THE IMPACT OF ACCESS TO CANCER CARE ON ADJUVANT ENDOCRINE THERAPY USE AMONG BREAST CANCER SURVIVORS IN APPALACHIA

by

Xi Tan

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Dissertation Committee**:**

Associate Professor Rajesh Balkrishnan, Chair
Professor Roger T. Anderson, University of Virginia
Professor Richard P. Bagozzi
Associate Professor Steven R. Erickson
Professor Karen B. Farris

DEDICATION

This work is dedicated to my dearest parents: Lianping Zhao and Yongping Tan

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LIST OF ABBREVIATIONS AND ACRONYMS

ACR ─ American College of Radiology

AET ─ Adjuvant Endocrine Therapy

AI ─ aromatase inhibitor

AIC ─ Akaike's information criterion

AJCC ─ American Joint Committee on Cancer

ARC ─ Appalachian Region Commission

ASCO ─ American Society of Clinical Oncology

ATLAS ─ “Adjuvant Tamoxifen Longer Against Shorter” trial

BI-RADS ─ Breast Imaging Reporting and Data System

BIC ─ Bayesian information criterion

BSC ─ breast conserving surgery

CBE ─ clinical breast examination

CCI ─ Charlson Comorbidity Index

CDC ─ Centers for Disease Control and Prevention

CMS ─ Centers for Medicare and Medicaid services

CoC ─ Commission on Cancer

DVT ─ deep venous thrombosis

EBCTCG ─ Early Breast Cancer Trialists' Collaborative Group

EBRT ─ external beam radiation therapy

ER ─ estrogen receptor

FFS ─ fee for service

HER2 ─ Human Epidermal Growth Factor 2 Receptor

HMO ─ health maintenance organization

HPSA ─ Health Professional Shortage Area

HR ─ hormonal receptor

IRB ─ Institutional Review Board

LHRH ─ luteinizing hormone-releasing hormone

LIS ─ low-income subsidy

MPR ─ Medication Possession Ratio

MRI ─ Magnetic Resonance Imagining

MSA ─ medical savings account

MTM ─ medication therapy management

NCCN ─ National Comprehensive Cancer Network

NCHS ─ National Center for Health Statistics

NCI ─ National Cancer Institute

NIH ─ National Institutes of Health

NPI ─ National Provider Identifier

OR ─ Odds Ratio

PDP ─ prescription drug plan

PE ─ pulmonary embolism

PH ─ proportional hazards

PR ─ progesterone receptor

PPACA ─ Patient Protection and Affordable Care Act

RCT ─ randomized clinical trial

SEER ─ Surveillance, Epidemiology and End Results program

SERM ─ selective estrogen receptor modulator

SES ─ socioeconomic status

US ─ United States

UPIN ─ Unique Physician Identification Number

ABSTRACT

OBJECTIVES: The Appalachia region experiences excess cancer mortality and a lack of access to cancer care resources. There is limited research examining adjuvant treatment use disparities in this region. This study aims to explore adjuvant endocrine therapy (AET) utilization in Appalachia, and delineate the effects of access to cancer on AET use.

METHODS: Female breast cancer patients were identified in cancer registries from the Appalachian counties in four states (KY, NC, OH, and PA) and linked to 2006-2008 Medicare claims data. We included patients with invasive, non-metastatic, hormone-receptor-positive breast cancer and assessed the prevalence of receiving guideline-recommended AET. We then assessed AET adherence among those who received guideline-recommended AET using the Medication Possession Ratio (MPR), and determined non-persistence, defined as exceeding a 60-day medication gap. We also used survival analyses to examine the influences of AET adherence and persistence on overall survival.

RESULTS: Only 450 of the 946 eligible patients (47.6%) received guideline-recommended AET, which was significantly associated with shorter travel time to receive care, dual Medicare and Medicaid eligibility, being unmarried (vs. married), and living in Pennsylvania (vs. Ohio). The non-adherence rate was about 31% and non-persistence rate was 30% over an average follow-up period of 421 days. Tamoxifen, relative to aromatase inhibitors, was associated with higher odds of adherence (Odds

Ratio = 2.82, $p < 0.001$) and a lower risk of non-persistence (Hazard Ratio = 0.40, $p < 0.001$). Side effects like pain may be an important factor leading to non-adherence and early discontinuation. Non-adherence to and non-persistence with AET were associated with higher risks of all-cause mortality.

CONCLUSIONS: In Appalachia, geographic and socioeconomic factors such as travel time to receive care and healthcare plan type are important elements that could contribute to disparities in access to adjuvant treatment, while treatment choice and medication-related factors may exert strong influences on AET use behaviors.

CHAPTER 1

INTRODUCTION

1.1 Background to the problem

The Appalachian region of the United States (U.S.) covers 204,452 square miles in 420 counties along the spine of the Appalachian Mountains.[1,2] This region contains all of West Virginia, and portions of 12 other states: New York, Pennsylvania, Ohio, Maryland, Kentucky, Virginia, Tennessee, North Carolina, South Carolina, Georgia, Alabama, and Mississippi. Forty-two percent of the population of this region lives in rural, mountainous environments.[2] Appalachia is much less racially diverse than the rest of the U.S.: only 16.1% of the population is non-white.[1] The population have high poverty rates (16.1% overall, compared to a national average of 14.3%) and low educational attainment rates.[1] According to the Appalachian Regional Commission (ARC), 108 of 420 counties (25.7%) are high-poverty areas with poverty rates over 1.5 times the national average in the period 2007-2011.[3] The regional per capita income is 16.7% lower than the U.S. average; in central Appalachia, it is 34.8% lower than the U.S. average.[1] About 16.5% of Appalachian residents have less than a high school education, compared to 14.6% in the U.S. overall.[1]

Poor access to adequate healthcare is a continuing problem in Appalachia. The National Cancer Institute (NCI) classifies the Appalachian region as a special population of interest due to significant cancer care and outcome disparities for most common cancers.[4–6] Among Appalachian women, breast cancer is the most commonly

diagnosed cancer and has the second highest mortality rate following lung and bronchus cancer.[7] In terms of early breast cancer detection and screening, the percentage of Appalachian women aged 40 years or older who get mammograms or clinical breast examinations (CBE) is significantly lower than the national average.[8,9] In addition, Appalachian women are subject to a higher prevalence rate of modifiable risk factors associated with breast cancer including inadequate fruit and vegetable consumption, little or no physical activity, and obesity.[7,8] Appalachian women are also less likely to receive guideline-appropriate adjuvant radiation therapy after breast conserving surgery (BCS),[10] which raises concerns about potential disparities in the utilization of other recommended adjuvant treatments.

Breast cancer mortality has declined in recent decades, but the breast cancer mortality decline in Appalachia has been only about half of that in the non-Appalachian regions.[11] Among the factors that are likely to contribute to cancer disparities in Appalachia, lack of access to adequate, effective cancer care is a critical factor. Rural residence, geographic isolation, lack of public transportation, underdeveloped telecommunication infrastructure, high poverty and unemployment rates, inadequate medical resources, a shortage of healthcare professionals, lower levels of educational attainment, and attitudinal and cultural factors in Appalachia may all result in poor access to care.[9,12–14] Currently, surgery remains the primary treatment modality for breast cancer, but recent marginal gains in survival may be largely attributable to the adjuvant therapy that usually follows primary therapy,[15–17] including adjuvant radiation, chemotherapy, targeted therapy, and endocrine therapy. With the growing number of breast cancer survivors, breast cancer care should not only provide active treatment but also

survivorship care such as post-treatment monitoring and risk-reducing maintenance behaviors.

Oral adjuvant endocrine therapy (AET) such as tamoxifen and aromatase inhibitors (AIs) is a secondary prevention therapy recommended for use among hormone-receptor (HR) positive breast cancer survivors for a period of five to ten years to reduce recurrence and improve survival.[18–21] Breast cancer survival disparities may also be partly attributable to the receipt of appropriate AET, which in turn may be related to patient access to care, especially in a region like Appalachia. Additionally, patient adherence and persistence to AET are critical in maximizing treatment benefits; this has been identified as a significant issue in clinical practice, with non-adherence and non-persistence rates as high as 59% and 73%, respectively.[22,23] In all, there is increasing recognition in the literature that greater effort should be made to improve adjuvant treatment use to pursue better cancer outcomes.

1.1 Need for the study

AET is associated with lower risks of breast cancer recurrence, contralateral breast cancer, and death.[18–21] Apart from its benefits in improving clinical outcomes, AET is also associated with fewer side effects or more tolerable side effects than adjuvant chemotherapy and increased convenience of drug administration. Based on consistent findings of long-term benefits, the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) guidelines recommend extended use of AET for five to ten years among breast cancer survivors with positive HRs and without contraindications.[24–26] Despite the long-term benefits of AET, however, the use of guideline-recommended AET is unsatisfactory in actual practice, especially

among underserved populations.[27] And in spite of the importance of adherence and persistence to AET for the prescribed period, non-adherence and non-persistence are prevalent and increase with time.[22,23]

AET use is related to several access-related factors, including patients' socioeconomic status, out-of-pocket costs, and facility and provider types.[23,27,28] However, there are no studies that systemically evaluate the relationship between access to cancer care and AET use patterns, adherence, and persistence, which leaves a significant gap in breast cancer treatment research. In addition, the literature examining AET use behaviors among breast cancer survivors in underserved regions, though warranted, is very limited.[22] Furthermore, current research into the reasons for breast cancer outcome disparities in Appalachia still mainly focuses on breast cancer prevention and screening, as well as primary cancer treatment, and does not include adjuvant treatment use.

