskal Wallis tests were used to test for a difference in median duration of ET usage by age/race subgroups as previously defined.

We also examined temporal trends in endocrine therapy (ET) non-initiation, non-adherence, and duration. Temporal trend was measured by calendar year of breast cancer diagnosis. The objective was to study participants in groups by year of breast cancer diagnosis since much of the information and motivation a woman receives for taking ET in the long-term is provided in the initial conversation with a provider when the patient receives the first ET prescription.

We used binary logistic regression to model whether an individual initiated ET or not. We also used binary logistic regression to model whether an individual was adherent to ET or not. We used ordinary least squares regression to estimate an individual’s ET usage duration in months. In each of the three models, we controlled for the covariates age (continuous variable centered at the mean) and race (0 = White, 1 = African American).

The data was first examined visually and descriptive statistics were calculated. The data did not meet the assumptions for linearity for any of the three outcomes, so non-linear time trend models were chosen. Non-initiation rates resembled a cubic pattern, so the time period was divided into three sub-periods to capture different trends occurring during these three sub-periods. Non-adherence and duration seemed to generally increase until the year 2006 and decrease thereafter, so time was divided into two sub-periods for these analyses.
To allow for nonlinear changes in ET non-initiation over time, we used a linear spline with knots at 2004 and 2009. For non-initiation, we divided time into the periods 2000 – 2004, 2005 – 2009, and 2010 – 2014. To allow for changes in ET non-adherence and duration observed before and after 2006, we used a linear spline with a knot at 2006. For non-adherence and duration, we observed changes in the periods 2000 – 2006 and 2007 – 2012. Wald tests were used to determine whether the coefficients for the different time periods were equivalent. Adjusted trends were examined by generating predicted probabilities of ET non-initiation and non-adherence as well as average duration. Stata 14.2 was used for all analyses.

Statistical Analysis: Aim 2

Multiple linear regression models were built to explore the impact of demographic, clinical, and pharmaceutical factors on ET usage duration in months (α = 0.05) for survivors diagnosed in 2000 – 2012 who filled at least one ET prescription (N=1,399). First, a series of models was made by singularly entering each of the independent variables with the dependent variable ET usage duration. Then, the combined effect of the independent variables that were significantly associated with the dependent variable was examined. Interactions terms were generated for each pair of significant independent variables and entered as a block to test for significant association with ET usage duration. The final model was generated by removing variables from the model that were no longer significant when controlling for other factors and adding the significant interaction terms. The final model included ET type; receipt of the following concurrent prescriptions: adrenals, nonsteroidal anti-inflammatory agents, anti-
inflammatory agents, and/or vitamins; and two-way interaction terms for ET
type/adrenals and anti-inflammatory agents/vitamins. StataMP 14.0 was used for all
analyses.

**Qualitative Research Design**

The qualitative study will aim to understand from the patient perspective which
modifiable factors have the greatest impact on the likelihood of ET continuation.

**Recruitment**

Breast cancer survivors were recruited through breast cancer support groups and
advocacy organizations and a local cancer survivorship institute. These included the
Greenville Health System Center for Integrative Oncology and Survivorship, the Komen
Foundation, and the South Carolina Witness Project as well as local breast cancer support
groups. Inclusion criteria for participation were female, English speaker, diagnosed with
Stage 0-III hormone receptor-positive breast cancer since 2000, completed breast cancer
treatment, and prescribed endocrine therapy between the ages of 18-64 years.

Recruitment for the fourth focus group heavily targeted women who had not initiated or
who had discontinued use of ET.

Patients meeting the study inclusion criteria were notified about the study during
clinic visits at the Center for Integrative Oncology and Survivorship. An e-mail invitation
was sent to a listserv of patients in the Greenville Health System Survivorship Registry, a
group of cancer survivors who had already consented to receive periodic notifications of
research studies for possible enrollment. In addition, the Komen Foundation, South
Carolina Witness Project, and local breast cancer support groups used the recruitment flyer (see APPENDIX C) to publicize the opportunity to participate in the study among their members through meeting announcements, personal contact, e-mail, and social media posts.

The recruitment flyer introduced potential participants to the project and invited them to participate. Interested participants were directed to call a project team member at an advertised phone number if willing to participate in a focus group. The project team member receiving the call used a script for screening (see APPENDIX D) interested participants and scheduled eligible participants for a focus group date and location. A reminder call was made one week prior to the focus group, and a reminder e-mail was sent one day prior to the group meeting. A Walmart gift card in the amount of $50 was provided to each participant in return for their time and transportation costs.

Data Collection

The focus groups lasted approximately 1.5 hours each and were held in neutral, private locations. All focus groups were conducted in English by two trained members of the project staff. Participants received an informational letter at the beginning of the focus group introducing them to the potential benefits and risks of the study. The moderators used a focus group guide developed by the research team members with qualitative, cancer-focused research experience after reviewing the existing literature to elicit participants’ experiences with ET. The guide was driven by elements of the Health Belief Model, specifically probing about perceived susceptibility to and seriousness of breast cancer recurrence, perceived benefits and barriers to ET continuation, and cues to action
that may support or encourage ET continuation. The various probes stimulated discussion about specific events and experiences that shaped participants’ opinions and attitudes regarding ET usage. The focus group guide is provided in APPENDIX E. Each focus group was audio-recorded and then transcribed by a reputable medical transcription service and verified by a member of the project staff. The group demographics were obtained via a brief, anonymous survey (see APPENDIX F) that was administered prior to the focus group. These demographics (e.g. age group, race, sex, ET type) were collected for purposes of external validity.

Data Analysis

Data analysis was completed by three members of the research team with input from a breast cancer survivors’ panel. The team used a grounded theory approach to identify themes and an inductive narrative approach to data analysis (Bradley, Curry & Dever, 2007; Kidd & Parshall, 2000; Thomas, 2006; Thorne, 2000). The team members began by analyzing one of the focus group transcripts to create a codebook. The codebook was expanded as the other three transcripts were analyzed. The analysis team followed a process detailed by Miles and Huberman (Miles & Huberman, 1994), dividing the coding duties so that each transcript was coded by at least two independent coders. The team met during the coding process to address consensus, update the coding structure, and revisit any previously coded text as needed. Codes were applied to transcripts using Atlas.ti software Version 7.5.10 (Friese, 2013).

Themes emerged during a subsequent review and analysis of code based queries using the Atlas.ti software. A priori codes drawn from the focus group guide, as informed
by the Health Belief Model served as the organizing analysis framework. As new themes emerged, the narrative was expanded. Two survivors who were not focus group participants assisted with identifying themes and expanding the narrative. There were fifteen final codes. Themes were examined by participant decision to continue or discontinue ET, and quotations exemplifying each theme are provided in the results.

Patient Engagement Studio Involvement

The Meharry-Vanderbilt Community-Engaged Research Core began developing the idea of a Community Engagement Studio in 2009, based on the idea of the Clinical and Translational Research Studio (Joosten et al., 2015). While the Clinical and Translational Research Studio convenes a panel of academic experts to provide project-specific input to researchers, the Community Engagement Studio convenes a panel of patients to consult with investigators on specific projects. These patients are viewed as consultants as opposed to research subjects and are recruited and paid accordingly. The novelty of the Community Engagement Studio as compared to other forms of patient-centered or community-based participatory research is that the investigators do not spend time recruiting the stakeholders (Joosten et al., 2015). The Community Engagement Studio staff members recruit and orient stakeholders, arrange and moderate the discussion, take notes during the meeting, and prepare a written summary after the meeting for the investigator. Through these means, investigator burden is minimized and efficiency is maximized (Joosten et al., 2015).

A team of staff, faculty, and community partners from the Meharry-Vanderbilt Community Engagement Studio developed a tool kit that other sites can use to replicate
their Community Engagement Studio model. The Greenville Health System has recently adapted the Meharry-Vanderbilt Community Engagement Studio model to form their own Patient Engagement Studio. The qualitative branch of the proposed research study was informed and guided by the input of a general Patient Engagement Studio and a breast cancer specific Patient Engagement Studio, both from the Greenville Health System.

A project team member presented the proposed study to the Greenville Health System Patient Engagement Studio in January 2017 at the beginning of the study design phase to ask for patient input regarding the qualitative study. This studio meets monthly to review research and to provide feedback to researchers regarding their projects. Two scientists with experience in quality initiatives, two academic physician clinicians from the Greenville Health System, a Patient Experience expert, an Engagement Navigator, five patient “experts,” and two breast cancer patients were present for the meeting. The two breast cancer patients were recruited specifically for this studio meeting due to the nature of the research topic.

The studio provided recommendations for patient recruitment including potential concerns of Medicaid patients and the need to be sensitive to those during recruitment planning, differences in older and younger patients and the need for clarifying the study population and research questions accordingly as well as distrust or disinterest among patients receiving a flyer through the mail and ways to overcome that barrier. Other tangible suggestions included conducting the focus groups in a neutral location in the community as opposed to a healthcare office, the appropriate amount to provide for
incentives, and adding an anonymous demographic survey to the focus groups so that the population could be generally described. Patients were intrigued by the project and its potential significance.

In addition to this first interaction with the Greenville Health System Patient Engagement Studio, a breast cancer specific Patient Engagement Studio was recruited by the Greenville Health System Patient Engagement Studio director. This breast cancer specific Patient Engagement Studio reviewed and provided input on the Health Belief Model framework and the focus group guide in June 2017. Feedback from the Studio included the following points, all of which were incorporated into the recruitment and production of the focus groups:

• Be more neutral in the recruitment flyer language. For instance, “Taking endocrine therapy is a ‘challenge’ for many women, rather than a using a negative word such as “struggle.”

• In recruitment, be specific about the names of the medications since some patients may not recognize the term “endocrine therapy.”

• Be more direct during the focus group introduction in telling women that if they have shared a lot, we might call on someone else (and ask you to stop) so that others can have a chance to share.

• When asking women to give the name they would like to be called by, don’t say “or a pseudonym.” That “creeps people out” and makes them feel scared of why this is so top secret. They’ve volunteered to come and want to share, so don’t make it weird.
• When asking about the initial conversation between the patient and “the” doctor, be aware that the patient is not treated by one doctor but usually a team of doctors. The patient has multiple appointments with multiple providers. In some clinics, this means going room to room on the same day. In others, it means driving to multiple offices over a period of time. Patients can receive mixed messaging from multiple providers.

• It would be helpful to add a question about whether the patient had someone who accompanied her to these appointments (like an advocate - someone who could help listen and help in decision making).

• Rather than asking if the patient was “hesitant” to ask questions when talking with the providers, ask if the patient felt “comfortable.”

• The patient may not understand the term “risk score,” so be more general and discuss “risk of the cancer coming back.”

• Patients and providers should take mutual responsibility for the patient’s healthcare. Rather than asking questions as if the provider was “doing something” to the patient, ask in a more open way such as, “When you were talking about the next steps, what came up? What did you and the provider discuss?” versus “Did your doctor tell you…”

• Understand that worry is volatile. The patient’s amount of worry about the cancer coming back is probably not the same all the time. Ask about a specific point in time.
• Be careful with how the conversation is directed in terms of future interventions. Do not imply that the patients have made the wrong choice if they have chosen to discontinue or not be adherent to the pill taking.

• Possibly use case scenarios to ask for intervention ideas, or possibly be more general and discuss any medication in general. For instance, “Sometimes doctors ask us to do things that are difficult/challenging. What are some strategies…”

• It may be helpful to note participant body language during the focus groups.

• Be more general with the conversation. For instance, instead of asking a series of pointed questions about the patient/provider interaction, say, “Tell us about your first conversation with your provider about taking Tamoxifen. How did it make you feel?”

• Eliminate the participant activities such as having patients come and mark their level of worry on a chart. Participants will be more comfortable just responding verbally instead.

Two members from this breast cancer specific Patient Engagement Studio helped interpret the focus group results in December 2017. The patient perspective added much value to the data analysis process. This meeting was especially helpful to hear ideas from the patient perspective on how to practically and concisely organize the results. For instance, Table 3.1 below presents the Cues to Action before and after the Patient Engagement Studio meeting.
Table 3.1 Cues to action before and after patient engagement studio involvement

<table>
<thead>
<tr>
<th>Cues to Action BEFORE Patient Engagement Studio Meeting to Analyze Focus Group Results</th>
<th>Cues to Action AFTER Patient Engagement Studio Meeting to Analyze Focus Group Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Doctor listens to patient, does not judge, &amp; does not minimize patient ET experience</td>
<td>• Provider listens, does not judge, &amp; does not minimize the survivor’s unique, individual ET experience</td>
</tr>
<tr>
<td>• Doctor open to helping lessen side effects with holistic approaches and switching ET meds</td>
<td>• Provider is transparent about side effects and shares upfront that there are possible ways, including holistic options, to alleviate potential side effects</td>
</tr>
<tr>
<td>• Doctor engages with patient as patient researches on her own and is part of social media platforms &amp; Medical community engagement in social media outlets</td>
<td>• Provider engages with survivor as survivor researches on her own and is part of social media platforms; provider shares latest ET research in patient-friendly manner</td>
</tr>
<tr>
<td>• Doctor initiates partnership with patient in recommending what is best for patient (patient desire to be treated as an individual – “We are all different”)</td>
<td>• Nurse navigator available to discuss the risk vs. benefit analysis of taking ET and answer “weird questions;” even better if nurse navigator initiates call</td>
</tr>
<tr>
<td>• Doctor openly shares latest ET research in patient-friendly manner</td>
<td>• Concept of a “pharmacy home” where survivor feels welcomed to ask questions</td>
</tr>
<tr>
<td>• Doctor is transparent about side effects and shares upfront that there are possible ways to alleviate potential side effects</td>
<td>• Nutritionist gives personalized dietary information based on medications and conditions</td>
</tr>
<tr>
<td>• Nutritionist gives personalized dietary information based on medications and conditions</td>
<td></td>
</tr>
<tr>
<td>• Concept of a “pharmacy home,” especially for rural patients</td>
<td></td>
</tr>
<tr>
<td>• Nurse navigator available to discuss the cost/benefit analysis of taking ET and answer “weird questions”; even better if nurse navigator initiates call</td>
<td></td>
</tr>
<tr>
<td>• Staff is friendly, caring, and prompt in returning messages</td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER FOUR

PAPER 1: “ENDOCRINE THERAPY USE IN THE 21ST CENTURY: TEMPORAL TRENDS ILLUSTRATE OPPORTUNITIES FOR IMPROVEMENT FOR SOUTH CAROLINA MEDICAID WOMEN”

Abstract

This study examines endocrine therapy (ET) non-initiation, non-adherence, and duration by age, race, temporal trend for South Carolina Medicaid-enrolled women diagnosed with hormone receptor-positive breast cancer between 2000 and 2014 (N=3,830).