To fill these gaps, we analyzed a large combined dataset to examine AET utilization and its relationships with access to cancer care and survival among breast cancer survivors in the Appalachian counties of four Appalachian states. The contribution of this study is to identify the effects of access to cancer resources on AET utilization and, in turn, on survival outcomes. The contribution is significant because the study findings will advance understanding of the complexity of the relationship between access to cancer care and AET use in Appalachia. This study also adds to the current literature about whether and to what extent AET adherence and persistence influence survival after controlling access factors. All of these contributions are informative for the design and development of evidence-based interventions and public health policies to improve AET use and reduce survival disparities in Appalachia and similar rural and underserved

regions. This study also demonstrates the importance of tailoring research hypotheses and intervention strategies for medication-use behaviors based on the characteristics of a specific population or geographic region. Our long-term goals are to maximize the benefits of breast cancer treatment, reduce breast cancer disparities, and improve breast cancer survival in Appalachia.

1.2 Purpose of the study

We aimed to explore the relationships between access to cancer care resources, adjuvant treatment use, and therapeutic outcomes among Appalachian breast cancer survivors. Our central hypothesis was that breast cancer patients who had better access to cancer care were more likely to receive appropriate adjuvant treatment and conform to treatment recommendations, which could lead to better therapeutic outcomes. We planned to test our central hypothesis by pursuing the following two specific aims:

(1) Assess the relationship between access to cancer resources and the receipt of guideline-appropriate adjuvant endocrine therapy.

Working hypothesis 1.1: Breast cancer patients who had better access to cancer care resources were more likely to receive guideline-appropriate adjuvant endocrine therapy.

(2) Examine the association between access to cancer care resources and adjuvant endocrine therapy adherence and persistence, as well as the influences of AET adherence and persistence on survival.

Working hypothesis 2.1: Among those who received guideline-appropriate adjuvant endocrine therapy, patients who had better access to cancer care resources were more likely to have better treatment adherence and persistence.

Working hypothesis 2.2: Among breast cancer patients who received guideline-appropriate adjuvant treatment, those who were adherent to and persistent with their adjuvant treatments had a lower risk of death during the study period, after controlling for access to cancer care.

1.3 Nature of the study

This project was a retrospective cohort study of female breast cancer survivors who resided in the Appalachian counties of four states (PA, OH, KY, and NC) from January 1, 2006 to December 31, 2008. We integrated data from multiple sources: the primary data sources were cancer registries from the four states and the Centers for Medicare & Medicaid Services (CMS) Medicare claims data. The primary outcome measures were AET utilization, AET adherence/persistence, and survival outcomes. The expected outcome of this study was a description of adjuvant treatment utilization among breast cancer survivors in Appalachia, the manner in which the determinants of access to cancer care resources impact AET adherence and persistence, and the influence of these factors on survival. Such outcomes may have a positive impact on future endeavors to improve medication use and health outcomes among breast cancer survivors, ultimately improving the quality of breast cancer survivorship care.

To the best of our knowledge, this is one of few studies comprising a large, representative sample and substantial data to study access to care and cancer treatment use in Appalachia. Most of the previous studies of this size and capacity used data from the Surveillance, Epidemiology, and End Results (SEER) program, which does not include most of the Appalachian states.[29] Furthermore, this study is among the

first to integrate the theoretical concepts of access to care, to link them to AET utilization and use behaviors, and to determine their influence on cancer survival. To guide our study design, measures, and analyses, we utilized a new integrated conceptual framework based on research about access to care, cancer disparities, medication adherence, and health outcomes. This conceptual framework can also guide future research to explore medication use disparities in other rural areas and develop effective interventions for improving adherence to oral anticancer medications.

CHAPTER 2

LITERATURE REVIEW

To better understand how access to care impacts AET utilization in Appalachian breast cancer survivors, it is important to review the trajectory of breast cancer and to identify where AET plays a role. A good knowledge of the multilevel landscape of breast cancer disease course and management can help us to understand and assess decision-making and associated behaviors of prescribers and patients, including related predictors and consequences. The following sections describe the relevant context of breast cancer care and the role of AET in it. In addition, this chapter describes the measurement framework of this study, which is guided by both empirical evidence about AET use and theoretical constructs of patient health utilization, health disparities, and health outcomes.

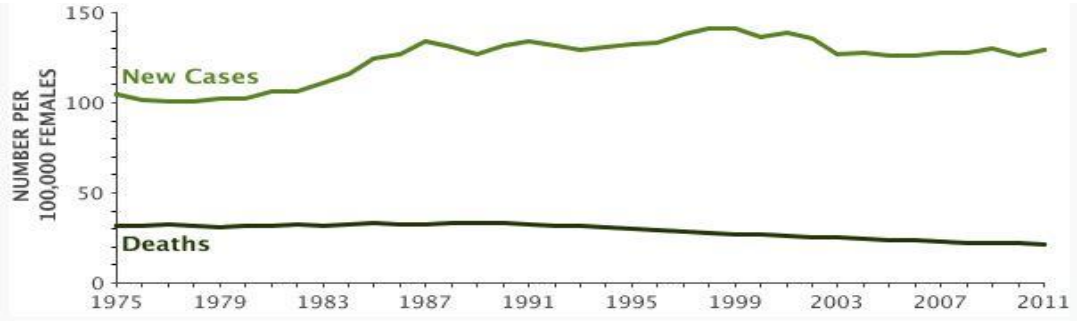
2.1 Overview of female breast cancer

2.1.1 Epidemiology and economic burden of female breast cancer

Breast cancer is the most common cancer in women worldwide.[30] This is also true in the U.S., where the incidence of breast cancer was 122.8 per 100,000 women in the years 2007-2011, almost twice as high as the incidence rate of the second most common cancer.[31] In fact, the U.S. has one of the highest incidence rates of breast cancer in the world.[32] Fourteen percent of all new cancer cases in the U.S. are breast cancer cases, and 12.3% of females are diagnosed with breast cancer at some time point in their

lives.[33] The current five-year breast cancer survival rate in the U.S. is 89.2%, though an individual's prognosis is largely influenced by the cancer stage at the time of diagnosis. Average five-year survival rates vary from 25% for distant stage breast cancer to 98.5% for local stage breast cancer. Figure 2.1 shows the trends of breast cancer incidence and mortality in the U.S. during the last few decades (adopted from SEER stat fact sheets: breast cancer).[33]

Figure 2.1 Breast cancer incidence and mortality trends in the U.S., 1975-2011



Adopted from SEER stat fact sheets: breast cancer[33]

From Figure 2.1, we can see that incidence has increased overall, which is due, in part, to an increase in new cases diagnosed as a result of improved breast cancer screening. The trend seems to have stabilized over the last 10 years. The figure also shows that the annual reduction in the death rate was about 1.9% from 2002 to 2011, which may be largely attributable to advancements in breast cancer screening, care, and management.

Overall, the combination of high incidence and increased survival rates leads to high prevalence: in the U.S., an estimated 2,899,726 women were living with breast cancer as of 2011.[33] The breast cancer survivor population is expected to continue to grow, increasing awareness of the need for breast cancer survivorship care and support to further improve survivors' life expectancy and quality of life.

It is not surprising that, globally, cancer imposes a greater economic burden, to both patients and to society, than any other disease; this includes the costs of productivity loss due to premature death and disability, as well as health expenditures.[34,35] According to a report from the National Institutes of Health (NIH), the estimated total annual cost of all cancers in 2009 was about $216.6 billion in the U.S., 40% of which was direct medical costs and 60% of which was indirect mortality costs.[35] A major proportion of direct medical costs covered cancer treatments. Due to the high costs associated with cancer treatments, insurance status and coverage play a very critical role in access to and utilization of these treatments, which leads to disparities in cancer care quality and outcomes. In addition, the financial costs associated with cancer are expected to grow faster than overall healthcare expenditures because, in an aging population, more people are at increased risk of cancer, and because more novel, advanced, and expensive cancer treatments are now included in standard cancer care.[36]