Age, race, relative risk and median duration of ET use were compared. Temporal trends in ET non-initiation, non-adherence, and duration were observed using linear and logistic regression models, controlling for age and race.

Fifty three percent of women in the sample did not initiate ET, with highest non-initiation rates among African Americans and survivors under age 50. Of those who did initiate ET, 42% were non-adherent with a median ET usage duration of 37 months. Twenty one percent of initiators continued taking ET for five years or more. There was no change in the odds of ET non-initiation from 2000 – 2004 (OR = 1.02, p = 0.67). The odds of ET non-initiation decreased from 2005 – 2009 (OR = 0.81, p < 0.001) but then increased from 2010 – 2014 (OR = 1.08, p = 0.002). There was no change in the odds of ET non-adherence from 2000 – 2006 (OR = 1.02, p = 0.53), but from 2007 – 2012, the odds of ET non-adherence decreased each year (OR = 0.93, p = 0.02). The average ET
usage duration was increasing from 2000 – 2006 ($\beta = 2.74, p < 0.001$) but decreasing from 2006 – 2012 ($\beta = -1.46, p < 0.001$).

This study provides a realistic picture of the challenges associated with ET usage among South Carolina Medicaid breast cancer patients. It particularly highlights small improvements over time in ET usage rates, indicating more opportunities for improvement in ET initiation, adherence, and duration among younger women of lower socioeconomic status.

### Introduction

With advances in breast cancer screening and treatment, the population of female breast cancer survivors in the United States continues to grow and was estimated at over 3.5 million as of January 2016 [1]. This population is expected to total over 4.5 million by 2026 [1]. An important issue for female breast cancer survivors is reducing the risk of cancer recurrence. The risk of cancer recurrence can be influenced by many factors, including the original cancer and the initial treatment.

Endocrine therapy (ET) has been used for decades as the primary means of reducing the risk of breast cancer recurrence and improving disease-free survival in women with hormone receptor-positive Stage 0-III disease [2]. However, non-initiation, non-adherence, and discontinuation rates remain high [3, 4]. Numerous cross-sectional studies have been published highlighting subgroups of women experiencing the highest rates of ET non-initiation, non-adherence or discontinuation in certain populations, which have often included women younger than age 50 or older than age 70, of African American race, and/or of economically disadvantaged populations [5-11].
Even though there has been greater attention given to ET in oncology literature and practice [12, 13], a gap persists in the literature regarding how ET usage rates have changed over time. There is an impetus to particularly explore longitudinal patterns among populations that are known to experience special challenges related to cancer care, especially younger and economically disadvantaged women [6, 8, 9, 14]. The purpose of this study is to describe ET non-initiation, non-adherence, and duration by age, race, and temporal trend for South Carolina Medicaid-enrolled women who had hormone receptor-positive breast cancer diagnosed between 2000 and 2014.

Methods

Data Source

South Carolina Central Cancer Registry incidence data from 2000-2014 were used to identify the study sample and then linked with South Carolina Medicaid prescription claims and administrative data from 2000 through 2016 [15]. The data were linked by South Carolina Department of Revenue and Fiscal Affairs using probabilistic match by patient first name, last name, Social Security number, and date of birth. Data was de-identified prior to release to the researchers. Clemson University (IRB2017-133) and South Carolina Department of Health and Environmental Control Institutional Review Boards approved the study.

Sample

This retrospective cohort study included South Carolina (SC) women ages 18-64 at diagnosis with Stage 0-III or unstaged hormone receptor-positive breast cancer diagnosed between 2000 and 2014 (N=34,791). Breast cancer survivors who had SEER
summary stage 7 cancer (N=1,531), who did not have estrogen receptor-positive cancer (N=5,183), who had prior cancer diagnoses (N=3,016), or whose cancer was identified through autopsy or death certificate (N=72) were excluded. After linking with SC Medicaid prescription data, breast cancer survivors who did not meet Medicaid eligibility inclusion criteria (i.e. no prescription data; N=18,762 or dually enrolled in Medicare; N=2,397) were also excluded. Those who were dually enrolled in Medicare were excluded because Medicare prescription claims were not available and therefore, ET usage could not be reliably tracked. After exclusions, there were 3,830 breast cancer survivors included in this study. (Figure 4.1)

Definition of Non-initiation, Non-adherence, and Duration of ET Usage

ET was defined as Tamoxifen or one of the following aromatase inhibitors: Anastrozole/Arimidex, Letrozole/Femara, or Exemestane/Aromasin, which were identified using National Drug Codes from the Medicaid prescription claims. Non-initiation was defined as not having any Medicaid prescription claims in the entire study period (from 2000-2016). The non-initiation rate was calculated by dividing the number of women who were ET non-initiators by the total number of eligible women (N=3,830). Non-adherence was defined as an ET medication possession ratio of less than 80 percent, meaning that the pill supply covered less than 80 percent of the days from the first ET prescription dispense date through the last [16]. Duration of ET usage was calculated as the number of months between the first and last ET prescription dispense date. The proportion of women taking ET for at least 5 years was calculated by dividing the total number of women taking ET for at least 5 years by the total number of women initiating
ET. Non-adherence and duration were calculated using the date dispensed and days supplied variables from the South Carolina Medicaid pharmacy claims file.

**Statistical Analysis**

Demographic characteristics were compared between ET initiators and non-initiators using Chi-square tests. Relative risk was calculated for ET non-initiation for each of the age/race subgroups, with white/age ≥ 50 years as the reference group.

ET non-adherence and usage duration analyses were conducted among women who had filed at least one ET prescription claim through South Carolina Medicaid and who were diagnosed between 2000 – 2012 (N=1,366). Women diagnosed in 2013 and 2014 were excluded due to the shortened follow-up time since prescription records were only available through 2016. Chi-square tests were used to test for a difference in non-adherence rates among age/race subgroups (i.e. White/age < 50 years, African American/age < 50 years, White/age ≥ 50 years, African American/age ≥ 50 years). Relative risk of ET non-adherence was calculated for each of the age/race subgroups, with White/age ≥ 50 years as the reference group. Kruskal Wallis tests were used to test for a difference in median duration of ET usage by age/race subgroups as previously defined.

We also examined temporal trends in endocrine therapy (ET) non-initiation, non-adherence, and duration. Temporal trend was measured by calendar year of breast cancer diagnosis. The objective was to study participants in groups by year of breast cancer diagnosis since much of the information and motivation a woman receives for taking ET
in the long-term is provided in the initial conversation with a provider when the patient receives the first ET prescription.

We used binary logistic regression to model whether an individual initiated ET or not. We also used binary logistic regression to model whether an individual was adherent to ET or not. We used ordinary least squares regression to estimate an individual’s ET usage duration in months. In each of the three models, we controlled for the covariates age (continuous variable centered at the mean) and race (0 = White, 1 = African American).

The data was first examined visually and descriptive statistics were calculated. The data did not meet the assumptions for linearity for any of the three outcomes, so non-linear time trend models were chosen. Non-initiation rates resembled a cubic pattern, so the time period was divided into three sub-periods to capture different trends occurring during these three sub-periods. Non-adherence and duration seemed to generally increase until the year 2006 and decrease thereafter, so time was divided into two sub-periods for these analyses.

To allow for nonlinear changes in ET non-initiation over time, we used a linear spline with knots at 2004 and 2009. For non-initiation, we divided time into the periods 2000 – 2004, 2005 – 2009, and 2010 – 2014. To allow for changes in ET non-adherence and duration observed before and after 2006, we used a linear spline with a knot at 2006. For non-adherence and duration, we observed changes in the periods 2000 – 2006 and 2007 – 2012. Wald tests were used to determine whether the coefficients for the different time periods were equivalent. Adjusted trends were examined by generating predicted
probabilities of ET non-initiation and non-adherence as well as average duration. Stata 14.2 was used for all analyses.

**Results**

**Initiation**

There were 3,830 Medicaid-eligible women who had hormone receptor-positive breast cancer diagnosed between 2000 and 2014 who met the inclusion criteria for this analysis. Approximately half of these women (53%, N=2,030) did not fill an ET prescription as evidenced by Medicaid prescription claims.

Demographic characteristics of ET initiators and non-initiators were examined. (Table 4.1) The highest non-initiation rates were seen in African Americans (55% non-initiation) and survivors under age 50 (56% non-initiation). Compared to White women ≥ 50, the relative risks for African Americans < 50, White women < 50 and African American women ≥ 50 were 1.24 (95% CI: 1.14, 1.36), 1.23 (95% CI: 1.12, 1.34), and 1.16 (95% CI: 1.05, 1.28), respectively. Non-initiation rates and risk ratios by age/race subgroups are presented in Table 4.2.

**Non-Adherence**

Among all initiators, 42% (N=755) of survivors were non-adherent. There was a statistically significant difference in the non-adherence rates among the age/race subgroups ($\chi^2 = 57.91$, df = 3, $p < 0.001$). African American women younger than 50 years old had the highest non-adherence rates (55%) and were 1.67 (95% CI: [1.43, 1.95]) times as likely to be non-adherent to ET compared to the most adherent group (i.e.
White women age 50 or older). Risk ratios for non-adherence by age/race subgroups are presented in Table 4.3.

**Duration**

The median duration of ET usage from 2000 – 2012 was 37 months (Range: 0 – 184). Twenty-one percent of survivors (N=288) who initiated ET during 2000 – 2012 continued taking ET for five or more years. Five percent (N=90) only filled one ET prescription and did not refill after the first prescription. A Kruskal Wallis test showed there was no significant difference in median duration of ET usage by age/race subgroups ($\chi^2 = 1.12, \text{df} = 3, p = 0.77$).

**Temporal Trends**

The non-initiation rates by year of diagnosis are presented in Table 4.4. We found a significant difference in the ET non-initiation trends in the three time periods examined ($\chi^2(3) = 126.74, p < 0.001$). There was no change in the odds of ET non-initiation from 2000 – 2004 (OR = 1.02, $p = 0.67$). The odds of ET non-initiation decreased from 2005 – 2009 (OR = 0.81, $p < 0.001$) but then increased from 2010 – 2014 (OR = 1.08, $p = 0.002$).

The non-adherence rates and median duration of ET usage by year of breast cancer diagnosis are presented in Table 4.5. Results showed that there was a significant difference in the ET non-adherence trends before and after 2006 ($\chi^2(2) = 7.01, p = 0.03$). There was no change in the odds of ET non-adherence from 2000 – 2006 (OR = 1.02, $p = 0.53$), but from 2007 – 2012, the odds of ET non-adherence decreased each year (OR = 0.93, $p = 0.02$).
There was also a significant difference in the ET usage duration trends before and after 2006 (F(2, 1361) = 15.51, \( p < 0.001 \)). The average ET usage duration was increasing from 2000 – 2006 (\( \beta = 2.74, p < 0.001 \)) but decreasing from 2007 – 2012 (\( \beta = -1.46, p < 0.001 \)).

Figure 4.2 presents the adjusted average probabilities of ET non-initiation and non-adherence by year of breast cancer diagnosis as well as the adjusted average ET usage duration by year of breast cancer diagnosis.

**Conclusion**

This is the first study to use longitudinal data to examine trends in ET non-initiation, non-adherence, and duration among South Carolina Medicaid-enrolled women. Our findings point to several opportunities for further investigation and possible intervention. First, 53% of Medicaid enrollees never initiated treatment. This is of concern for multiple reasons. Secondly, when examining the subgroups for possible intervention to increase ET adherence, women under 50 years of age, and especially African American women under age 50, demand particular attention. Thirdly, the odds of ET non-initiation was increasing from 2010 – 2014 and the average duration of ET usage was decreasing from 2007 – 2012.

There was, however, a significant decline in the odds of ET non-adherence from 2007 to 2012, and the odds of ET non-initiation had decreased previously in the period from 2005 – 2009 with average duration increasing from 2000 - 2006. These positive findings are encouraging given the recent attention touting the benefits of ET adherence.
for women [6]. Because the study spans more than a decade, this data offers one of the first long-term assessments of these challenges. The opportunity is to build on the modest positive improvements seen earlier in the past decade.

Those who initiated ET had a median ET usage duration of 37 months (Range: 0 – 184), with 21% of initiators continuing ET for five years or more. Given ASCO’s recommendations since 2014 to increase ET usage to up to ten years and multiple trials showing disease-free survival benefits for those who take ET for 5-10 years [12, 13, 17-19], it is alarming that only one-fifth of initiators continued for five years or more and that the temporal trends showed negative results for the most recent periods concerning improvement in individual level ET initiation and duration.

We found that women under age 50 were less likely to be adherent to ET. These findings are consistent with the literature on ET usage [8], which suggests that younger women have unique considerations in their ET decision-making framework, including fertility [20] and reluctance to believe ET was a necessary part of their breast cancer treatment [21]. These explanatory factors are not fully understood and warrant further research [22].

Some important limitations accompany this analysis. First, we assumed that if a person was Medicaid-eligible and did not have a Medicaid pharmacy claim for ET, she did not take ET, as there was no other way to document ET received through other payment sources. Medicaid recipients do not typically have secondary payment sources other than self-pay, so it is not anticipated that significant missed data resulted from this limitation. Second, we assumed that if a person filled a prescription, then she took those
pills. There was no way to account for whether the women actually took the medication. Furthermore, our findings were based on data from the South Carolina Medicaid population and may not be generalizable to other populations.