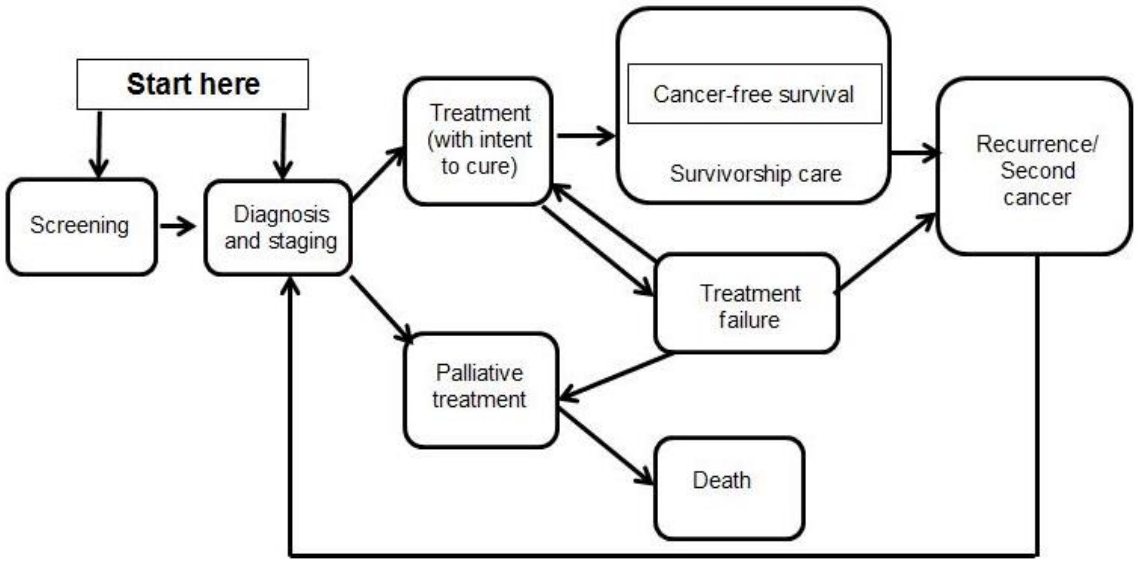
With regard to direct medical expenditures, female breast cancer is the most expensive type of cancer in the U.S.[37] It was associated with $16.5 billion in healthcare expenditures in 2010. Costs are generally highest in the first year after diagnosis (initial phase) and the last year of life (last phase), following a “U” shape.[36,38] Breast cancer care expenditures also depend on cancer staging; it is more expensive to treat late-stage breast cancer than to treat early-stage breast cancer.[39,40] If we further examine indirect costs associated with productivity loss due to premature death or disability, female breast cancer is the third most costly type of cancer worldwide and the second most costly in the U.S. [34,36] The indirect costs associated with female breast cancer

were estimated at $12.1 billion in the U.S. in 2005.[41] Given this significant economic burden, there is a need to develop and employ cost-effective treatment strategies to reduce recurrence and improve survival rates.

2.1.2 Breast cancer care trajectory

Figure 2.2 depicts a simplified overview of the breast cancer care trajectory (Adapted from “From Cancer Patient to Cancer Survivor: Lost in Transition (2005)”).[42] A typical, hypothetical patient, Ms. A, shows something suspicious during a screening test or presents signs or symptoms. She is given diagnostic tests, which may include an imaging test or biopsy. Ms. A is diagnosed with breast cancer and the stage is confirmed. If she is diagnosed with metastatic breast cancer with a poor prognosis, she is unlikely to be cured and palliative therapy (without the intention to cure) can be offered to her. On the other hand, if her prognosis is better and she is willing to receive active primary treatment, one of two things happens: either the treatment works and she is cancer-free or the treatment fails. In the latter case, she can either receive other treatment options or palliative care. If Ms. A survives her primary treatment and becomes cancer-free, she can also receive survivorship care with the goal of keeping her healthy and reducing the risks of breast cancer recurrence, metastasis, and death. The survivorship phase is also where AET comes into play, which is the focus of our research. But before we describe our research, we will briefly introduce several important components of breast cancer care.

Figure 2.2 Breast cancer care trajectory



Adapted from "From Cancer Patient to Cancer Survivor: Lost in Transition (2005)"[42]

2.1.2.1 Breast cancer screening, diagnosis and staging

Assessing breast cancer risks and conducting screenings can both significantly improve survival rates by detecting breast cancer early and preventing treatment delay. There are three classic screening modalities: breast self-examination, clinical breast examination (CBE), and mammography. Breast self-examination tends to be discouraged now due to questions about its effectiveness.[43] Mammography, a powerful tool that is able to detect the smallest cell mass size at 1mm, has been shown to reduce breast cancer mortality by 15%.[44,45] Most current guidelines in the U.S. therefore recommend that women over 40 get mammograms annually or biennially. However, its role in screening is not uncontroversial: issues of safety, false positive rates, and costs with regard to its application as a screening tool in the large general population are all

concerns. CBE provides a unique complement to imaging tests, especially given that mammography still misses 10% -15% of palpable masses. In addition, CBE benefits those patients who are not yet 40; therefore, most current screening guidelines in the U.S. recommend CBE for women aged 20-39 every one to three years.[43]

Diagnostic examinations include diagnostic mammography, biopsies, and supplemental imagining views such as ultrasounds and magnetic resonance imagining (MRI) scans. The majority of breast cancer cases (>90%) are identified based on abnormal mammograms.[46] After reviewing diagnostic mammogram results, which have a higher sensitivity and lower specificity than screening mammogram results, the radiologist uses the American College of Radiology (ACR) BI-RADS (Breast Imaging Reporting and Data System) final diagnostic assessment categories to standardize the report of mammographic findings and provide recommendations for future management.[47]

Two important breast cancer receptor tests can affect treatment strategy choices: hormonal receptor tests and human epidermal growth factor 2 (HER2) receptor tests. Estrogen receptor (ER) and progesterone receptor (PR) overexpression are prognostic factors for newly diagnosed invasive breast cancer.[48] The presence of ER or PR in >1% of the cancer cells indicates a positive result.[48] The recurrence rate is significantly higher for ER-negative cancer than ER-positive cancer.[49] ER and PR tests are warranted because ER and/or PR positive patients may be eligible for endocrine therapy as neoadjuvant (pre-primary treatment) or adjuvant treatments. HER2 receptor overexpression, a marker of poor prognosis, occurs in about 15%-20% of breast cancer cases.[50] The value of this test lies in predicting candidates for HER2-directed therapy, since positive HER2 receptors are the target of HER2-directed therapy.

Clinicians use cancer staging information to determine the size and location of the tumor, which may help them make a prognosis, guide treatment plan development, and facilitate communication with patients.[51] Table 2.1 illustrates breast cancer staging in detail (Adopted from American Joint Committee on Cancer [AJCC] breast cancer staging, 7th edition).[52] Based on the TNM staging system, five-year survival rates are about 95%, 85%, 70%, 52%, 48%, and 18% for patients presenting with stage I, IIA, IIB, IIIA, IIIB, and IV breast cancer, respectively.[53]

Table 2.1 Breast cancer staging

Stage	T category	N category	M category
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T0	N1mi	M0
	T1	N1mi	M0
Stage IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1
Descriptions:			
	Tis: carcinoma in situ T0: no evidence of primary tumor T1: tumor size≤20mm T2: 20mm<tumor size≤50mm T3: tumor size >50mm T4: tumor of any size with direct extension to the chest wall and/or to the skin	N0: no regional lymph node metastases N1mi: lymph nodal micrometastases N2: metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases N3: Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement	M0: no evidence of distant metastases M1: distant detectable metastases

Adapted from the American Joint Committee on Cancer [AJCC] breast cancer staging, 7th edition[52]

2.1.2.2 Survivorship care

According to the most recent NCCN survivorship guidelines,[54] survivorship care for patients who have survived primary cancer treatment and are in remission should 1) monitor and prevent cancer recurrence, metastases, and new cancer; 2) evaluate long term physical and psychological effects; 3) deal with the consequences of cancer and treatment; and 4) coordinate care including primary care providers and specialists. The discussion of survivorship care may also be appropriate for patients with metastatic cancer. For breast cancer survivors, the ASCO recommends physical examinations, mammography, and pelvic examinations.[55] Adjuvant therapy including adjuvant chemotherapy and AET may also be administered to breast cancer survivors to prevent breast cancer recurrence, contralateral breast cancer, and death. However, these treatments are associated with increased risk of side effects such as infertility, osteoporosis, and symptoms of estrogen deprivation, cardiovascular diseases, and weight gain, though prevention and management strategies related to these side effects also exist. Pain management for patients experiencing pain from cancer or treatment is crucial and involves different treatments for various types of pain. Women who received axillary dissection and/or radiation therapy may experience arm lymphedema, which can be managed by massage and exercise, elastic compression garments, and complex decongestive therapy. All survivors are encouraged to maintain adequate levels of physical activity and healthy lifestyles, especially in the case of fatigue. In addition, regular screenings for psychological distress and depression are important, as are appropriate referrals and interventions. Finally, genetic counseling may also be conducted to determine the risk to family members.

2.2 Managing breast cancer

2.2.1 Breast cancer treatment options

In this section, we discuss current available treatment options for breast cancer. Not all women with breast cancer receive all of these treatments, and the order of treatments varies across individuals.[50] Surgery is the primary treatment in most non-metastatic breast cancer cases, but when a woman is not eligible, other primary treatment options may be available. Neoadjuvant treatment precedes primary treatment. For example, chemotherapy can be used as a neoadjuvant treatment to reduce the size of a tumor and facilitate surgery. Adjuvant treatment follows primary treatment.