While promising that rates of non-initiation showed slight yet significant decreasing trends and duration showed a slight yet significant increasing trend, these results sound a call for greater improvements in ET usage rates among populations of low socioeconomic status. More research is needed to decipher potential factors influencing slight improvements seen since 2000 in order to capitalize on these efforts to further reduce rates of non-initiation and non-adherence and increase duration in the future. Moreover, longitudinal analyses among women with private insurance or Medicare are warranted to compare changes in ET usage rates over time among these populations. Additional analyses should also consider grouping participants by the year corresponding to the middle or end of an individual’s ET duration period, where this study chose to group participants by year of breast cancer diagnosis.

References


**Figures**

**Figure 4.1.** Cohort selection criteria

Females diagnosed with breast cancer between ages 18-64 during 2000-2014 residing in South Carolina, identified by SC Central Cancer Registry (N=34,791)

1. Not estrogen receptor-positive (N=5,183)
2. Cancer identified through autopsy or death certificate (N=72)
3. Dually enrolled in Medicare (N=2,397)

**Figure 4.2** Adjusted trends in South Carolina Medicaid breast cancer survivors’ endocrine therapy non-initiation, non-adherence, and duration by year of breast cancer diagnosis

*Gallick & Breyer, 2017*
### Tables

**Table 4.1** Demographic characteristics of South Carolina Medicaid breast cancer survivor endocrine therapy initiators and non-initiators, 2000 – 2014

<table>
<thead>
<tr>
<th></th>
<th>Initiators (N=2,030)</th>
<th>Non-initiators (N=1,800)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>50%</td>
<td>53%</td>
<td>0.025</td>
</tr>
<tr>
<td>African American</td>
<td>49%</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td><strong>Age, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50 years old</td>
<td>40%</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>≥ 50 years old</td>
<td>60%</td>
<td>53%</td>
<td></td>
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</tbody>
</table>

Note: The statistical differences were tested using $\chi^2$ tests.

**Table 4.2** Endocrine therapy non-initiation rates (%) and relative ratios (95% CI) by age and race subgroups of South Carolina Medicaid breast cancer survivors

<table>
<thead>
<tr>
<th></th>
<th>Rate</th>
<th>&lt; 50 Years</th>
<th>≥ 50 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>56%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>57%</td>
<td>53%</td>
<td></td>
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</tbody>
</table>

**Relative Risk**

<table>
<thead>
<tr>
<th></th>
<th>Rate</th>
<th>&lt; 50 Years</th>
<th>≥ 50 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1.23 (1.12, 1.34)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>1.24 (1.14, 1.36)</td>
<td>1.16 (1.05, 1.28)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4.3** Endocrine therapy non-adherence rates (%) and relative ratios (95% CI) by age and race subgroups of South Carolina Medicaid breast cancer survivors

<table>
<thead>
<tr>
<th></th>
<th>Rate</th>
<th>&lt; 50 Years</th>
<th>≥ 50 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>45%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>55%</td>
<td>34%</td>
<td></td>
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</tbody>
</table>

**Relative Risk**

<table>
<thead>
<tr>
<th></th>
<th>Rate</th>
<th>&lt; 50 Years</th>
<th>≥ 50 Years</th>
</tr>
</thead>
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<tr>
<td>White</td>
<td>1.36 (1.18, 1.63)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>1.67 (1.43, 1.95)</td>
<td>1.04 (0.86, 1.27)</td>
<td></td>
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</table>
Table 4.4 Endocrine therapy non-initiation rates among South Carolina Medicaid breast cancer survivors by year of diagnosis, 2000 – 2014

<table>
<thead>
<tr>
<th>Year of Breast Cancer Diagnosis</th>
<th>White/age &lt; 50 years (N=1,093), %</th>
<th>African American/age &lt; 50 years (N=1,034), %</th>
<th>White/age ≥ 50 years (N=872), %</th>
<th>African American/age ≥ 50 years (N=757), %</th>
<th>All Women in Sample (N=3,830), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>66.2</td>
<td>69.2</td>
<td>63.4</td>
<td>61.5</td>
<td>65.3</td>
</tr>
<tr>
<td>2001</td>
<td>75.0</td>
<td>69.4</td>
<td>40.0</td>
<td>65.9</td>
<td>64.0</td>
</tr>
<tr>
<td>2002</td>
<td>69.2</td>
<td>68.1</td>
<td>61.0</td>
<td>73.2</td>
<td>68.2</td>
</tr>
<tr>
<td>2003</td>
<td>73.1</td>
<td>63.0</td>
<td>73.5</td>
<td>66.7</td>
<td>69.2</td>
</tr>
<tr>
<td>2004</td>
<td>64.1</td>
<td>71.1</td>
<td>64.9</td>
<td>74.4</td>
<td>67.3</td>
</tr>
<tr>
<td>2005</td>
<td>53.2</td>
<td>64.7</td>
<td>60.0</td>
<td>57.1</td>
<td>58.3</td>
</tr>
<tr>
<td>2006</td>
<td>52.5</td>
<td>50.0</td>
<td>43.5</td>
<td>74.3</td>
<td>53.4</td>
</tr>
<tr>
<td>2007</td>
<td>50.0</td>
<td>49.2</td>
<td>41.9</td>
<td>56.8</td>
<td>49.0</td>
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<tr>
<td>2008</td>
<td>58.7</td>
<td>53.7</td>
<td>52.5</td>
<td>50.0</td>
<td>53.4</td>
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<tr>
<td>2009</td>
<td>47.1</td>
<td>43.2</td>
<td>28.3</td>
<td>38.9</td>
<td>40.7</td>
</tr>
<tr>
<td>2010</td>
<td>41.4</td>
<td>46.2</td>
<td>32.8</td>
<td>38.9</td>
<td>40.3</td>
</tr>
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<td>2011</td>
<td>45.3</td>
<td>50.7</td>
<td>31.1</td>
<td>48.1</td>
<td>42.6</td>
</tr>
<tr>
<td>2012</td>
<td>55.4</td>
<td>52.5</td>
<td>41.9</td>
<td>47.3</td>
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<tr>
<td>2013</td>
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<td>54.5</td>
<td>42.0</td>
<td>37.9</td>
<td>46.0</td>
</tr>
<tr>
<td>2014</td>
<td>58.3</td>
<td>54.3</td>
<td>46.0</td>
<td>39.5</td>
<td>50.1</td>
</tr>
<tr>
<td>2000-14</td>
<td>57.3</td>
<td>57.3</td>
<td>48.2</td>
<td>55.4</td>
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</table>
Table 4.5 Demographics and endocrine therapy usage non-adherence and duration patterns in South Carolina Medicaid breast cancer survivors by year of diagnosis, 2000 – 2014

<table>
<thead>
<tr>
<th>Year of Diagnosis(a)</th>
<th>Total No. in Sample(b)</th>
<th>No. White, age &lt; 50 years</th>
<th>No. African American, age &lt; 50 years</th>
<th>No. White, age ≥ 50 years</th>
<th>No. African American, age ≥ 50 years</th>
<th>Percent Non-adherent (N)</th>
<th>Median Duration of ET (range), months(b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>74</td>
<td>22</td>
<td>16</td>
<td>15</td>
<td>20</td>
<td>46% (34)</td>
<td>20.5 (0 – 184)</td>
</tr>
<tr>
<td>2001</td>
<td>77</td>
<td>14</td>
<td>22</td>
<td>24</td>
<td>15</td>
<td>47% (36)</td>
<td>22 (0 – 142)</td>
</tr>
<tr>
<td>2002</td>
<td>77</td>
<td>20</td>
<td>29</td>
<td>16</td>
<td>11</td>
<td>47% (36)</td>
<td>30 (0 – 167)</td>
</tr>
<tr>
<td>2003</td>
<td>74</td>
<td>18</td>
<td>27</td>
<td>13</td>
<td>16</td>
<td>50% (37)</td>
<td>23.5 (0 – 112)</td>
</tr>
<tr>
<td>2004</td>
<td>54</td>
<td>14</td>
<td>13</td>
<td>13</td>
<td>10</td>
<td>44% (24)</td>
<td>21.5 (0 – 147)</td>
</tr>
<tr>
<td>2005</td>
<td>78</td>
<td>29</td>
<td>18</td>
<td>14</td>
<td>15</td>
<td>50% (39)</td>
<td>34 (0 – 123)</td>
</tr>
<tr>
<td>2006</td>
<td>88</td>
<td>28</td>
<td>23</td>
<td>26</td>
<td>9</td>
<td>50% (44)</td>
<td>49.5 (0 – 119)</td>
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<tr>
<td>2007</td>
<td>103</td>
<td>27</td>
<td>33</td>
<td>25</td>
<td>16</td>
<td>47% (48)</td>
<td>46 (0 – 111)</td>
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<tr>
<td>2008</td>
<td>96</td>
<td>26</td>
<td>25</td>
<td>19</td>
<td>23</td>
<td>47% (45)</td>
<td>39 (0 – 90)</td>
</tr>
<tr>
<td>2009</td>
<td>162</td>
<td>45</td>
<td>42</td>
<td>38</td>
<td>33</td>
<td>42% (68)</td>
<td>46.5 (0 – 138)</td>
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<tr>
<td>2010</td>
<td>173</td>
<td>51</td>
<td>42</td>
<td>43</td>
<td>33</td>
<td>42% (72)</td>
<td>41 (0 – 79)</td>
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<tr>
<td>2011</td>
<td>179</td>
<td>47</td>
<td>36</td>
<td>62</td>
<td>28</td>
<td>34% (61)</td>
<td>45 (0 – 137)</td>
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<td>2012</td>
<td>164</td>
<td>41</td>
<td>38</td>
<td>54</td>
<td>29</td>
<td>38% (62)</td>
<td>39 (0 – 142)</td>
</tr>
</tbody>
</table>

\(a\)Survivors diagnosed in 2013 and 2014 could only be followed for 48 and 36 months, respectively.

\(b\)Sample included all female Medicaid recipients ages 18-64 at diagnosis with Stage 0-III or unstaged hormone receptor-positive breast cancer diagnosed between 2000 and 2014 who filled at least one ET prescription. Survivors with prior cancer diagnoses, who were dually enrolled in Medicare, or whose cancer was identified through autopsy or death certificate were excluded.
CHAPTER FIVE

PAPER 2: “FACTORS ASSOCIATED WITH LONGER ENDOCRINE THERAPY USE BY SOUTH CAROLINA MEDICAID-INSURED BREAST CANCER SURVIVORS”

Abstract

Endocrine therapy (ET) discontinuation rates remain high, despite its use for decades as the primary means of increasing disease free survival in women with hormone receptor-positive Stage 0-III breast cancer. Research informing enhanced intervention methods is needed as is research regarding the optimal timing of these interventions. The objective of this study is to determine demographic, clinical, and pharmaceutical factors that are associated with longer ET usage duration.

South Carolina Central Cancer Registry incidence data linked with South Carolina Medicaid prescription claims and administrative data were used. The study included a sample (N=1,399) of female South Carolina Medicaid recipients with hormone receptor-positive breast cancer diagnosed between 2000 and 2012 who filled at least one ET prescription. A series of multiple regression models were built to explore the association of demographic, clinical, and pharmaceutical factors with ET usage duration.

Multiple linear regression analysis showed that none of the demographic or clinical factors tested were significantly associated with ET usage duration. However, the type of ET taken as well as receipt of the prescriptions that could have been used to alleviate side effects (adrenals, nonsteroidal anti-inflammatory agents, anti-inflammatory agents, and vitamins) were significantly associated.
Our study highlights the potential value of concurrent prescriptions for improving ET usage duration, with an optimal intervention point before 14 months post ET initiation. Further research is needed to test pharmacologic interventions that may significantly increase ET duration as well as other non-pharmacologic strategies for side effect management.

Introduction

Endocrine therapy (ET) has been used for decades as the primary means of increasing disease free survival in women with hormone receptor-positive Stage 0-III breast cancer, yet discontinuation rates remain high [1, 2]. Murphy et al. (2012) conducted a systematic review to examine literature from 1998-2012 related to ET adherence and continuation in routine clinical settings. The percentage of tamoxifen users who discontinued treatment ranged from 15–20% in the first year of therapy to 31–60% at the end of five years [3]. The percentage of aromatase inhibitor users who discontinued treatment ranged from 5–25% during the first two years of therapy [3]. Studies examining both tamoxifen and aromatase inhibitor users showed discontinuation rates between 32-73% by the end of five years of treatment [3].

Numerous studies have been conducted to examine factors that contribute toward non-adherent, non-persistent ET use. The following subgroups have been highlighted as at-risk: low socioeconomic status [4-6], low social support [3, 7-8], greater comorbidity [7-8], greater drug cost [3, 7], greater side effects [3, 8], lack of provider communication
regarding the importance of ET [3, 8], extremes of age [3, 8], and follow-up care with a general practitioner versus a cancer specialist [3, 8].