2.2.1.1 Surgery

The breast conserving surgery (BCS) and mastectomy are the two most common breast cancer surgeries. A BCS can be a simple lumpectomy, with the tumor mass and some surrounding normal tissue removed, or a quadrantectomy, which is like a lumpectomy plus a partial mastectomy. A mastectomy, on the other hand, involves removing a large part or the whole breast.[50] In 1990, the NIH consensus report advised that BCS followed by radiation was a safe and effective choice for early-stage breast cancer based on the evidence of a few well-known randomized clinical trials (RCTs).[56–58] And for the next two decades, follow-up studies showed non-inferior outcomes for BCS in combination with radiation compared to mastectomy.[59,60] In addition, radiation was critical in marginally decreasing breast cancer deaths. Recently, however, there have been some changes in clinical recommendations on whether to administer radiation after BCS for HR-positive

stage I breast cancer patients; specifically, endocrine therapy is an alternative to radiation after BCS. [61–63]

In addition, lymphadenectomy is a procedure for checking whether cancer has spread to the lymph nodes and to remove lymph nodes.[50] There are two types of lymphadenectomies: sentinel lymph node biopsy for the further examination of lymph nodes if no signs of cancer are present in the first test, and axillary lymph node dissection for the removal of all lymph nodes under the armpit in cases of malignant lymph nodes.

2.2.1.2 Radiation therapy

Radiation therapy, a procedure that uses high-energy rays or particles to kill remaining cancer cells after surgery, is considered a local adjuvant therapy because it usually follows surgery and targets local, specific areas such as the breast.[50] Radiation can also be focused on just the original tumor site instead of the whole breast, which is called partial breast irradiation. Currently, there are two types of radiation: external beam radiation therapy (EBRT), which delivers radiation from a machine outside the body (externally), and brachytherapy, which places flexible plastic catheters with radioactive material into or around the original tumor (internally). Radiation therapy often follows BCS to destroy remaining cancer cells. If cancer cells spread to lymph nodes, radiation therapy can be used to target these affected areas as well.

2.2.1.3 Systemic therapy

Breast cancer cells have the ability to spread cancer to other parts of the body. The drugs that have systemic effects to treat or prevent this are called systemic therapy and can include chemotherapy, endocrine therapy, targeted/biologic therapy, or a combination of these agents. Systemic therapy is usually an adjuvant therapy, but it is sometimes used as a neoadjuvant therapy for shrinking the tumor before surgery.

2.2.1.3.1 Chemotherapy

Chemotherapy plays an important role in the management of invasive, non-metastatic breast cancer and can also be used to help control metastatic cancer. A single agent or a combination of several drugs can be used. Chemotherapy usually targets certain phases of the cell cycle, so it not only intervenes in the growth of cancer cells but also damages normal cells. It may cause side effects, some of which greatly impact quality of life. Chemotherapy generally has very narrow therapeutic windows; very careful planning is required for dosing and scheduling.[64] To balance effectiveness and safety and to give normal cells a recovery period, chemotherapy is administered at regular intervals called cycles.[64] Cycles vary depending on the chemotherapy used. For instance, cycles are often 14, 21, or 28 days long with treatment days followed by treatment breaks. The number of cycles administered is based on tumor characteristics and overall patient health.

2.2.1.3.2 Targeted therapy

Traditional chemotherapy can damage normal cells in the process of killing cancer cells. Targeted therapy is specific to cancer cells and produces fewer and less severe side effects. It often targets carcinogenesis, a process in which genes change and can cause cancer. HER2-directed therapy targets the overexpressed HER2 protein, which is present in approximately 20% of breast cancer cases.[65] The therapy includes trastuzumab (herceptin), a recombined DNA-derived humanized monoclonal antibody that inhibits the growth of tumor cells by attaching to the HER2 protein. Trastuzumab is a commonly used adjuvant or neoadjuvant therapy for HER2-positive breast cancer. In addition, Everolimus (Afinitor®), another targeted therapy for breast cancer, is a FKBP-12 complex that attaches and blocks the mammalian Target Of Rapamycin (mTOR) and its substrate. It can be combined with exemestane to treat advanced cases of HR-positive and HER2-negative breast cancer after letrozole or anastrozole has failed.

2.2.1.3.3 Endocrine therapy

Endocrine therapy is a critical part of standard adjuvant therapy for invasive, HR-positive, non-metastatic breast cancer. Different types of endocrine therapy work through distinct mechanisms to treat breast cancer.[66] One mechanism blocks estrogen, while the other reduces estrogen levels. Drugs associated with the first mechanism include tamoxifen, toremifene (Fareston®), and fulvestrant (Faslodex®). Among them, tamoxifen and toremifene belong to the drug class called selective estrogen receptor modulators (SERMs). The second mechanism uses ovarian suppression/ablation and aromatase inhibitors (AIs). Ovarian suppression/ablation is indicated for premenopausal

women and works either by removing the ovaries that are the main source of estrogen or by using luteinizing hormone-releasing hormone (LHRH) agonists such as goserelin (Zoladex®) or leuprolide (Lupron®).[66] So far, the benefits of combining ovarian suppression/ablation with other systemic adjuvant therapies remain unclear, so it is only recommended, alone or in combination, if the patient is not eligible for other systemic therapies or cannot tolerate the side effects.[67] This particular study focuses on the most commonly used oral endocrine therapy: tamoxifen and aromatase inhibitors (AIs).

Tamoxifen

Tamoxifen is a SERM that competes with estrogen on HR-positive breast cancer. It has been the gold standard endocrine therapy for HR-positive breast cancer for decades. In line with the latest research, the ASCO and NCCN clinical practice guidelines recommend tamoxifen as the first-line systemic adjuvant therapy for HR-positive invasive breast cancer treatment for up to 10 years.[24,25] It can also be used as neoadjuvant therapy. The Early Breast Cancer Trialists' Collaborative Group's (EBCTCG) meta-analysis of 20 clinical trials with a total sample of 21,457 patients compared the five-year use of tamoxifen as AET with no tamoxifen in the treatment of ER-positive breast cancer.[68] After controlling for age, lymph node status, tumor size and grade, and the use of chemotherapy, the study found that tamoxifen significantly decreased the 15-year risk of breast cancer-specific mortality by about 30% and reduced the 15-year risk of recurrence rate by 39%. More specifically, it lowered the risks of local recurrence by 46%, contralateral breast cancer by 38%, and distant recurrence by 37%. In addition, the recent ATLAS (Adjuvant Tamoxifen Longer Against

Shorter) trial,[69] found that 10-year use of tamoxifen compared to 5-year use was associated with an absolute mortality reduction of 2.8% (p = 0.01). Extended use of tamoxifen can also reduce the risks of breast cancer recurrence[69–71] and contralateral breast cancer.[69]

Due to the long history of tamoxifen use, its side effects, risks, and impacts on quality of life have been relatively well studied. Common side effects include menopausal symptoms (e.g., hot flashes and vaginal changes).[67] Rare but severe side effects involve pulmonary embolism (PE), deep venous thrombosis (DVT), and endometrial cancer. The risks of ischemic heart disease remain controversial.[25,67] Even though some adverse effects such as menopausal symptoms may be bothersome to patients, tamoxifen use does not negatively impact overall quality of life.[25,67]

Aromatase inhibitors (AIs)

Three AIs are available: anastrozole, letrozole, and exemestane. AIs are recommended as AET for postmenopausal women with HR-positive breast cancer.[24,25,67] The EBCTCG meta-analysis of AIs vs. tamoxifen found that AI had a lower breast cancer recurrence rate than tamoxifen but showed no significant difference in mortality after 5 years of use [72]; switching from tamoxifen to AI after two to three years (for a total of five years of AET) was associated with an absolute 3.1% recurrence rate decrease and a 0.7% decrease in breast cancer-specific mortality, compared to the use of only tamoxifen for 5 years. Another meta-analysis of RCTs also suggested that switching therapy (from tamoxifen to AI) was preferable in terms of the increase in overall survival.[73] Emerging evidence also supports the use of AIs as initial therapy for postmenopausal women.[67] In terms of

effectiveness and safety, AIs are considered equivalent to tamoxifen as an initial therapy for postmenopausal women.[24,26] Currently, there is no evidence suggesting the advantages of AIs or AI and LHRH agonists combination therapy over tamoxifen and ovarian suppression/ablation for premenopausal women.[67] There are also no data to support the extended use of AI (>5 years) in postmenopausal women.[25]

Generally, AIs have a different side effect and risk profile than tamoxifen. Common side effects of AIs include osteoporosis, musculoskeletal and joint pain, and cardiovascular events such as hypertension and hypercholesterolemia. While overall quality of life may not be significantly impacted, physical function may be impaired due to musculoskeletal and joint pain.[25] AIs are associated with a lower risk of PE/DVT but a higher risk of cardiovascular disease than tamoxifen,[74] and a higher rate of bone fracture compared to a placebo.[75] For postmenopausal women, drug choice depends on effectiveness but also on patients' tolerance of side effects and their preferences, especially when the drug must be used for an extended time period. If patients cannot tolerate side effects or if side effects are not carefully monitored and well managed, patient adherence to and persistence with AET may be jeopardized, which could further impact the effectiveness of the therapy.