As literature has established, the Medicaid population is at high risk for poor ET usage [4-6]. Interventions to improve ET usage have been conducted in various populations, but there is especially a lack of evidence of how to improve ET usage among Medicaid recipients [9-12]. Qualitative studies reveal that side effects, primarily menopausal symptoms and/or joint pain, emerge as the major barrier to continuing ET for the recommended duration [13-17]. Tested interventions have focused on patient education and side effect management, including elements such as educational materials, phone or text message reminders, vaginal moisturizers, topical oil for joint pain, and cool pad pillow toppers [9, 18-21]. Recent systematic reviews of interventions targeted at improving ET usage showed no meaningful improvements over usual care, highlighting the urgent need for more effective interventions [9, 21-22]. Medications have been recommended to alleviate ET side effects, including alpha-agonist hypertensives, antidepressants, anticonvulsants, adrenals, nonsteroidal anti-inflammatory agents, anti-inflammatory agents, and vitamins [23-28]. While the most effective methods for necessary intervention are still under development, there is also a gap in the literature regarding the optimal timing for intervention. The aim of this study is to identify demographic, clinical, and pharmaceutical factors that are associated with an individual’s ET usage duration in hopes that these factors can better inform emerging interventions.
Methods

Data Source

The study sample was identified using South Carolina Central Cancer Registry incidence data from 2000-2012 linked with South Carolina Medicaid prescription claims and administrative data from 2000 through 2016 [29]. Probabilistic match by patient first name, last name, Social Security number, and date of birth was used for the linkage performed by the South Carolina Department of Revenue and Fiscal Affairs. Data was de-identified prior to release to the researchers. Clemson University and South Carolina Department of Health and Environmental Control Institutional Review Boards approved this study.

Sample

The study sample (N=1,399) included all female South Carolina Medicaid recipients ages 18-64 at diagnosis with stage 0-III or unstaged hormone receptor-positive breast cancer diagnosed between 2000 and 2012 and who filled at least one ET prescription. Exclusion criteria were SEER summary stage 7 cancer, estrogen receptor-negative cancers, prior cancer diagnoses, cancer identification through autopsy or death certificate, and dual enrollment in Medicare (since Medicare prescription claim data was not available).

Dependent Variable

ET included tamoxifen and the following aromatase inhibitors: Anastrozole/Arimidex, Letrozole/Femara, or Exemestane/Aromasin. Drugs were identified using therapeutic class and National Drug Codes from Medicaid prescription
claims. ET usage duration was calculated as the number of months between the first and last ET prescription dispense dates using the date dispensed and days supplied variables from the South Carolina Medicaid pharmacy claims file. Participants were followed from the time of their first ET prescription filled through 2016.

**Independent Variables**

Independent variables included the factors hypothesized to be associated with ET usage duration based on literature review. The following demographic, clinical, and pharmaceutical factors were examined:

- **Demographic:** race (white, African American, or other), age at diagnosis, marital status (married/unmarried), and rural/urban residency status (2013 Rural-Urban Continuum Codes)

- **Clinical:** SEER summary breast cancer stage, receipt of chemotherapy (yes/no), and receipt of radiation therapy (yes/no)

- **Pharmaceutical:** Type of endocrine therapy (Tamoxifen, Anastrozole/Arimidex, Exemestane/Aromasin, Letrozole/Femara, switched between aromatase inhibitors, switched between Tamoxifen and aromatase inhibitors), and filled alpha-agonist hypertensives prescription (yes/no), filled antidepressants prescription (yes/no), filled anticonvulsants prescription (yes/no), filled adrenals prescription (yes/no), filled nonsteroidal anti-inflammatory agents prescription (yes/no), filled anti-inflammatory agents prescription (yes/no), and filled vitamins prescription (B, C, D, K, and/or multivitamin) (yes/no). The prescriptions were identified by
therapeutic class code and measured as ever having filled prescription during the study period as evidenced by Medicaid claims.

Provider specialty data had a high number of missing values and therefore was not included in the study.

**Statistical Analysis**

Multiple linear regression models were built to explore the impact of demographic, clinical, and pharmaceutical factors on ET usage duration in months ($\alpha = 0.05$). First, a series of models was made by singularly entering each of the independent variables with the dependent variable ET usage duration. Then, the combined effect of the independent variables that were significantly associated with the dependent variable was examined. Interactions terms were generated for each pair of significant independent variables and entered as a block to test for significant association with ET usage duration. The final model was generated by removing variables from the model that were no longer significant when controlling for other factors and adding the significant interaction terms. The final model included ET type; receipt of the following concurrent prescriptions: adrenals, nonsteroidal anti-inflammatory agents, anti-inflammatory agents, and/or vitamins; and ET type/adrenals and anti-inflammatory agents/vitamins interactions. StataMP 14.0 was used for all analyses.

**Results**

The study sample consisted of 1,399 hormone receptor-positive cancer survivors. Fifty-three percent of women in the study sample were white ($N=744$), and 44% were
African American (N=622). The median age at diagnosis was 49 years (Range: 21 – 64). Twenty-nine percent (N=376) were single, 36% (N=456) were married, and 16% (N=210) were divorced. Following the 2013 Rural-Urban Continuum Codes for South Carolina, 79% (N=1,101) of the women resided in metropolitan counties. The breakdown by SEER summary breast cancer stage was as follows: Stage 0 (N=164, 12%), Stage 1 (N=576, 41%), Stage 2 (N=24, 2%), Stage 3 (N=530, 38%), Stage 4 (N=88, 6%), and unknown (N=17, 1%). Fifty-three percent (N=743) of the sample had received chemotherapy, and 44% (N=612) had received radiation therapy.

Forty-one percent (N=577) of the women were taking Tamoxifen, and 36% were taking aromatase inhibitors (Anastrozole/Arimidex: N=199, 14%, Exemestane/Aromasin: N=34, 2%, Letrozole/Femara: N=186, 13%, switched between different aromatase inhibitors: N=91, 7%). Twenty-two percent (N=312) of the women switched between Tamoxifen and aromatase inhibitors.

Eight percent (N=110) had filled a prescription for alpha-agonist hypertensives, 60% (N=838) had filled a prescription for antidepressants, 32% (N=447) had filled a prescription for anticonvulsants, 60% (N=843) had filled a prescription for adrenals, 57% (N=801) had filled a prescription for nonsteroidal anti-inflammatory agents, 28% (N=386) had filled a prescription for anti-inflammatory agents, and 27% (N=379) had filled a prescription for vitamins (B, C, D, K, and/or multivitamins).

Multiple linear regression analysis showed that none of the demographic or clinical factors tested (race, age at diagnosis, marital status, and rural/urban status, SEER summary breast cancer stage, receipt of chemotherapy, receipt of radiation
therapy) were significantly associated with ET usage duration. When base models were created with each of the pharmaceutical variables and ET usage duration as the dependent variable, each of the pharmaceutical variables were significantly associated with ET usage duration except Alpha-agonist hypertensives \( (\beta = -1.80, p = 0.51) \). The results are shown in Table 5.1 as Models A – G.

Next, all of the pharmaceutical variables were included in a regression model with ET usage duration as the dependent variable. See Table 5.1, Model H. The results showed that receipt of antidepressants and anticonvulsants was no longer significantly associated with ET usage duration when controlling for the other pharmaceutical variables. These variables were removed from the model. Interaction terms were generated between each pair of pharmaceutical variables and entered as a block in the model; however, only the interactions between ET type/adrenals \( (\beta = -2.5, p < 0.001) \) and anti-inflammatory agents/vitamins \( (\beta = -9.96, p = 0.04) \) were significant. The final model was developed and included ET type; receipt of the following concurrent prescriptions: adrenals, nonsteroidal anti-inflammatory agents, anti-inflammatory agents, and/or vitamins; and anti-inflammatory agents/vitamins and ET type/adrenals interactions. See Table 5.2.

**Conclusion**

**Key Results & Interpretation**

Our study found that none of the demographic or clinical factors examined were significantly associated with an individual’s ET usage duration. The sample’s socioeconomic and age (<64) homogeneity possibly overwhelmed differences in race,
marital status, or rural/urban residency status, or as other studies have shown, side effect management may be more impactful than demographic or clinical aspects [13-17, 30].

Similarly, Friese et al. found that race, SEER stage, worry about recurrence, and primary oncology provider were not significantly associated with ET usage in a population of Los Angeles County and Detroit metropolitan area breast cancer survivors; however, age and taking two or more medications weekly were significantly associated with greater ET persistence [31]. Women ages 20-79 were included in the Friese et al. study. [31]. Calip et al. also found that in a sample of 40,009 women, increasing polypharmacy and pill burden were associated with greater ET adherence, but different effects were found depending on the medication class [32]. For example, lipid-lowering drugs and antihypertensives were associated with higher adherence, and opioid-containing analgesics, anxiolytics/antipsychotics, antidepressants, and insulin therapy were associated with lower adherence [32].

Our study highlights the association between ET usage duration with ET type and with other prescriptions that were possibly prescribed for side effect management. The final model included ET type and receipt of certain prescriptions, which can be used to alleviate common side effects of Tamoxifen and aromatase inhibitors: adrenals, nonsteroidal anti-inflammatory agents, anti-inflammatory agents, and vitamins. The model showed that the average ET duration was 14 months for women meeting the sample inclusion criteria, taking Tamoxifen, and who had not filled a prescription for any of the following: adrenals, nonsteroidal anti-inflammatory agents, anti-inflammatory agents, and/or vitamins. Taking Anastrozole/Arimidex significantly
increased ET usage duration by an average of 12.2 months over the duration for Tamoxifen, and taking Letrozole/Femara significantly increased duration by 8.9 months. Women who switched between different aromatase inhibitors or between Tamoxifen and aromatase inhibitors took ET for an average of 23.6 or 29.3 months longer, respectively, than Tamoxifen-only users. Having the following prescriptions was also significantly associated with increased ET duration: adrenals (+10.9 months), nonsteroidal anti-inflammatory agents (+8.5 months), anti-inflammatory agents (+9.9 months), and vitamins (+11.24 months). As shown by the interaction terms in Table 2, the results are not additive for survivors taking adrenals in combination with Letrozole/Femara, switching between aromatase inhibitors, or switching between Tamoxifen and aromatase inhibitors; or for survivors taking anti-inflammatory agents with vitamins.

Study Strengths & Limitations

The literature contains many studies on subpopulations affected by low rates of ET usage. This study helps fill a gap in the literature regarding factors positively associated with ET usage duration among the socioeconomically disadvantaged that could potentially be used to better emerging interventions. The most effective methods for these necessary interventions are still under development, and there is a gap in the literature regarding the optimal timing for intervention. This study identifies that demographic and clinical factors were not associated with ET usage duration for this population; however, ET type and having prescriptions for drugs commonly known to alleviate side effects was significantly associated.

This analysis should be viewed as a hypothesis-generating study and can be used
to further investigate the relationship between ET type and other prescriptions taken with ET with ET usage duration. The variables significantly associated with ET usage duration explain 23% of the variance in ET usage duration among the sample, so further investigation is warranted to determine other associated factors. The purpose of the additional prescriptions was unknown, so it is also not known if these prescriptions were written to specifically alleviate side effects or for other purposes. Next steps would include looking at the timing of side effect prescriptions and ET medications. Dosage and usage patterns of other prescriptions were also not examined, only that the individual filled at least one prescription for the medication during the study period. Furthermore, over-the-counter NSAIDS or vitamins could not be accounted for due to the nature of Medicaid prescription claims data.

Generalizability & Future Research

This study focused on South Carolina Medicaid recipients who were hormone receptor-positive breast cancer survivors. The results of this study point to an effective point of intervention before 14 months for ET initiators who meet the sample inclusion criteria and that ET type and other prescriptions taken by survivors are more important for increasing the length of ET duration than the demographic and clinical factors examined. Further research is warranted to test these findings in other populations. Further research is also needed to test pharmacologic intervention strategies associated with longer ET duration in this study in addition to other non-pharmacologic interventions among low income populations [33].

Interventions aimed at enhancing the ET experience for breast cancer survivors to
increase disease free survival and quality of life are an immediate need. The results of this study can be seen as an important first step at examining factors associated with longer ET usage.

References


### Table 5.1 Multiple regression results for variables associated with endocrine therapy usage duration for the South Carolina Medicaid population, 2000 - 2012 (models A – H)

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Constant</strong></td>
<td>30.00 (1.07)**</td>
<td>33.37 (1.15)**</td>
<td>35.06 (1.08)**</td>
<td>31.23 (1.15)**</td>
<td>30.11 (1.09)**</td>
<td>34.09 (0.84)**</td>
<td>34.86 (0.85)**</td>
<td>17.22 (1.52)**</td>
</tr>
<tr>
<td><strong>Type of Endocrine Therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastrozole/Arimidex</td>
<td>8.77 (2.11)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.22 (2.01)**</td>
</tr>
<tr>
<td>Exemestane/Aromasin</td>
<td>1.06 (4.53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.31 (4.30)</td>
</tr>
<tr>
<td>Letrozole/Femara</td>
<td>0.76 (2.17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.35 (2.06)</td>
</tr>
<tr>
<td>Switched Between AIs</td>
<td>13.73 (2.90)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.65 (2.76)**</td>
</tr>
<tr>
<td>&amp; Tamoxifen</td>
<td>24.96 (1.81)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22.82 (1.73)**</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td>7.62 (1.49)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.75 (1.42)</td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td>8.69 (1.56)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.44 (1.49)</td>
</tr>
<tr>
<td><strong>Adrenals</strong></td>
<td></td>
<td></td>
<td>10.96 (1.48)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.18 (1.40)**</td>
</tr>
<tr>
<td><strong>Nonsteroidal anti-inflammatories</strong></td>
<td></td>
<td></td>
<td></td>
<td>13.49 (1.44)**</td>
<td></td>
<td></td>
<td></td>
<td>8.22 (1.41)**</td>
</tr>
<tr>
<td><strong>Anti-inflammatory agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13.56 (1.61)**</td>
<td></td>
<td></td>
<td>7.58 (1.52)**</td>
</tr>
<tr>
<td><strong>Vitamins (A, B, C, D, E, K, and/or multi)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.99 (1.63)**</td>
<td></td>
<td>8.41 (1.50)**</td>
</tr>
</tbody>
</table>

| R-squared               | 0.13             | 0.02             | 0.02             | 0.04             | 0.06             | 0.05             | 0.03             | 0.23             |
| Adjusted R-squared      | 0.13             | 0.02             | 0.02             | 0.04             | 0.06             | 0.05             | 0.03             | 0.22             |
| No. observations        | 1,399            | 1,399            | 1,399            | 1,399            | 1,399            | 1,399            | 1,399            | 1,399            |

Standard errors are reported in parentheses; AI = Aromatase Inhibitor; *, ** indicates significance at the 95% and 99% level, respectively.
Type of Endocrine Therapy – Tamoxifen and non-receipt of medications through Medicaid were set as the reference groups for the models.
Table 5.2  Multiple regression results for variables associated with endocrine therapy usage duration for the South Carolina Medicaid population, 2000 - 2012 (final model)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>14.06</td>
<td>1.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endocrine Therapy Type – Anastrozole/Arimidex</td>
<td>12.20</td>
<td>3.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endocrine Therapy Type – Exemestane/Aromasin</td>
<td>4.63</td>
<td>5.48</td>
<td>0.398</td>
</tr>
<tr>
<td>Endocrine Therapy Type – Letrozole/Femara</td>
<td>8.88</td>
<td>3.02</td>
<td>0.003</td>
</tr>
<tr>
<td>Endocrine Therapy Type – Switched Between AIs(^1)</td>
<td>23.58</td>
<td>5.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endocrine Therapy Type – Switched Between Tamoxifen &amp; AIs(^1)</td>
<td>29.27</td>
<td>2.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Receipt of Adrenals Prescription</td>
<td>10.90</td>
<td>2.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Receipt of Nonsteroidal Anti-Inflammatory Agents Prescription</td>
<td>8.46</td>
<td>1.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Receipt of Anti-Inflammatory Agents Prescription</td>
<td>9.91</td>
<td>1.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Receipt of Vitamins Prescription</td>
<td>11.24</td>
<td>1.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endocrine Therapy Type * Adrenals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastrozole/Arimidex</td>
<td>-5.32</td>
<td>4.11</td>
<td>0.196</td>
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<tr>
<td>Exemestane/Aromasin</td>
<td>0.75</td>
<td>8.75</td>
<td>0.932</td>
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<tr>
<td>Letrozole/Femara</td>
<td>-13.66</td>
<td>4.09</td>
<td>0.001</td>
</tr>
<tr>
<td>Switched Between AIs(^1)</td>
<td>-15.50</td>
<td>6.33</td>
<td>0.014</td>
</tr>
<tr>
<td>Switched Between Tamoxifen &amp; AIs(^1)</td>
<td>-10.33</td>
<td>3.56</td>
<td>0.004</td>
</tr>
<tr>
<td>Anti-Inflammatory Agents * Vitamins</td>
<td>-7.06</td>
<td>3.13</td>
<td>0.024</td>
</tr>
</tbody>
</table>

N=1,399; R\(^2\) = 0.23; Adj R\(^2\) = 0.22

Endocrine Therapy Type – Tamoxifen was set as the reference group

\(^1\)AIs=Aromatase Inhibitors
CHAPTER SIX

PAPER 3: “‘WALK A MILE IN MY SHOES’ – BREAST CANCER SURVIVORS’ PERSPECTIVES ON THE ENDOCRINE THERAPY EXPERIENCE”

Abstract

This study aims to understand, from the survivor perspective, modifiable factors that have the greatest impact on the likelihood of endocrine therapy (ET) continuation.

Twenty-two hormone receptor-positive breast cancer survivors under age 64 who had been prescribed ET since 2000 were recruited for participation in focus groups conducted in four South Carolina locations. Qualitative data analysis was completed by a three-member research team using an inductive narrative approach with input from a breast cancer survivors’ panel at a local hospital. Themes were examined by participant decision to continue or discontinue ET. Quotations exemplifying each theme are provided.

Participants’ feedback centered on a risk vs. benefit analysis unique to the individual survivor. Main themes included the importance of an open, honest patient/provider relationship and the need for personal information seeking and affirmation in the decision to take ET. There was clear support for the utility of multidisciplinary cancer care teams and incorporating integrative approaches.

This study highlights key elements that can be incorporated in interventions to enhance the endocrine therapy experiences for breast cancer survivors, with the goal of informing improvement in supportive therapy and care. The few studies that have addressed currently used interventions to improve adherence showed little to no
improvement over usual care. Research employing patient-centered perspectives is imperative. Novel and practical patient-centered interventions in research exploring openness in the patient/provider relationship, survivor information seeking practices, multidisciplinary teams, and integrative approaches are needed.

**Introduction**

Following surgery, radiation therapy, and/or chemotherapy, a woman with Stage I-III hormone receptor-positive breast cancer is typically prescribed endocrine therapy (ET) for five years or longer [1, 2]. The purpose of ET is to reduce a woman’s risk of breast cancer recurrence. Taking ET (Tamoxifen or an aromatase inhibitor) as prescribed for five years can reduce the risk of recurrence by 40% and death by one-third [3].

Research and clinical practice confirm that rates of ET are quite low [4-6]. A systematic review by Murphy et al. (2012) showed that discontinuation ranged from 31–73%, measured at the end of 5 years of treatment [7]. ASCO and the National Comprehensive Cancer Network currently recommend that women with Stage I-III breast cancer take Tamoxifen, an aromatase inhibitor, or a combination of the two types of endocrine therapies for up to ten years [1, 8-9].

Knowledge of the population affected by ET early discontinuation in South Carolina (SC) is limited, as is knowledge of how to improve the ET experience for survivors. The few studies that have addressed interventions showed limited to no improvement over usual care and have included elements such as educational materials, reminder notifications, acupuncture, and vaginal moisturizers [10-12]. This qualitative
study aims to understand from the survivor perspective which modifiable factors could have the greatest impact on the likelihood of ET continuation.

Methods

A qualitative study utilizing focus groups of breast cancer survivors was conducted. Four focus groups were held between June and October 2017 in four SC towns. This research was approved by the Greenville Health System and Clemson University Institutional Review Boards.

In addition, this qualitative study has been informed and guided by the input of a general Patient Engagement Studio and a breast cancer specific Patient Engagement Studio. The Studio provided recommendations for patient recruitment, raised potential survivor concerns, and offered valuable suggestions focus group guide revisions and results interpretation.

Recruitment

Breast cancer survivors were recruited through breast cancer support groups and advocacy organizations and a local cancer survivorship institute. Targeted inclusion criteria were female, English speaker, diagnosed with Stage I-III hormone receptor-positive breast cancer since 2000, completed breast cancer treatment, and prescribed endocrine therapy between the ages of 18-64 years.

Project staff contacted potential participants through flyer invitation. Interested participants contacted a research project staff member as directed by the flyer, were
screened by phone or e-mail, and were assigned to a focus group based on location. Participants were incentivized with $50 gift cards.

Data Collection

The focus groups lasted approximately 1.5 hours each and were held in neutral, private locations. All focus groups were conducted in English by two trained members of the project staff. Participants received an informational letter at the beginning of the focus group introducing them to the potential benefits and risks of the study. The moderators used a focus group guide developed by the research team members with qualitative, cancer-focused research experience after reviewing the existing literature to elicit participants’ experiences with ET. The guide was driven by elements of the Health Belief Model, specifically probing about perceived susceptibility to and seriousness of breast cancer recurrence, perceived benefits and barriers to ET continuation, and cues to action that may support or encourage ET continuation [13]. The various probes stimulated discussion about specific events and experiences that shaped participants’ opinions and attitudes regarding ET usage. (See “Focus Group Guide” in Supplementary Materials.) Each focus group was audio-recorded and then transcribed by a reputable medical transcription service and verified by a member of the project staff. The group demographics were obtained via survey.

Data Analysis

Data analysis was completed by three members of the research team with input from a breast cancer survivors’ panel. The team used a grounded theory approach to identify themes and an inductive narrative approach to data analysis [14-17]. The team
members began by analyzing one of the focus group transcripts to create a codebook. The codebook was expanded as the other three transcripts were analyzed. The analysis team followed a process detailed by Miles and Huberman [18], dividing the coding duties so that each transcript was coded by at least two independent coders. The team met during the coding process to address consensus, update the coding structure, and revisit any previously coded text as needed. Codes were applied to transcripts using Atlas.ti software Version 7.5.10 [19].

Themes emerged during a subsequent review and analysis of code based queries using the Atlas.ti software. A priori codes drawn from the focus group guide, as informed by the Health Belief Model served as the organizing analysis framework. As new themes emerged, the narrative was expanded. Two survivors who were not focus group participants assisted with identifying themes and expanding the narrative. There were fifteen final codes. Themes were examined by participant decision to continue or discontinue ET, and quotations exemplifying each theme are provided.

**Results**

There were 22 total participants. Participants were a median age of 52 when first prescribed ET (Range: 37–63 years). Sixty-four percent were Caucasian, 23% were African American, and 14% were of other race. Participants varied by highest education attained: 18% high school diploma, 14% associates’ degree, 41% bachelors’ degree, 18% post-baccalaureate degree, and 9% preferred not to answer. Seventy-seven percent had private insurance, 9% were on Medicaid, 5% were on Medicare, and insurance type was
unknown for 9% of the group. Fifty percent were prescribed Tamoxifen, 41% were prescribed aromatase inhibitors, and 9% switched between Tamoxifen and aromatase inhibitors. Five participants (approximately 23%) had discontinued ET. Two of the 17 who continued ET said they had taken a break of at least six weeks before deciding to continue again. Table 1 provides more detail on participants’ ET usage. (See Table 6.1.)

The Health Belief Model was chosen to summarize the survivors’ responses, as the women’s perceived susceptibility to breast cancer recurring and perceived seriousness/severity of that event influenced the perceived threat of breast cancer recurrence, which influenced the likelihood of a survivor continuing endocrine therapy. Informed by various sources, survivors’ perceptions of endocrine therapy’s benefits and barriers also influenced the likelihood of a survivor continuing ET. (See Figure 6.1.) The five main themes that emerged from the analysis are described below.

**Risk vs. Benefit Analysis**

Across the four focus groups, discussion centered on the perceived risks vs. perceived benefits that respondents felt was unique to the individual and could not be generalized by providers. Continuers and discontinuers alike had experienced many side effects that affected quality of life and were the major barrier to continuing ET. These included joint pain, bone pain, muscle aches, depression, weight gain, eye problems, anger, personality changes, hot flashes, lack of energy, vaginal dryness, and painful sex. Many women said that taking the medication made them feel “like a 90 year old.” Most discontinuers made statements such as “I just couldn’t take this anymore” and decided to focus on quality of life, believing that ET’s benefits did not outweigh its harms. Some
discontinuers said their decision was influenced by a low recurrence risk score given by a healthcare provider. The majority of discontinuers expressed understanding of their risk but were very keen to incorporate dietary changes and supplements to improve overall health instead of taking ET. Continuers largely expressed that they were weathering the ET experience, though difficult for most, primarily due to fear of recurrence and not wanting to have “regrets.” See Table 6.2. This risk vs. benefit analysis did not occur at one time point and the decision to continue was not permanent. Participants alluded to often re-evaluating their reduction in quality of life due to ET vs. ET’s benefit in reducing recurrence risk often through conversations with the provider, husband, or other survivor, and/or seeking online information.

Patient/Provider Relationship

The patient/provider relationship carried great significance in a survivor’s decision to continue or discontinue ET. Survivors valued a provider who transparently provided information about the purpose, benefits, and side effects of ET and ways side effects may be alleviated. There were mixed opinions among survivors as to how much information was “enough” regarding side effects. Some participants wanted to know any possibilities upfront saying they would rather be “forewarned,” whereas other survivors said being given too much information upfront was frightening and overwhelming:

If I have one, then I don’t say, ‘Oh my gosh, what’s wrong here?’ Okay, that might be a side effect from this because it’s a new medication I’m taking. It’s kind of nice to be forewarned.
All survivors agreed that they desired a provider who listened to their concerns and was not judgmental in minimizing the side effects a survivor experienced. Survivors often made remarks such as, “We know our bodies because we live in them” and wanted to be heard by providers. A continuer related her experience with a supportive provider:

*You can be totally blunt with him. And he just really wants to help do what’s best for you, but he listens to your issues. He doesn’t minimize how you’re feeling.*

Several discontinuers indicated that their providers still think the survivors are taking ET, and the survivors were not planning to inform the providers otherwise, agreeing that they did not want to have to “argue.” Continuers said they valued supportive providers’ willingness to help alleviate side effects by switching ET medications and/or offering integrative approaches such as exercise, dietary changes, and herbs. Some continuers reported changing providers to find someone that could support them in this way. Many continuers reported continuing ET simply because it was their providers’ recommendation, and they trusted their providers.

**Information Seeking**

The term “research” repeatedly surfaced in all four of the focus groups and among both continuers and discontinuers. Participants were probed regarding their information seeking behaviors. All groups expressed an understanding for the need to be cautious with online research:

*You have to take it with a grain of salt. There are a lot of blogs out there that are just really misinformed completely. And you have to read it sort of weigh it...with your oncologist and sort of figure it out.*
Participants also appreciated their cancer clinic or provider supplying links to reputable sources. In addition to specific sites mentioned (e.g. Mayo Clinic and American Cancer Society), participants also expressed an affinity for joining either online or in-person discussion groups of breast cancer patients and survivors, citing that the groups had been a very supportive place to ask questions, seek advice, and be encouraged by women who understood what they were going through. Some participants found groups very comforting and what they described as the best source of information because the information shared by other survivors is “experiential.” Still others expressed a desire to be more private about their care and seek information only from medical professionals.

Some participants related that their providers were dismissive when survivors mentioned the topic of joining online communities or researching information on their own. Providers cautioned the women that they should not become part of such communities for fear of the survivors becoming misinformed, which was described by a discontinuer as “insulting” and “frustrating.” One continuier related a more positive experience of chatting with other survivors online and learning about a medication that had helped alleviate hot flashes for a woman in another state. After sharing the woman’s experience with her provider, the provider prescribed the medication, consequently helping the woman and allowing her to continue ET.