The sequence and optimal duration of tamoxifen and AIs

Recommendations from the NCCN and the ASCO regarding AET use in HR-positive, invasive, non-metastatic breast cancer patients are generally consistent.[24,25] The choice of drug is based on menopausal status: AIs are indicated for postmenopausal women only. The optimal durations for tamoxifen and AI are ten and five years, respectively. So

for a woman who is pre- or peri-menopausal or of unknown menopausal status, tamoxifen can be initiated for five years. Later, if the patient becomes postmenopausal, she can either continue with tamoxifen for a total of ten years or switch to AI for five more years. On the other hand, for postmenopausal women, either AI or tamoxifen can be initiated as AET for five and ten years, respectively. If a patient cannot tolerate the side effects during these years, she can switch to the other AET. She can also start with tamoxifen or AI for two to three years and then to switch to the other AET for five additional years.

In all, treatment choices for breast cancer are based on cancer staging, as well as tumor characteristics such as HR positivity and HER2 status. According to current guidelines, AET is recommended in all cases of HR-positive, invasive, non-metastatic breast cancer. Adjuvant chemotherapy is recommended in more advanced cases, but not for women older than 70 due to a lack of evidence about its effectiveness in these patients. The addition of trastuzumab is recommended for HER2-positive breast cancer.

2.3 Breast cancer disparities

Disparities in cancer survival involve interactions between multiple factors at both the individual and healthcare system levels. Some factors, like genetic risks, are inherent and hard to change, while some factors like health behaviors, cultural beliefs, and health practices are modifiable. These factors can influence every stage of breast cancer care, from prevention to survivorship and palliative care. Here we discuss some important disparities in the U.S. breast cancer patient population.

Racial/ethnic disparities

Black women have the highest breast cancer mortality rate of any racial group in the U.S., and this disparity has persisted over time, although the gap has narrowed slightly.[33] From 1975 to 2010, the 5-year survival rate among white females with breast cancer increased from 75.6% to 91.8%, while for black women, it rose from 62.0% to 80.0%.[76] The mortality gap may reflect the fact that black women have a higher likelihood of receiving a late-stage diagnosis relative to white women (45% vs 35%).[77] Because black women also tend to be younger at diagnosis,[78] they are more likely to have aggressive tumors with a poor prognosis. Furthermore, this disparity in survival still exists after controlling for clinical factors, socioeconomic status (SES), and primary treatment.[79] Livaudais et al (2013) used self-reported measures to explore another possible explanation for the racial/ethnic difference in survival: whether racial disparities exist in the use of adjuvant therapy.[80] However, they found no significant differences in the use of adjuvant therapy by race or ethnicity. Silber et al. (2013) also suggested that differences in breast cancer treatment explained only 0.81% of the 12.9% difference in survival rates by race.[81] Social or cultural factors may also exacerbate the problem including poor access to care; greater perceived barriers; inadequate knowledge; and misbeliefs about screening, treatment, and follow-up care.[82] The contributions of these factors may be more significant to the racial/ethnic disparities in survival than biological factors or prognosis based on tumor characteristics.[83,84]

Socioeconomic disparities

Socioeconomic disparities, measured by economic status, level of educational attainment, or health insurance, in breast cancer care and outcomes also remain prevalent. For the general population of female cancer patients, low SES was associated with a 3% higher death rate relative to high SES.[84] For breast cancer, in particular, SES may influence almost all aspects of care, from prevention to end-of-life care. Significant SES disparities have existed in mammography screening rates over the decades; the disparities in mammography use increased by 161% from 1987 to 2004.[85] The percentage of women diagnosed with early-stage breast cancer in economically competitive census tracts was higher than those in distressed census tracts (67% vs 59%, respectively).[84,86] Uninsured patients or patients with public insurance were also more likely to be diagnosed with late-stage breast cancer and to have worse survival outcomes than those with private insurance.[87,88] Compared to fee-for-service (FFS) plans, capitated health insurance plans seemed to provide higher quality cancer care and better clinical outcomes including the reduced likelihood of late-stage diagnosis[89] and increased likelihood of receiving HER2 testing.[90] Moreover, breast cancer patients living in high-poverty areas were much less likely to receive BCS and radiation compared to their counterparts in low-poverty areas.[63] Bradley et al (2002)[91] also argued that SES might account for most of the racial/ethnic differences in breast cancer survival. Their study population lived in the Metropolitan Detroit area, which had a good representation of minority and economically distressed communities. The researchers found no evidence of racial disparities after controlling for SES but found that low SES was related to greater likelihood of late-stage diagnosis, unfavorable

primary treatment choices, and death. A study among Medicare enrollees in Alabama made similar conclusions.[92] In addition, SES might also be related to the biological and prognostic characteristics of breast cancer, such as ER status and obesity.[93]

Healthcare system-level disparities

Variations in physicians' practice may also account for disparities in patients' health and cancer survival. Physicians process and synthesize complex information to interpret patients' presentation of signs and symptoms and to make clinical decisions. Consciously or unconsciously, they not only rely on patients' clinical status and prognosis but also social and economic factors such as health insurance, race/ethnicity, and SES, as well as cognitive and behavioral factors such as confidence in communication, intention to adhere to clinical recommendations, and patient preferences.[84,94] Physicians who treat more minority patients are less likely to recommend mammography screening or promote immunizations for elderly patients.[95] In addition to patients' features, physicians' own characteristics can influence their practice patterns considerably; these include education, training, experience, beliefs, cultural competence, communication capability, and style, as well as accessibility and availability.[94] For example, physicians who graduated from medical school between 1984 and 1988 were more likely to prescribe guideline-concordant endocrine therapy to patients with non-metastatic breast cancer than those who graduated after 1989,[63] which might reflect the emergence in the late 80s of literature on the benefits of endocrine therapy. Moreover, external environmental factors may also influence physicians' practice, including physician incentives, reimbursements, medical resources,

practice guidelines, and federal and local policy. According to a study by Anderson et al (2014), physicians at Commission on Cancer (CoC) accredited facilities, for instance, were more likely than other physicians to provide guideline-concordant treatments for patients with non-metastatic breast cancer.[96]

Cancer care calls for adequate medical resources, sophisticated technology, advanced and specialized practice, and communication and coordination across various settings and healthcare providers. The limited real-world supply of resources means that not every eligible cancer patient can receive optimal cancer care. System-level disparities depend, in part, on the features of the healthcare system including facility specialty, size, case volume, and quality of care. It is well recognized in the literature that treatment facilities with a larger volume of complicated procedures and a higher level of specialization such as American College of Surgeons-approved or NCI-designated cancer centers were associated with better cancer outcomes.[97–101] These types of facilities tend to be concentrated in more economically competitive, non-rural areas, which can result in geographic disparities in medical resource allocation and cancer outcomes.[40] Furthermore, patients may have to travel longer distances to these high-volume facilities and designated cancer centers, partly because oversight agencies and insurance providers attempt to move complicated cancer care to these types of facilities.[102]

In all, the effects induced by the abovementioned disparities may interact, leading to geographic differences in breast cancer care and outcomes. In other words, geographic disparities are a consequence of system-level characteristics such as the geographic distribution of medical resources along with the social, economic, and cultural

segregation of the population. Appalachian is a good example of a region in which significant cancer disparities exist. In the next section, we discuss disparities specific to Appalachia.

2.4 Breast cancer in Appalachia

The NCI has designated the Appalachian region as a special population of interest due to substantial cancer disparities for most leading cancers, including female breast cancer.[4–6] Nevertheless, the Appalachian cancer patient population is still not well studied. Most of the epidemiologic data on breast cancer given above are based on the SEER data, which only included cancer registries in two of the thirteen Appalachian states, Georgia and Kentucky.[29]

Incidence and mortality

Among Appalachian women, breast cancer is the most diagnosed cancer and the second leading cause of cancer death following lung and bronchus cancer.[7] The average annual female breast cancer incidence in the Appalachian counties in six states (NY, KY, WV, OH, PA, VA) was 117.1 per 100,000 females in 2002-2006, which was lower than the incidence in the non-Appalachian counties in these states (123.5 per 100,000 females). However, the incidence of late-stage breast cancer at diagnosis was higher in the Appalachian region than the non-Appalachian region,[103,104] which may be partially attributable to the lack of access to care in Appalachia, including a lack of diagnostic doctors and mammography centers and area social deprivation.[5,105]

In general, breast cancer mortality in the thirteen Appalachian states was about 7% higher than in the other thirty-seven states ($p < 0.05$).[106] But there was no significant difference in breast cancer mortality between the Appalachian counties and non-Appalachian counties in these thirteen Appalachian states. Breast cancer mortality in the U.S. has declined in recent decades, but the Appalachian region has not experienced a comparable decline.[11] For example, the decline of breast cancer mortality over the period from 1969 to 2007 in Appalachian counties was only about half that of the non-Appalachian counties in the Appalachian states (17% vs 30%).[11]

Risk factors, screening and treatment

The Appalachian region has a higher prevalence of modifiable risk factors associated with breast cancer such as inadequate fruit and vegetable consumption, no physical activity, and obesity.[7,8] In terms of breast cancer early detection and screening, the percentage of Appalachian women over 40 who get mammograms or CBE is significantly lower than in the rest of the U.S.[8,9] A patient self-reported study in West Virginia found that having health insurance and reliable transportation was significantly associated with better adherence to mammography screening guidelines.[107] Likewise, the findings of another qualitative study suggested that common barriers to screening were inadequate individual and community resources, negative attitudes or lack of knowledge, and competing demands.[108]

There are considerable breast cancer treatment disparities between Appalachia and the rest of the country. First, regarding primary surgery choice, the Appalachian region had a much higher rate of mastectomy than the national average (45.9% vs 37.0%).[10] In

addition, Appalachian women received guideline-appropriate radiation therapy after BCS at a lower rate than other American women.[10,109] In a study in North Carolina, Wheeler et al (2014)[110] found that urban/rural residence and travel distance to the radiation center could predict whether or not patients received radiation therapy.