Multidisciplinary Cancer Care Teams

There was clear support for the utility of multidisciplinary cancer care teams. The roles of nurse navigator, rural pharmacist, and nutritionist were specifically highlighted.
Survivors whose cancer clinics had a nurse navigator differed in their opinion on the role. All agreed it was comforting to have the nurse navigator’s phone number in case “you have one of those weird questions.” However, many said it would have been very helpful for the nurse navigator to have made an introductory contact. One survivor summarized her experience in deciding whether to take ET and how the nurse navigator could have assisted:

I’m sure she could have helped me a great deal because I was panicking going, do I do this, do I not do this, you know, talking into my head and I didn’t want to really talk it out to everybody else, because I didn’t want to hear everybody else’s opinion. You know, because their opinion may not be in my best interest, but they’re just going on what other people did. I really wanted somebody knowledgeable.

Many participants said that they did not have any regular contact with a pharmacist; however, in the most rural focus group location, the local pharmacist was highlighted and discussed as a key source of trusted information for the participants. Participants related instances of asking the pharmacist questions, saying “They will take the time to talk with you.” and “What a blessing to have her!” Establishing trusting relationships with pharmacists and these other mentioned allied health professionals was reported as beneficial to survivors.

Integrative Approaches

Both continuers and discontinuers overwhelmingly expressed a desire for more integrative approaches to help alleviate the side effects of ET and improve overall health.
Some described providers who were excellent in sharing these options with survivors, whereas others were frustrated with the lack of assistance they were receiving from providers in this area. Many survivors discussed trying dietary modifications such as excluding soy, sugar, grapefruit, and meat or including more fruits and vegetables, turmeric, Calcium, Vitamin B, Vitamin C, Vitamin D and lemon drops in addition to lifestyle changes such as more physical activity, less stress, yoga, and mindfulness. A participant summarized the resounding call for these options as follows:

*What we feel with the medical establishment is all they know is drugs and they cut people and they dope people. We hear all the time, and most people are educating themselves, but there’s all kinds of other healthy, exercise, diet, all those things that you can do. But medical providers don’t do a whole lot to help you with that or point you in the right direction.*

Some participants were survivors at cancer clinics that offered nutrition counseling but were not pleased with the services, saying that the information they had received was the “same old, same old.” Nutrition and dietary change was of great interest. Participants expressed a desire for more individualized counseling rather than rather than generalized, elementary nutrition information.

**Conclusion**

ET discontinuation rates remain high despite the use of ET for decades as the primary means of reducing the risk of breast cancer recurrence in women with hormone receptor-positive Stage I-III disease [3, 20]. Existing studies have examined variables
associated with ET continuation and adherence or address patient reported barriers but highlight a gap in understanding from the patient perspective which modifiable factors could improve the ET experience for patients [21-24].

In our qualitative study, we found clear survivor support for an open, honest, ongoing patient/provider relationship, support for personal information seeking and affirmation for continual ET risk vs. benefit re-evaluation, and multidisciplinary cancer care teams that can provide integrative approaches to supplement conventional care. There were several issues raised regarding the risk vs. benefit analysis that participants felt was unique to the individual and could not be generalized by providers. Participant feedback provided clear support for patient-centered and individualized cancer care.

These findings were consistent with other qualitative studies conducted among similar populations. Van Londen et al. reported that women view taking ET as something necessary for their health but re-evaluate the decision to take ET due to unanticipated side effects [25]. Discussing these side effects with providers, family, and others was difficult, and women were dissatisfied overall with the side effect symptom management information and strategies available [25]. In addition, Pellegrini et al. similarly found that women shared the distress and tension they felt while taking Tamoxifen because of the paradoxical situation that the drug’s purpose was to save life but it was causing their youthful looks and femininity to diminish [26].

One strength of our study is that it provides unique comparisons between the opinions and concerns of ET continuers and discontinuers. While novel and informative for hypothesis generation, a major limitation of this study is that the findings cannot be
generalized to all breast cancer survivors, since the majority of women in the sample were in the 40 to 50’s age group, above the state’s average education level, and proactive toward their health and wellness. There was repetition in themes, indicative of saturation, so we believe the sample was large enough to capture the most important opinions and concerns of SC breast cancer survivors taking ET.

The knowledge gained from these focus groups is critical to guide future development of interventions aimed at increasing ET continuation in this population. Most notably, researchers and clinicians must consider how to address survivor concerns regarding a more open, honest, ongoing two-way discussion between survivors and their providers. Consistent with other studies of breast cancer survivors’ preferences, our study showed that it may be helpful to employ a shared decision making model as the standard of care when approaching the concept of endocrine therapy continuation and modification of breast cancer recurrence risk factors, as is already being implemented for initial breast cancer diagnosis and treatment [27-29]. As recommended by Charles, Gafni, and Whelan (1997), shared decision making includes that 1) both the physician and patient are involved, 2) both parties share information, 3) that both parties take steps to build a consensus about the preferred treatment, and 4) that an agreement is reached on the treatment to implement [30].

Survivors expressed a strong desire to make their own decisions with information and guidance from their providers, consistent with the findings of Wells et al. [31]. Some survivors indicated they were not able to have honest conversations about ET with their providers. Others alluded to feeling condemned when trying to raise the issue of side
effects or information found online or from other women. In order for a shared decision making model to be implemented more effectively, it may be useful to train breast cancer survivors to more assertively communicate with their providers, as has been effective with other patient populations [32]. Likewise, the principles and practice of shared decision-making should continually be incorporated in medical education and oncology residency training programs.

Another main topic in patient/provider communication centered on discussions of patient information seeking. Our study showed that survivors whose doctors criticized or dismissed the online information they presented were more likely to follow advice from other sources or go against the doctor’s advice possibly due to this perceived dissonance. Tan and Goonawardene (2017) conducted a systematic review of Internet Health Information Seeking and the Patient-Physician Relationship [33]. Similar to accounts reported by some of the survivors in our study, this systematic review showed that some survivors felt physicians avoided online information-related dialogues in order to reclaim the traditional, authoritarian consultation model. Tan and Goonawardene affirm the importance of allowing or encouraging survivors to discuss their online information searches with physicians [33]. Their findings showed that survivors mainly used the internet to be actively involved in decision making related to their health (i.e. preparing for visits, asking better questions, better understanding information from physicians) but still very much trusted their physicians and valued their consultations. This finding offers a specific opportunity to provide patient centered care: provider’s recognition of a patient’s efforts in the self-education process.
The systematic review findings showed these information seeking behaviors actually empowered survivors to play a more active role in their disease management, to become more effective in understanding and communicating with their physicians, and to be more confident in and comfortable with their physicians’ advice. In addition, as Falisi et al. (2017) reported in a systematic review of breast cancer survivors’ use of social media, more study is needed to better understand social media engagement and content to psychosocial, behavioral, and physical health outcomes and how best to leverage social media to meet these needs [34].

The utility of multidisciplinary oncology teams that can incorporate integrative approaches was highlighted in the focus groups. Some survivors had benefitted from care by such teams while others had not. Multidisciplinary cancer care can be defined as a “deliberately designed system that creates a common communication platform among different providers of cancer care, enabling complex decision making and resulting in a tailored individual management plan” [35]. The need for multidisciplinary care arose from survivors feeling overwhelmed and confused after being transferred between clinicians at various stages of diagnosis and treatment without an integrated approach [36]. While existing multidisciplinary teams may typically be physician-led, our study shows that it may be helpful to also include allied health professionals such as pharmacists, nurse navigators, and nutritionists who may be working directly with the patient over the course of five to ten years and can provide more individual counsel and information related to integrative approaches as survivors continually re-evaluate the decision of whether to continue ET [37]. Incorporating these individuals as part of the
care team may also help improve the continuity of care, especially throughout the cancer survivorship journey. Multidisciplinary teams that include allied health professionals and nurse navigators align with the transition to a more patient-centered approach in cancer care, in which increasing emphasis is placed on a survivor's overall well-being and quality of life, and survivorship [38-39].

As breast cancer survivors become an increasingly larger population, there is imminent need for novel patient-centered interventions to enhance the ET experience. This research and other patient-centered approaches are increasingly valuable in providing insight into survivor care needs and perceptions, with a goal of ensuring that cancer survivors have an opportunity for the most comprehensive and highest quality cancer care possible.

References


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**Figures**

**Figure 6.1** Health belief model for endocrine therapy usage to reduce risk of breast cancer recurrence among low income South Carolina breast cancer survivors ages 18-64
**Tables**

**Table 6.1** Participant endocrine therapy usage characteristics (N=22)

<table>
<thead>
<tr>
<th>Breast Cancer Stage at Diagnosis</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0*</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>I</td>
<td>10 (45%)</td>
</tr>
<tr>
<td>II</td>
<td>6 (27%)</td>
</tr>
<tr>
<td>III</td>
<td>4 (18%)</td>
</tr>
<tr>
<td>IV*</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Endocrine Therapy</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>11 (50%)</td>
</tr>
<tr>
<td>Aromatase Inhibitor</td>
<td>9 (41%)</td>
</tr>
<tr>
<td>Switched from Tamoxifen to Aromatase Inhibitor</td>
<td>2 (9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endocrine Therapy Continuation</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plans to Continue Endocrine Therapy for Recommended Duration</td>
<td>17 (77%)</td>
</tr>
<tr>
<td>Declined or Discontinued Endocrine Therapy</td>
<td>5 (23%)</td>
</tr>
</tbody>
</table>

**Median (Range)**

<table>
<thead>
<tr>
<th>Years on Tamoxifen</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All Participants</td>
<td>2.5 (0 – 5)</td>
</tr>
<tr>
<td>Participants who Plan to Continue</td>
<td>3.7 (1.5 – 6)</td>
</tr>
<tr>
<td>Participants who Declined or Discontinued</td>
<td>0 (0 – 0.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years on Aromatase Inhibitor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All Participants</td>
<td>2 (0 – 10)</td>
</tr>
<tr>
<td>Participants who Plan to Continue</td>
<td>3.3 (1-10)</td>
</tr>
<tr>
<td>Participants who Declined or Discontinued</td>
<td>0.6 (0 – 0.1)</td>
</tr>
</tbody>
</table>

*While Stage I-III was the target group for recruitment, one participant was Stage 0, and one participant was Stage IV.*
Table 6.2 Sample quotes exemplifying participant perceptions regarding susceptibility and severity of breast cancer recurrence and motivation for continuing or discontinuing endocrine therapy

<table>
<thead>
<tr>
<th>Continuer</th>
<th>Discontinuer</th>
</tr>
</thead>
<tbody>
<tr>
<td>• I feel like if it comes back it’s not because I’m not doing everything I was supposed to do.”</td>
<td>• “I don’t have any family history of breast cancer, so it wasn’t something that I was worried about as far as a risk factor.”</td>
</tr>
<tr>
<td>• “You feel like an 80-year-old woman in the mornings sometimes, but I have to have a security blanket.”</td>
<td>• “If cancer’s gonna take me out, then let cancer take me out. I’m not doing these drugs. I don’t like to take drugs. I took it a couple of days and it just made me feel so bad until I decided this is not it. If the Lord is ready for me, I’m going home, but in the meantime, I was telling my story. Letting other people know, because folks were just afraid of cancer.”</td>
</tr>
<tr>
<td>• “It’s bones and joints and all that, but I just feel like I want to do everything that I can because if it were to come back, I am a guilty person…I should have done this or I should have done that. This way, if it does come back, okay, I’ve done everything I can and it’s in God’s hands.”</td>
<td>• “My doctors says without anything, the difference is 3%. So, at my highest, it would be like 16% recurrence. And I said you know, I’m just at a point in my life where I’m not worried about getting cancer again. I’m not worried about my body. My quality of life is more important than what this could offer.”</td>
</tr>
<tr>
<td>• “There really aren’t alternatives…I want to be here. I’ve got little kids; I will do it.”</td>
<td></td>
</tr>
<tr>
<td>• “My mom regretted not doing treatment.”</td>
<td></td>
</tr>
<tr>
<td>• “Many went before us young.”</td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER SEVEN

DISCUSSION

Overview of Study Findings and Strengths

This dissertation work had three major aims: 1) To describe ET non-initiation, non-adherence, and duration by age, race, and temporal trend, 2) To identify demographic, clinical, and pharmaceutical factors that are associated with an individual’s ET usage duration, and 3) To understand from the survivor perspective which modifiable factors could have the greatest impact on the likelihood of ET continuation. These aims were achieved by a convergent parallel mixed methods research study. The answers to each of the research questions are summarized Table 7.1.

Table 7.1 Summary of research aims, questions, hypotheses, and results

<table>
<thead>
<tr>
<th>Research Question</th>
<th>Hypothesis</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AIM #1 To describe ET non-initiation, non-adherence, and duration by age, race, and temporal trend</strong></td>
<td></td>
<td>53% of Medicaid enrollees never initiated treatment. 21% of initiators continued ET for five years or more, with a mean and median of 37 months. African American women under age 50 had the lowest rates of non-initiation and non-adherence. There was no significant difference in median duration of ET usage by age/race subgroups</td>
</tr>
<tr>
<td>#1 How do rates of ET non-initiation, non-adherence, and duration vary by age and race?</td>
<td>ET non-initiation, non-adherence, and duration rates are worse among younger women and women of African American race.</td>
<td></td>
</tr>
<tr>
<td>#2 How have rates of ET non-initiation, non-adherence, and duration changed during the study period?</td>
<td>There has been no change over the study period in ET non-initiation, non-adherence, and duration.</td>
<td>There was a significant decline in the odds of ET non-initiation from 2005 – 2009 but a significant increase from 2010 – 2014. Non-adherence decreased from 2007 – 2012. Average duration of ET usage increased from 2000 – 2006 but decreased from 2007 – 2012.</td>
</tr>
<tr>
<td><strong>AIM #2 To identify demographic, clinical, and pharmaceutical factors that are associated with an individual’s ET usage duration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#3 Which demographic, clinical, and pharmaceutical factors are associated with an individual’s ET usage duration?</td>
<td>Women taking Tamoxifen will have lower ET usage duration than women taking aromatase inhibitors. Filling prescriptions for drugs known to alleviate side effects will increase ET usage duration.</td>
<td>None of the demographic or clinical factors examined were significantly associated with an individual’s ET usage duration. The final model showed the following were significantly associated with longer ET usage duration: type of ET and receipt of prescription for the following medications: adrenals, nonsteroidal anti-inflammatory agents, anti-inflammatory agents, and vitamins.</td>
</tr>
</tbody>
</table>

**AIM #3 To understand from the survivor perspective which modifiable factors could have the greatest impact on the likelihood of ET continuation.**

| #4 What are women’s perceptions regarding susceptibility/severity of breast cancer recurrence? | Women’s susceptibility to breast cancer recurrence will be influenced by provider-patient communication. Women will perceive recurrence as severe but also be influenced by short-term quality of life preferences. | Continuers “just want to live” and are fearful of regret/guilt if cancer recurs. Discontinuers emphasize importance of quality of life; cite low risk score, no family history, and/or not afraid of cancer or death. |

| #5 What are the perceived benefits/barriers to ET continuation? | Side effects will emerge as a major perceived barrier to ET continuation. | Benefits: Understanding that endocrine therapy reduces estrogen levels which feed ER+ breast cancer. Barriers: Side effects, drugs are toxic/harmful. |

| #6 What are the cues to action that encourage and support ET continuation? | Provider-patient communication will play a key role in supporting ET continuation. | • Provider listens, does not judge, & does not minimize the survivor’s unique, individual ET experience. • Provider is transparent about side effects and shares upfront that there are possible ways, including holistic options, to alleviate potential side effects. • Provider engages with survivor as survivor researches on her own and is part of social media platforms; provider shares latest ET research in patient-friendly manner. • Nurse navigator available to discuss the risk vs. benefit analysis of taking ET and... |
This is the first study to use longitudinal data to examine trends in ET non-initiation, non-adherence, and duration among South Carolina Medicaid-enrolled women. Our findings point to several opportunities for further investigation and possible intervention. First, 53% of Medicaid enrollees never initiated treatment. This is of concern for multiple reasons. Secondly, when examining the subgroups for possible intervention to increase ET adherence, women under 50 years of age, and especially African American women under age 50, demand particular attention. Thirdly, the odds of ET non-initiation was increasing from 2010 – 2014 and the average duration of ET usage was decreasing from 2007 – 2012.

There was, however, a significant decline in the odds of ET non-adherence from 2007 to 2012, and the odds of ET non-initiation had decreased previously in the period from 2005 – 2009 with average duration increasing from 2000 - 2006. These positive findings are encouraging given the recent attention touting the benefits of ET adherence for women (Hershman et al., 2011). Because the study spans more than a decade, this data offers one of the first long-term assessments of these challenges. The opportunity is to build on the modest positive improvements seen earlier in the past decade.
Those who initiated ET had a median ET usage duration of 37 months (Range: 0 – 184), with 21% of initiators continuing ET for five years or more. Given ASCO’s recommendations since 2014 to increase ET usage to up to ten years and multiple trials showing disease-free survival benefits for those who take ET for 5-10 years (Helwick, 2016; Goodman, 2017; Burstein et al., 2014; “ASCO Guideline Update,” 2014; “Hormonal Therapy for Early-Stage,” 2016), it is alarming that only one-fifth of initiators continued for five years or more and that the temporal trends showed negative results for the most recent periods concerning improvement in individual level ET initiation and duration.

We found that women under age 50 were less likely to be adherent to ET. These findings are consistent with the literature on ET usage (Murphy et al., 2012), which suggests that younger women have unique considerations in their ET decision-making framework, including fertility (Rosenberg & Partridge, 2015) and reluctance to believe ET was a necessary part of their breast cancer treatment (Walker et al., 2016). These explanatory factors are not fully understood and warrant further research (Wassermann et al., 2017).

Our study also found that none of the demographic or clinical factors examined were significantly associated with an individual’s ET usage duration. The sample’s socioeconomic and age (<64) homogeneity possibly overwhelmed differences in race, marital status, or rural/urban residency status, or as other studies have shown, side effect management may be more impactful than demographic or clinical aspects (Wagner et al.,
Our study highlights the association between ET usage duration with ET type and with other prescriptions that were possibly prescribed for side effect management. The final model included ET type and receipt of certain prescriptions, which can be used to alleviate common side effects of Tamoxifen and aromatase inhibitors: adrenals, nonsteroidal anti-inflammatory agents, anti-inflammatory agents, and vitamins.

The literature contains many studies on subpopulations affected by low rates of ET usage. This study helps fill a gap in the literature regarding factors positively associated with ET usage duration among the socioeconomically disadvantaged that could potentially be used to better emerging interventions. The most effective methods for these necessary interventions are still under development, and there is a gap in the literature regarding the optimal timing for intervention. This study identifies that demographic and clinical factors were not associated with ET usage duration for this population; however, ET type and having prescriptions for drugs commonly known to alleviate side effects was significantly associated.

In our qualitative study, we found clear survivor support for an open, honest, ongoing patient/provider relationship, support for personal information seeking and affirmation for continual ET risk vs. benefit re-evaluation, and multidisciplinary cancer care teams that can provide integrative approaches to supplement conventional care. There were several issues raised regarding the risk vs. benefit analysis that participants felt was unique to the individual and could not be generalized by providers. Participant feedback
provided clear support for patient-centered and individualized cancer care. A major strength of the qualitative study is that it provides unique comparisons between the opinions and concerns of ET continuers and discontinuers.

**Limitations**

Some important limitations accompany this analysis. First, we assumed that if a person was Medicaid-eligible and did not have a Medicaid pharmacy claim for ET, she did not take ET, as there was no other way to document ET received through other payment sources. Medicaid recipients do not typically have secondary payment sources other than self-pay, so it is not anticipated that significant missed data resulted from this limitation. Second, we assumed that if a person filled a prescription, then she took those pills. There was no way to account for whether the women actually took the medication. Furthermore, our findings were based on data from the South Carolina Medicaid population and may not be generalizable to other populations.

This study should be viewed as a hypothesis-generating study and can be used to further investigate the relationship between ET type and other prescriptions taken with ET with ET usage duration. The variables significantly associated with ET usage duration explain 23% of the variance in ET usage duration among the sample, so further investigation is warranted to determine other associated factors. The purpose of the additional prescriptions was unknown, so it is also not known if these prescriptions were written to specifically alleviate side effects or for other purposes.
While novel and informative for hypothesis generation, a major limitation of the qualitative portion of this study is that the findings cannot be generalized to all breast cancer survivors, since the majority of women in the sample were in the 40 to 50’s age group, above the state’s average education level, and proactive toward their health and wellness. There was repetition in themes, indicative of saturation, so we believe the sample was large enough to capture the most important opinions and concerns of SC breast cancer survivors taking ET.

**Future Work**

While promising that rates of non-initiation showed slight yet significant decreasing trends and duration showed a slight yet significant increasing trend, these results sound a call for greater improvements in ET usage rates among populations of low socioeconomic status. More research is needed to decipher potential factors influencing slight improvements seen since 2000 in order to capitalize on these efforts to further reduce rates of non-initiation and non-adherence and increase duration in the future. Moreover, longitudinal analyses among women with private insurance or Medicare are warranted to compare changes in ET usage rates over time among these populations. Additional analyses should also consider grouping participants by the year corresponding to the middle or end of an individual’s ET duration period, where this study chose to group participants by year of breast cancer diagnosis.
Next steps also include looking at the timing of side effect prescriptions and ET medications. Dosage and usage patterns of other prescriptions were also not examined, only that the individual filled at least one prescription for the medication during the study period. Furthermore, over-the-counter NSAIDS or vitamins could not be accounted for due to the nature of Medicaid prescription claims data.

The results of this study point to an effective point of intervention before 14 months for ET initiators who meet the sample inclusion criteria and that ET type and other prescriptions taken by survivors are more important for increasing the length of ET duration than the demographic and clinical factors examined. Further research is warranted to test these findings in other populations. Further research is also needed to test pharmacologic intervention strategies associated with longer ET duration in this study in addition to other non-pharmacologic interventions among low income populations (David & Fallowfield, 2008).

The knowledge gained from the focus groups is critical to guide future development of interventions aimed at increasing ET continuation in this population. Most notably, researchers and clinicians must consider how to address survivor concerns regarding a more open, honest, ongoing two-way discussion between survivors and their providers. Consistent with other studies of breast cancer survivors’ preferences, our study showed that it may be helpful to employ a shared decision making model as the standard of care when approaching the concept of endocrine therapy continuation and modification of breast cancer recurrence risk factors, as is already being implemented for
Survivors expressed a strong desire to make their own decisions with information and guidance from their providers, consistent with the findings of Wells et al. (2016). Some survivors indicated they were not able to have honest conversations about ET with their providers. Others alluded to feeling condemned when trying to raise the issue of side effects or information found online or from other women. In order for a shared decision making model to be implemented more effectively, it may be useful to train breast cancer survivors to more assertively communicate with their providers, as has been effective with other patient populations (Lee et al., 2013). Likewise, the principles and practice of shared decision-making should continually be incorporated in medical education and oncology residency training programs.

Another main topic in patient/provider communication centered on discussions of patient information seeking. Our study showed that survivors whose doctors criticized or dismissed the online information they presented were more likely to follow advice from other sources or go against the doctor’s advice possibly due to this perceived dissonance. Tan and Goonawardene (2017) conducted a systematic review of Internet Health Information Seeking and the Patient-Physician Relationship. Similar to accounts reported by some of the survivors in our study, this systematic review showed that some survivors felt physicians avoided online information-related dialogues in order to reclaim the traditional, authoritarian consultation model. Tan and Goonawardene affirm the importance of allowing or encouraging survivors to discuss their online information
searches with physicians. Their findings showed that survivors mainly used the internet to be actively involved in decision making related to their health (i.e. preparing for visits, asking better questions, better understanding information from physicians) but still very much trusted their physicians and valued their consultations. This finding offers a specific opportunity to provide patient centered care: provider’s recognition of a patient’s efforts in the self-education process.

The utility of multidisciplinary oncology teams that can incorporate integrative approaches was highlighted in the focus groups. Some survivors had benefitted from care by such teams while others had not. Multidisciplinary cancer care can be defined as a “deliberately designed system that creates a common communication platform among different providers of cancer care, enabling complex decision making and resulting in a tailored individual management plan” (Jacobson, 2010). The need for multidisciplinary care arose from survivors feeling overwhelmed and confused after being transferred between clinicians at various stages of diagnosis and treatment without an integrated approach (Jnr, 2011). While existing multidisciplinary teams may typically be physician-led, our study shows that it may be helpful to also include allied health professionals such as pharmacists, nurse navigators, and nutritionists who may be working directly with the patient over the course of five to ten years and can provide more individual counsel and information related to integrative approaches as survivors continually re-evaluate the decision of whether to continue ET (Taplin et al., 2016). Incorporating these individuals as part of the care team may also help improve the continuity of care, especially throughout the cancer survivorship journey. Multidisciplinary teams that include allied
health professionals and nurse navigators align with the transition to a more patient-centered approach in cancer care, in which increasing emphasis is placed on a survivor’s overall well-being and quality of life, and survivorship (Borras et al., 2014; Lee Mortensen et al., 2017).

As breast cancer survivors become an increasingly larger population, there is imminent need for novel patient-centered interventions to enhance the ET experience. This research and other patient-centered approaches are increasingly valuable in providing insight into survivor care needs and perceptions, with a goal of ensuring that cancer survivors have an opportunity for the most comprehensive and highest quality cancer care possible. Interventions aimed at enhancing the ET experience for breast cancer survivors to increase disease free survival and quality of life are an immediate need. The results of this study can be seen as an important first step at examining factors associated with longer ET usage.
APPENDICES
Appendix A

Health Belief Model for Endocrine Therapy Usage to Reduce Risk of Breast Cancer Recurrence among South Carolina Breast Cancer Survivors Ages 18-64 at Diagnosis

Individual Perceptions

Perceived Susceptibility & Serumness/Severity of Breast Cancer Recurrence:
- Continuers “just want to live” and are fearful of regret/guilt if cancer recurs
- Discontinuers emphasize importance of quality of life; cite low risk score, no family history, and/or not afraid of cancer or death

Modifying Factors

Perceived Threat of Breast Cancer Recurrence

Cues to Action
- Provider listens, does not judge, & does not minimize the survivor’s unique, individual ET experience
- Provider is transparent about side effects and shares upfront that there are possible ways, including holistic options, to alleviate potential side effects
- Provider engages with survivor as survivor researches on her own and is part of social media platforms; provider shares latest ET research in patient-friendly manner
- Nurse navigator available to discuss the risk vs. benefit analysis of taking ET and answer “weird questions” even better if nurse navigator initiates call
- Concept of a “pharmacy home” where survivor feels welcomed to ask questions
- Nutritionist gives personalized dietary information based on medications and conditions

Likelihood of Action

Likelihood of Endocrine Therapy Continuation

Perceived Benefits of Endocrine Therapy Continuation:
- Understanding that endocrine therapy reduces estrogen levels which feeds ER+ breast cancer

Perceived Barriers to Endocrine Therapy Continuation:
- Side effects, drugs are toxic/harmful
## Appendix B