2.5 Medicare Part D

Because this study focuses on Medicare enrollees, particularly on those receiving Part D, this section briefly reviews the Medicare program. Medicare is a federal health insurance program that covers medical costs for the elderly and disabled. Medicare Part A is a hospital insurance program that covers inpatient services, home care services, nursing home services, and mental health services. Part B provides supplementary medical insurance benefits, which cover physician services, medical equipment and supplies, and outpatient services.[111] Part C, also called the Medicare Advantage program, provides enrollees with Medicare benefits through private insurance. Part C enrollees choose one or some combination of three types of healthcare plans: a coordinated care plan, a medical savings account (MSA)-based plan, or a private FFS plan.[111] Part D is a voluntary prescription drug benefit program launched in 2006; Part A, B, and C beneficiaries are eligible for Part D benefits. The implementation of Medicare Part D has reduced cost-related drug non-adherence.[112]

Prior to Part D implementation, Medicare Parts A and B covered most cancer drugs. After the implementation, oral cancer drugs including AET and anti-nausea drugs were newly covered under Part D instead of Part B. Part D enrollees generally receive their prescription drug benefits through private prescription drug plans (PDPs).[111] Under the

standard prescription drug coverage plan that most Part D enrollees first pay an annual deductible, then pay 25% coinsurance for their total drug costs until they reach an initial coverage limit. Between the coverage limit and an out-of-pocket threshold, the "donut hole," they pay 100% of total drug costs. Above the "donut hole," enrollees receive catastrophic coverage so that they only make a small copayment and pay 5% coinsurance. The Patient Protection and Affordable Care Act (PPACA) reduced beneficiary spending in the "donut hole" by providing a rebate of $250 (in 2010 only), increasing discounts for both generic and brand-name drugs, and expanding coverage of brand-name drugs. The ultimate goal is to close the "donut hole" by 2020.

Low-income Medicare beneficiaries may be eligible for additional subsidies. More than 6 million beneficiaries are "dual eligible" for both Medicare and Medicaid.[113,114] The dual-eligible population is generally vulnerable and tends to have significant medical care needs. Dual-eligible enrollees qualify for both Medicare and Medicaid because they are disabled or blind, aged, and meet the Medicaid income and asset requirements.[114] Compared to Medicare-only beneficiaries, they are more likely to be either much older or much younger, to be in fair to poor health, to have chronic and severe health conditions, and to be economically distressed.[114] Dual-eligible individuals are automatically enrolled in Part D drug plans and they do not pay monthly premium or deductibles.[115] Many states' Medicaid plans also help with copayments or out-of-pocket expenses for drugs not included in the Medicare Part D formulary. In addition, many states developed contingency plans during the rollout of Plan D to help dual-eligible enrollees obtain drug coverage through Medicaid before they were able to access to Part D drug benefits.[113] The series of benefits that dual-eligible enrollees receive may

reduce the financial burden of accessing, utilizing, and adhering to medication, which may improve their health outcomes. Furthermore, low-income Medicare beneficiaries who are not eligible for Medicaid may receive additional premium subsidies based on their resource or asset levels.[115]

2.6 Adjuvant Endocrine Therapy (AET) use

2.6.1 Endocrine therapy use pattern among American women with breast cancer

In U.S. clinical practice settings, the percentage of female breast cancer patients who receive tamoxifen or AI ranged from 58% to 88%, depending on study time, study population characteristics (e.g., age, menopausal status, HR status, residence location), and study methods.[27,63,116–120] Tamoxifen has been widely used in the adjuvant setting that is given after primary treatment, especially before the approval and emerging use of AI among postmenopausal women. Data collected via medical reports and phone interviews in the 1990s showed that, nationwide, 65% to 86% of women with breast cancer used tamoxifen.[118–120] None of those studies examined the Appalachian breast cancer patient population specifically.

Since 2000, with the approval of more and more AIs, data on AI use have become available and a growing body of literature has begun to use pharmacy claims data to examine both tamoxifen and AI use in the adjuvant setting. A study of 1,491 North Carolina Medicaid enrollees with breast cancer in 1998-2002 found that 64% of them received either tamoxifen or AI, a rate that increased to 70% among women with HR-positive breast cancer.[27] The same study found that tamoxifen was much more frequently prescribed than AI, at 88% vs. 12% of that population, respectively. Another

2000-2005 study examined 2,207 female breast cancer patients enrolled in a non-profit commercial health plan in Massachusetts and found that only 58% received AET within 12 months after diagnosis.[117] Of those who did, 54.6% received tamoxifen only, 25.1% received AI only, and the rest switched between the drug classes. This differed from other studies in that the eligible women were new AET users, and the use of AET was limited to one year following diagnosis, which may partly explain the low rate of AET use in this population. In another study, Riley et al (2011) used SEER data and Medicare Part D claims data from May 2006 to December 2007 to study a nationwide Medicare population with Part D benefits.[116] Seventy-four percent of the 15,542 Medicare enrollees with HR-positive breast cancer used AET; fifty-two percent of the total population received AIs and twenty-two percent of them obtained tamoxifen.

These reports showed a trend of increasing AI use in the past decade. It is also noteworthy that the SEER data may well represent the general U.S. cancer patient population but not the Appalachian cancer patient population since they only included two of the thirteen Appalachian states, Georgia and Kentucky, and did not focus particularly on the Appalachian counties.[29] One of the few Appalachian-focused breast cancer treatment studies so far, Kimmick et al (2014),[63] revealed that almost 76% of Appalachian women with HR-positive breast cancer received either tamoxifen or AI within one year after diagnosis. But based on the study design, these AET users may not have been new users, and it is unclear whether tamoxifen and AIs were used for other purposes such as chemoprevention or neoadjuvant therapy, or for metastatic cases.

Two factors were consistently related to the receipt of AET: age at diagnosis and cancer staging. Women diagnosed between the ages of 65 and 74 were more likely to receive AET, as were women with more advanced breast cancer.[63,116,119] In addition, Kimmick et al (2009) found that unmarried women were more likely than married women to receive AET (Odds Ratio [*OR*] =1.82, $p < 0.001$).[27] Other factors associated with AET use included number of co-administered medications,[27] breast cancer primary treatment used,[27,116] type of treatment facility,[27] provider's medical school graduation year,[63] and patient's physical function and ability to communicate.[119]

2.6.2 Outcomes associated with AET use

This section describes the evidence that exists for outcomes associated with AET use. A 13-year retrospective cohort study of 1,962 women with non-metastatic breast cancer in the Netherlands found that adherence to tamoxifen (Medication Possession Ratio [MPR] ≥ 80%) was associated with a 26% reduced risk of a recurrent breast cancer event, after adjusting for other clinical and treatment characteristics .[121] Furthermore, poor adherence to tamoxifen (MPR < 80%) was also significantly related to an increase in all-cause mortality (Hazard Ratio=1.10, 95% CI = 1.001–1.21) for both HR-positive and HR-negative breast cancer cases; among women with HR-positive breast cancer only, the risk of all-cause mortality became greater (Hazard Ratio=1.13, 95% CI = 1.01 – 1.26). In a large claims data study of 8,769 women enrolled in a private health plan in Northern California, Hershman et al (2011) found that non-adherence (MPR < 80%) to either tamoxifen or AI was associated with a 49% higher risk of all-cause mortality ($p < 0.0001$).[122] When non-adherence was defined as MPR < 60%, the risk of all-cause

mortality associated with non-adherence to AET increased from 1.49 to 3.71 (p < 0.0001). Another study in North Carolina Medicaid enrollees, however, did not find a significant relationship between adherence to AET and either breast cancer recurrence or breast-cancer-specific survival.[123] The inconsistent results found in this study compared to previous ones may result from the smaller sample size (N = 857), the population's demographic and diagnostic characteristics (e.g., low-income population, unknown HR status), and different outcome measures. Overall, existing evidence seems to support the survival outcome benefits of adherence to AET among women with HR-positive breast cancer. But there are still limited data on underserved populations. Further research with a large sample size and a rigorous study design is warranted.