### Table of Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Data Source</th>
<th>Research Question</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QUANTITATIVE STUDY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, age at diagnosis, SEER summary breast cancer stage, month/year of diagnosis</td>
<td>SC Central Cancer Registry</td>
<td>Inclusion/exclusion criteria; #1, #2, #3</td>
</tr>
<tr>
<td>Cancer recurrence date, type of reporting source (to distinguish autopsy or death certificate), vital status</td>
<td>SC Central Cancer Registry</td>
<td>Inclusion/exclusion criteria</td>
</tr>
<tr>
<td>Dual enrollment in Medicare</td>
<td></td>
<td>Inclusion/exclusion criteria</td>
</tr>
<tr>
<td>National Drug Code and drug name, date dispensed</td>
<td>SC Medicaid Pharmacy File</td>
<td>Inclusion/exclusion criteria; #1, #2, #3</td>
</tr>
<tr>
<td>Medicaid eligibility &amp; ineligibility dates</td>
<td>SC Medicaid Recipient File</td>
<td>#1, #2, #3</td>
</tr>
<tr>
<td>Quantity, number of this refill &amp; days supplied</td>
<td>SC Medicaid Pharmacy File</td>
<td>#1, #2, #3</td>
</tr>
<tr>
<td>Demographic: race</td>
<td>SC Central Cancer Registry</td>
<td>#1 &amp; #3</td>
</tr>
<tr>
<td>Demographic: rural/urban residency status, county of residence, marital status</td>
<td>SC Central Cancer Registry</td>
<td>#3</td>
</tr>
<tr>
<td>Demographic: marital status</td>
<td>SC Medicaid Recipient File</td>
<td>#3</td>
</tr>
<tr>
<td>Clinical: receipt of other treatments (i.e. chemotherapy, radiation therapy, surgery)</td>
<td>SC Central Cancer Registry</td>
<td>#3</td>
</tr>
<tr>
<td>Pharmaceutical: type of endocrine therapy, pharmacy ownership, and filled prescription for the following - alpha-agonist hypertensives, antidepressants, anticonvulsants, adrenals, nonsteroidal anti-inflammatory agents, anti-inflammatory agents, and/or vitamins (B, C, D, K, and/or multivitamin)</td>
<td>SC Medicaid Pharmacy File</td>
<td>#3</td>
</tr>
<tr>
<td><strong>QUALITATIVE STUDY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived susceptibility to and seriousness/severity of breast cancer recurrence</td>
<td>Focus groups</td>
<td>#4</td>
</tr>
<tr>
<td>Perceived benefits of and barriers to endocrine therapy continuation and adherence</td>
<td>Focus groups</td>
<td>#5</td>
</tr>
<tr>
<td>Cues to action that encourage and support ET continuation and adherence</td>
<td>Focus groups</td>
<td>#6</td>
</tr>
</tbody>
</table>
Appendix C

Recruitment Flyer

We want to talk to breast cancer survivors like you!

It is a challenge for many women to complete therapy for breast cancer. Were you or anyone you know prescribed Tamoxifen or an Aromatase Inhibitor?

We are interested to hear your recommendations to improve the cancer care experience for other women.

We want to speak with survivors like you about their experience with endocrine therapy (Tamoxifen or aromatase inhibitors), and are contacting recent Stage 1-3 breast cancer survivors diagnosed between ages 18-64 to help us. Even if you were prescribed endocrine therapy but chose not to take it, we would still like to talk to you!

In appreciation of your time and sharing your experience, you will receive a $50 Walmart gift card for your participation in a two-hour focus group.

Your Medicaid and other factors will not be affected by your participation and all correspondence will be kept confidential.

We really value your input!

Interested in participating?
Want more information?
An RSVP is required.
Space is limited.

Please RSVP by July 30
Please contact Julie at 864-270-3259 or summey2@clemson.edu.
Appendix D

Screening Questions

Hello, (name). Are you calling about the breast cancer study?

Thank you for calling and for your interest in this study. My name is Julie, and I am a research assistant at Clemson University. How are you today?

We understand that it is a challenge for many women to complete therapy for breast cancer. We would like to talk to you to find out more about your experience so that we can help other women in the future. To learn more about your experience, we would like to schedule a time when you and five or six other women could come and meet together with us to talk about your experiences.

First, I need to ask you several questions to see if you might qualify for our focus group. Is that okay?

We will have three different groups that meet, so to determine which group you best fit in, may I ask you a few questions?

- Were you ever prescribed Tamoxifen?
  - If don’t know, ask: Were you ever given a prescription by your doctor after they completed their initial treatment?
    - Do you remember what it was for? (If say, to reduce estrogen or hormones in the body, then assume Tamoxifen or AI)

- Were you ever prescribed an aromatase inhibitor?
  - Probe; (If they don’t know, then list all and ask one by one, e.g. Anastrozole/Arimidex, letrozole/Femara, or Exemestane/Aromasin?)

<<IF YES, continue with following questions. IF NO, then skip to Option 2, below…>>

- Did you ever fill your prescription for Tamoxifen (or AI)?
- If yes, for how long did you take Tamoxifen (or AI)?
- Do you remember how old you were when you were first prescribed Tamoxifen/aromatase inhibitor?
- Are you a female?
- What stage of breast cancer were you diagnosed with?

Eligibility criteria:
- ✓Either prescribed Tamoxifen and/or an aromatase inhibitor: yes
- ✓Female: yes
- ✓Age when began taking Tamoxifen/aromatase inhibitor: 18-64
- ✓English speaker: yes
☑ Completed treatment for hormone receptor-positive breast cancer: yes

Option 1 (if eligible to participate in study): Thank you so much for these responses. (Provide details of appropriate focus group – date, time, and location.) In case something comes up and you will be unable to attend the focus group, will you please call or text me at (864)270-3259? Also, to remind you about the event and to send you any updates, may I ask for your name, phone number, and e-mail address? How would you prefer that I be in contact with you? Thank you again for your interest and for your willingness to participate. We hope that our conversation and the information we learn from your experience can be used to help many other women. At the end of our focus group, we will be giving you a $50 Walmart gift card to thank you for your time. Do you have any questions about the focus group? Thank you again for your interest. Have a nice day.

Option 2 (if not eligible to participate in study): Thank you so much for these responses. Unfortunately, you do not meet the eligibility criteria for our study, so I will not be able to schedule you to participate in a focus group. (Explain why.) Thank you again for your interest. Have a nice day.
Appendix E

Focus Group Guide

WELCOME
Thank you so much for agreeing to be part of this focus group. We appreciate your willingness to participate and look forward to a fruitful discussion together.

Today, we are talking with women who are breast cancer survivors, and we are interested in learning more about your experience.

INTRODUCTIONS
Moderator; assistant moderator

PURPOSE OF FOCUS GROUPS
The reason we are having these focus groups is that it is a challenge for many women to complete endocrine therapy for breast cancer. When we say endocrine therapy, we are referring to either Tamoxifen or an Aromatase Inhibitor, medications you may have taken after your surgery, chemotherapy, radiation, or any other kind of treatment. We want to find out more about the obstacles that you and other women you know have faced in order to better aid women in the future. We need your input and want you to share your honest and open thoughts with us. This focus group will last approximately 1 ½ hours. Please feel free to get up to go to the restroom anytime. At the end of our time together, please see [assistant moderator] to receive your $50 Wal-Mart gift card as we value and appreciate your time today.

GROUND RULES
We would like to address a few important points before we begin.

1. WE WANT YOU TO DO THE TALKING.
We would like for everyone to participate.
We value each of you and your responses. If you have shared a lot, I may call on others who we haven't heard from in a while so that everyone can have a chance to share.

2. THERE ARE NO RIGHT OR WRONG ANSWERS
Every person's experiences and opinions are important.
Please feel free to speak up whether you agree or disagree.
We want to hear a wide range of opinions.

3. WHAT IS SAID IN THIS ROOM STAYS HERE
We want folks to feel comfortable sharing when sensitive issues come up.

4. WE WILL BE AUDIO RECORDING THE GROUP
We want to capture everything you have to say. We absolutely will not identify anyone by name in our report. You will remain anonymous. If we use your words we will simply say “one participant told us” – we will not use your name or describe you in a way that someone could identify you.

So, if you are ready, we will get started with the recording.

**Patient introductions/Icebreaker:** Please tell us you’re the name that you would like for us to call you as well as how long ago you were diagnosed with breast cancer.

*We understand that you have all had different types of breast cancer treatments, possibly involving chemotherapy, radiation therapy, or surgery, but we want to spend the rest of our time together today discussing what happened after these initial treatments.*

After your chemo, radiation, or surgery, how many of you received a prescription for Tamoxifen?

Did anyone receive a prescription for an aromatase inhibitor like Anastrozole/Arimidex, letrozole/Femara, or Exemestane/Aromasin? Or any other medication?

Did anyone switch from one medication to another? (*Probe as to why the switch from one to the other. What did the new drug do instead?*)

Do you remember what type of doctor wrote that first prescription? (Was it your surgeon or oncologist or a different type of doctor?) *During the remainder of our conversation, I may use the word “provider” when I talk about the doctor since your medical visits may have been with a doctor, a nurse, a nurse practitioner, or some other healthcare professional.*

**Perceived Benefits/Barriers:** *We understand that when you are finishing up cancer treatment, you may have lots of different appointments with several different doctors and that there is a lot of information to take in and decisions to make…We would like for you to think back if possible to that time when you had finished your chemo, radiation, and/or surgery and were given the option to take Tamoxifen or an aromatase inhibitor. Tell us about your experience of going to the doctor and receiving your first prescription. For example, we would like to hear what you and your doctors discussed, if more than one doctor talked to you about taking the medication and what those conversations were like, if you took someone with you to those appointments and what their role was, how you felt during those appointments, etc.*

How often did your doctor say you would need to take the medication each day (whole pills?), and for how long would you be on the medication?
(What did you and your providers discuss? Encouraged to fill the prescription and take the medicine? Comfortable asking questions? Same/different messages from each provider? Role of the “advocate”?)

**Perceived Susceptibility/Seriousness/Severity:** At that point when you were first given your Tamoxifen or aromatase inhibitor prescription, how much did worry about cancer coming back influence your decision of whether or not to fill the prescription?

We know that all of you did decide to fill your first prescription and took either Tamoxifen or an aromatase inhibitor, and we want to hear more about your decision making process. Can you tell us just in your own words more about the benefits you saw in taking this medication – for example, the purpose of the medication and how you learned about it?

**We know that all of you decided to take the medicine. Can you elaborate more for us on your experience with taking it - how easy or how difficult if may have been, and how it impacted your way of life, if at all?**

*It is a challenge for many women to continue taking their medicine for breast cancer for a variety of reasons. Based on your own experience or things you have heard from other women, we would like to brainstorm together why it can be very challenging for women to take their medicine regularly and stay on it for the duration the doctor recommends. Ask women to brainstorm.*

Prompts if needed:
- Side effects – please describe
- Cost/difficulty getting medicine refilled
- Feeling good so why continue, in denial/want to forget about cancer
- Conflicting advice from doctors/internet/other women
- Sexual problems/fertility concerns
- Developing other health problems or the fear of developing other health problems
- Can’t avail support services due to work
- Misunderstanding from family/physicians
- Distance from care

We would like to learn more about how it feels talking with your provider about your medication and any challenges you may have experienced. *(Did you wait til you had an appointment to share your concerns, or did you call ahead of time? Did you feel that your provider was open to listening to you and to helping you find a way to alleviate some of the problems you were experiencing? Did you ever feel embarrassed to talk to the doctor about your concerns? If you decided to stop taking the medicine, did you and your provider make that decision together or did you make that decision on your own?)*
Next, we want to ask specifically about your experience in getting the Tamoxifen or aromatase inhibitors with regard to the cost, insurance coverage, and convenience to the pharmacy, etc. Please tell us about your experience in getting the medicines with your insurance coverage. (Any difficulties obtaining the medicines? Any gaps or problems with your insurance coverage? Did your insurance cover the full expense of your medication? Is there anything about your experience with your insurance that could have better supported you if you wanted to stay on the medicine?)

Cues to Action: We would like to know what suggestions you have that would be helpful to women who are prescribed these medications and decide to take them daily for the entire duration needed. If you chose to take the medicine, while you were taking it, what are some things that were helpful to you? If you did not take the medicine, can you think of anything that may would be helpful to others? (Things to know before you began taking your medication, or to help you continue taking your medication? Examples of tried interventions below if needed.)

- Educational pamphlets in the mail (topics: breast cancer, treatments, medication side effects, strategies for enhancing adherence, and information about diet and physical exercise)
- Monthly reminders in the mail or by e-mail about medication adherence
- Phone calls from a nurse to provide motivation, reminders, and individualized information regarding the patient’s specific problems
- Text messaging app that allows the patient to text the provider
- Group exercise programs
- At home-based exercise programs
- Cool pad pillow topper to aid sleep
- Meditation training to decrease stress/anxiety

We are getting close to the end of our discussion time. What additional thoughts would you like to share with the group about your experience with endocrine therapy or any experiences of other people you know?

Thank the group
Appendix F

Participant Survey

Thank you so much for your willingness to come and participate in the focus group. We look forward to our time together and trust that the experiences and ideas you share can be used to help many women in the future. Below are some short survey questions to give us a better idea about your history with endocrine therapy.

1. Were you diagnosed with hormone receptor-positive breast cancer? □ YES □ NO
   • If yes, what year were you diagnosed? ________________________________
   • What was your stage at diagnosis?
     □ Stage 0 □ Stage I □ Stage II □ Stage III □ Stage IV

2. Have you completed your breast cancer treatment? □ YES □ NO
   • If yes, what year did you complete your treatment? ____________________

3. Were you ever prescribed Tamoxifen? □ YES □ NO
   • If yes, did you fill your prescription for Tamoxifen? □ YES □ NO
   • If yes, how long did you take Tamoxifen? ____________________________

4. Were you ever prescribed an aromatase inhibitor? (Aromatase inhibitors include the following medications: Anastrozole/Arimidex, Letrozole/Femara, or Exemestane/Aromasin.) □ YES □ NO
   • If yes, did you fill your prescription for an aromatase inhibitor? □ YES □ NO
   • If yes, how long did you take the aromatase inhibitor? __________________

5. How old were you when you were first prescribed Tamoxifen or an aromatase inhibitor? _______

6. What type of insurance did you have while taking Tamoxifen or an aromatase inhibitor? ________________________________

7. What is your race? ________________________________________________
8. Education received:
   □ Some High School □ High School Graduate or GED
   □ Associates Degree □ Bachelor’s Degree □ Masters or Doctorate
REFERENCES