2.6.3 AET adherence and persistence

Patient adherence and persistence are critical in maximizing AET treatment benefits. Current literature showed a broad range of adherence and early discontinuation rates ranging from 41% to 95.7% and 12% to 73%, respectively.[22,23] Variations in adherence and persistence in these studies may be attributable to heterogeneity in methodology and study population. There is no gold standard method for measuring adherence and persistence of AET in clinical practice, nor is there a good biomarker available to measure the use of tamoxifen or AI.[124] Therefore, almost all relevant studies used indirect methods to measure adherence and persistence, namely pharmacy claims/medical records data, or physician report/patient self-report data. In general, studies that used physician report or patient self-report data showed better results, with

adherence rates ranging from 77% to 94.7% [125–127] and non-persistence rates ranging from 21% to 31%.[118,125,128,129] Due to their study design, these results may suffer from recall bias or social desirability bias, but they may facilitate the examination of modifiable factors associated with adherence and persistence. Most studies of AET adherence and persistence utilized pharmacy claims data, which had the advantage of large sample sizes, long follow-up time, and objective results. But pharmacy claims data may not capture actual medication-taking behaviors. It is also difficult to use this type of data to investigate modifiable predictors.

Additionally, although adherence was defined as MPR ≥ 80% in these studies, non-persistence/discontinuation was not defined consistently but was often operationalized in retrospective claims data studies as the discontinuation of drugs after exceeding a permissible gap.[130] In AET persistence research, the definition of prescription fill gap ranged from 45 to 180 days, based on the pharmacological characteristics of the drugs; legitimate delays in refills, such as hospitalization; and the length of follow-up period.[122,123,125,131–133] The discrepancies in definition may also result in variations in discontinuation rates. Furthermore, the length of follow-up period is crucial to adherence and persistence results since the literature has consistently shown an inverse relationship between AET adherence and use time.[23,28,117,120,134–138] Many characteristics of study population such as age, race/ethnicity, SES, geographic residence, healthcare plan, and healthcare system factors may also influence patient adherence and persistence[23]; therefore, the inherent heterogeneity in study populations may cause differences in prevalence of AET adherence and persistence.

There is very limited research on AET use behaviors among breast cancer survivors in underserved regions such as Appalachia. And current research on the reasons for breast cancer disparities in Appalachia mainly focuses on breast cancer prevention, screening, and primary treatment and does not include adjuvant treatment use disparities. To facilitate comparison with the present study, we consulted previous pharmacy claims data studies in the U.S. and attempted to identify average AET adherence and persistence rates during the first two years. AET adherence rates were in the range of 70%-80%,[116,117,138,139] and the discontinuation rates were fairly consistent at around 20% .[27,28,117,123] Medicaid enrollees in North Carolina, one of the Appalachian states, had a below-average adherence to AET, at approximately 60%,[27] while patients using mail-order pharmacy services seemed to be more adherent to AET, with an adherence rate of about 90% .[28]

Several up-to-date systemic reviews [22,23,140] summarized potential factors associated with AET adherence and persistence among women with breast cancer. Factors associated with poor adherence and persistence, consistently demonstrated in the literature, included extreme age, increasing out-of-pocket costs of AET, seeing a general practitioner vs. an oncologist during follow-up care, switching between drugs, and treatment-associated side effects. Though the past two decades have produced a substantial literature on factors that contribute to AET adherence and persistence, there is still little research on modifiable factors like psychological or behavioral constructs that could guide the development of clinical interventions to improve AET use behaviors. In addition, there is a paucity of literature that systemically evaluates the relationship between access to cancer care and AET use. The addition of this literature could also

lead to policy intervention strategies that address the pathways linking social and behavioral factors to health disparities in underserved regions like Appalachia.

2.7 Conceptual model

To guide this study, we propose a conceptual model (Figure 2.3) that adapts the constructs from Donabedian's structure-process-outcome framework[141] and Andersen's behavioral model for health service use[142,143] and an extension of the Andersen's model proposed by Pam Short and Roger Anderson (unpublished work), links them to Hendren and colleagues' cancer health disparity model,[144] and integrates the findings of published empirical work regarding AET use. Donabedian's structure-process-outcome framework has been well developed as a comprehensive measurement of quality of medical care. Structure refers to the context and setting in which the health care is delivered,[145] process describes the interaction between patients and healthcare providers throughout health care delivery, and outcome includes economic, clinical, and humanistic outcomes. On the other hand, Andersen's behavioral model identifies the factors that affect access to and availability of healthcare and lead to the use of health services.[142,143] It has been extensively applied in empirical research, especially in secondary data analysis studies of health utilization.[146]

In cancer care, in particular, structural and process factors also reflect patient access to and quality of cancer care and could eventually influence cancer outcomes.[84,144,147] Structural factors may include structural barriers that patients experience in access to care and care coordination such as health insurance, financial burden, logistical barriers (e.g., geographic distance to the healthcare facility, transportation), follow-up care

referral, support, and the accessibility and availability of specialized cancer care. Process factors may include provider's decision-making and prescribing behaviors, patient's decision-making and treatment use behaviors, and cancer care coordination. The process of care may be influenced by patient-level clinical, demographic, and psycho-behavioral characteristics (e.g., cancer clinical status, marital status, race/ethnicity, SES, comorbidities), provider-level characteristics (e.g., competing demands, knowledge, practice experience, cultural competency), and the interaction between patient and provider (e.g., shared decision making, patient self-efficacy in provider-patient interaction, trust in healthcare system/provider). All these structural and process factors may in turn impact care outcomes, for instance, cancer survival, health-related quality of life (HRQoL), and patient satisfaction.[144]

The measures of access to care, as per the Andersen's model and the extension proposed by Pam Short and Roger Anderson, include potential access, defined as the presence of characteristics or resources that enable individuals to seek medical care or services, when needed, and realized access, which is the actual utilization of medical care or services.[142,143] According to the theory, which is supported by empirical evidence, potential access is assessed at the system- and individual- levels. System-level characteristics here refer to SES, educational attainment, transportation barriers, community health risks, and healthcare provider resources at the county or area levels. Research has proven repeatedly that these geographic factors contribute substantially to breast cancer disparities in Appalachia including those related to screening and late-stage diagnosis,[5] as well as the receipt of guideline concordant primary[10] and adjuvant treatments.[63] Individual-level potential access includes three main components:

predisposing factors that are pre-existing characteristics of patients to predict the probabilities of using medical services or products, enabling factors that refer to the ways available to patients to use the services or products, and need factors that generally indicate the severity of the disease and overall health status.[143] To depict access to and quality of breast cancer care in Appalachia, predisposing factors in the model include patient demographics like age, race/ethnicity, marital status, and educational level; enabling factors include household income level, health care insurance and drug insurance, travel time to receive care, health literacy, health/medication knowledge and beliefs, social support, and patient activation[144]; need factors include breast cancer-related clinical status and comorbidities.

Realized access, as a result of potential access, is operationalized by assessing the characteristics of the healthcare providers or facilities from which patients seek care.[142,143] The receipt of optimal cancer care depends, in part, on the choice of cancer providers or oncology resources, which is primarily influenced by the following features: 1) supply: the availability of standard and/or cutting-edge cancer care or treatment options; 2) demand: case volume; type and volume of cancer care procedures; 3) comprehensiveness or coordination: the type and range of services provided, or coordination of care if certain services like adjuvant chemotherapy are not provided at the facility; 4) proximity: geographic distance between patient and facility/provider, or transportation barriers. The specialization and accreditation status may partly reflect the supply and comprehensiveness features of the facility. Meanwhile, a phenomenon called “selective referral” may intertwine the features of demand and proximity. Selective referral indicates the possibility that patients who travel longer distances to

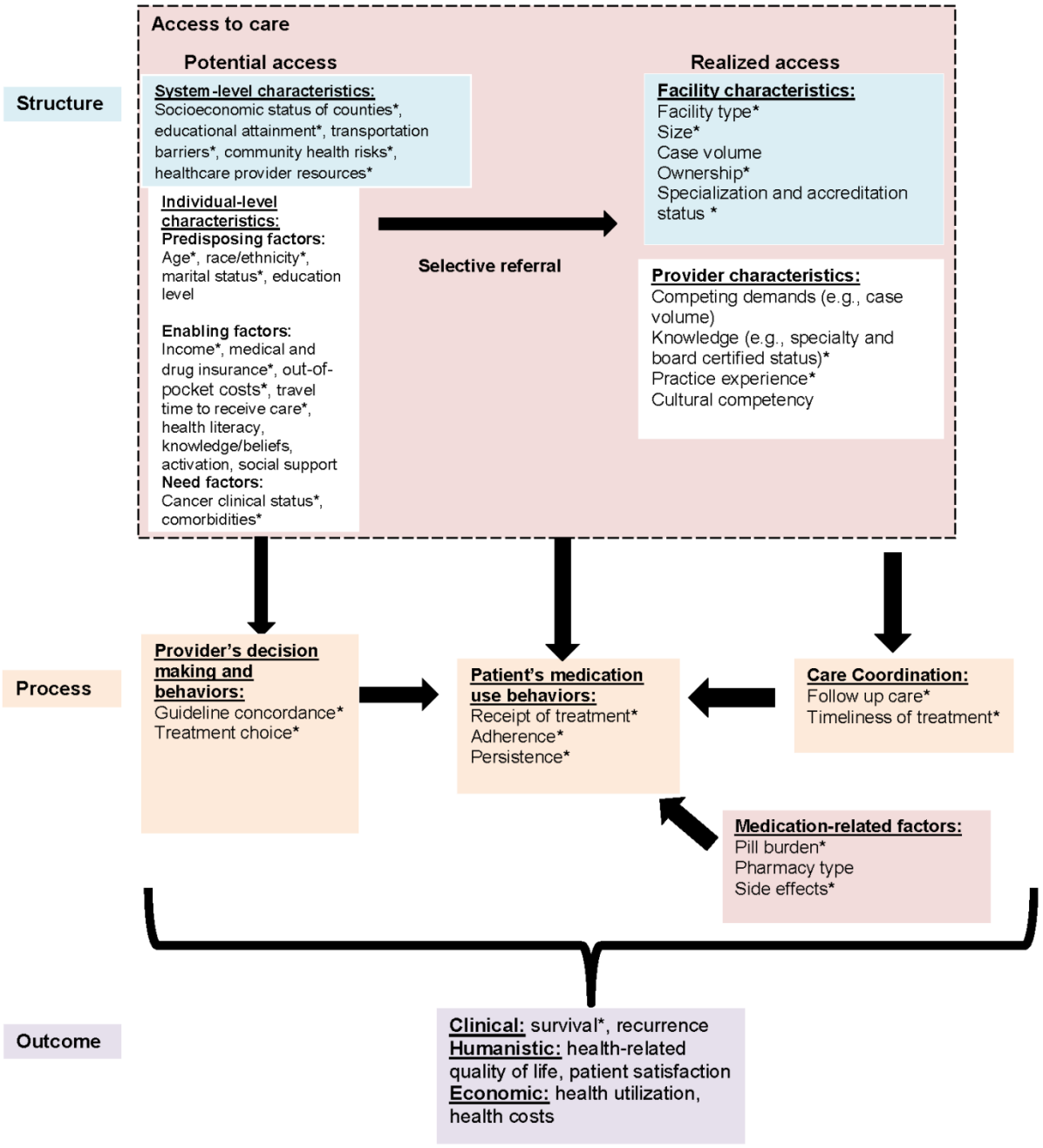
high-volume hospitals and designated cancer centers do so because oversight agencies and insurance providers attempt to move complicated cancer care to high-volume hospitals and designated cancer centers.[102] These patients may differ along unmeasured dimensions, such as clinical status, personality and sophistication, and patient-provider communication, which may also affect the providers' guideline concordance and the patient's adherence to provider recommendations. Furthermore, physicians' decisions about when and how to treat breast cancer is not only based on their patients' characteristics but also their own characteristics, including age, sex, years of practice, medical school, residency hospital, knowledge and specialty, and interaction with patients.[144,148,149]

Patients' medication adherence may also be affected by the factors discussed earlier, including access to care, care coordination, provider decision-making and behaviors, and medication-specific factors. Extremes of age, high out-of pocket costs, survivorship care by a general practitioner rather than an oncologist, drug-switching, treatment side effects or fear of side effects, lack of medication knowledge, insufficient social support, and low self-efficacy in provider-patient interactions are negatively associated with AET adherence and/or persistence.[23,133,140,150] Additionally, individual clinical status, treatment choice, and medication use behaviors may influence treatment outcomes at clinical (e.g., breast cancer recurrence and survival), humanistic (e.g., health-related quality of life, patient satisfaction), and economic (e.g., health utilization and costs) levels.

The current lack of strong evidence regarding the relative importance of the multidimensional factors associated with access to and quality of care limits our

knowledge and ability to develop targeted interventions to reduce cancer disparities in Appalachia. We develop a model that assesses multidimensional determinants to predict AET access, adherence and persistence by including systemic-level, individual-level, facility-level, provider-level, and medication-related factors. According to the model, this study tested the hypothesis that patients who had better access to care were more likely to receive guideline-appropriate AET. Better access factors included in the study were better counties' SES, higher county-level educational attainment, fewer transportation barriers and community health risks, higher household income, better medical and drug insurance benefits, poorer clinical prognosis, more comorbidities or more severe comorbidities, receiving BCS (vs. mastectomy), more breast-cancer-related follow-up visits, receiving timely breast cancer primary treatment, as well as being treated in CoC-accredited, large facilities and by oncologists (vs. generalists). In addition, we examined whether patients who experienced less pill burden, fewer or more tolerable AET-associated side effects, fewer out-of-pocket drug costs, as well as better access factors, had a higher likelihood of AET adherence and persistence. Lastly, after controlling access factors, we investigated if those who were adherent to and persistent with their adjuvant treatments had a lower risk of death during the study period. Overall, this integrated conceptual framework can help us systemically evaluate these factors and link them to providers' treatment guideline concordance and the patients' AET medication use behaviors, which together affect the therapeutic outcomes of breast cancer patients in Appalachia.

Figure 2.3 Conceptual model



* indicates the variables measured in this study

CHAPTER 3

METHODOLOGY

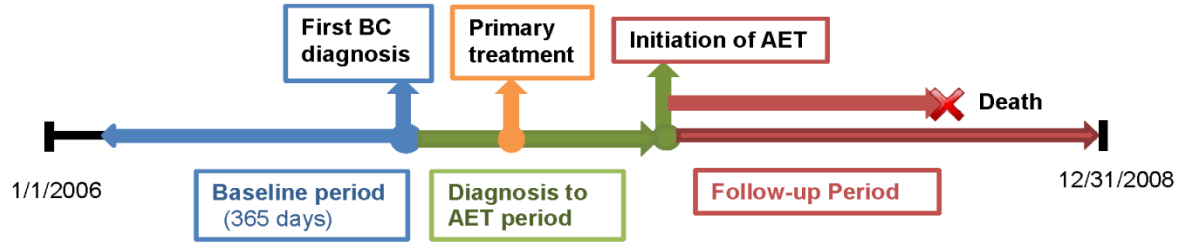
This study assessed the relationships between access to cancer care resources, AET use, and survival among female breast cancer survivors in Appalachia. This section details the study population, design, and measurement, as well as the specific means by which the two study aims were achieved.

3.1 Study design

This was a retrospective cohort study from January 1, 2006 to December 31, 2008 of female breast cancer survivors who resided in the Appalachian counties of four states (PA, OH, KY, and NC) as defined by the ARC. We utilized claims data for Medicare, the primary health insurance for Americans aged ≥65 years. Medicare claims data have been extensively utilized in breast cancer care research for two main reasons.[5,63,151,152] First, older age is a significant risk factor for breast cancer. Second, Medicare claims data tend to be comprehensive and cover the full continuum of health care for enrollees who are not enrolled in a HMO.[5] Furthermore, the Medicare Part D claims dataset is a good source for investigating AET use because AET is covered under Part D and Part D was initiated at around the same time as our study period.

The overall study design illustrated in Figure 3.1 comprised three main periods: the baseline period (one year before the first breast cancer diagnosis), the diagnosis-to-AET period (the interval between the first diagnosis and the initiation of AET), and the follow-up period (from the date of the first AET prescription filled until death or the end of the observation, 12/31/2008). The primary outcomes were the receipt of guideline-recommended AET, AET adherence and persistence, and overall survival. The study was approved by the University of Michigan's Institutional Review Board (IRB), and data use was approved by CMS and each state's cancer registry.

Figure 3.1 Overall study design



3.1.1 Data sources and linkage

To achieve the study aims, we integrated data from multiple sources: we obtained individual characteristics from cancer registries and CMS Medicare claims data; system-level characteristics from the ARC data reports, the 2010 U.S. census, the Area Resource File, the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), and the National Cancer Institute (NCI); and provider/facility characteristics mainly from Medicare Provider of Service files and Medicare Physician Identification and Eligibility Records files. First, we linked women

who were diagnosed with breast cancer during 2006-2008 and tracked in the four states' cancer registries to Medicare claims data using patient identifiers including name, social security number, gender, and birthdate. Then, we established the cross-link between patient data and system-level characteristics using county codes. We utilized Unique Physician Identification Numbers (UPIN) and National Provider Identifiers (NPI) to link patient claims to provider/facility factors. Completely de-identified data were used for final analyses.

3.1.2 Study population

For Aim 1, we followed these steps to obtain the study sample:

1) Start with the 17,074 adult women who were diagnosed with primary breast cancer in the four states' cancer registries.

Adult women with breast cancer who lived in the Appalachian counties of four states (PA, OH, KY, and NC)

N= 17,074

2) Confirm the breast cancer diagnosis and clinical stage in more detail (using data from cancer registries).

- **Include**: 1) cases in which the first diagnosis of primary breast cancer with a positive histology, cytology, or microscopic confirmation was in 2007 and for which there were not multiple/concurrent non-breast cancer solid tumors within 90 days; 2) cases of cancer stage I-III; and 2) cases with an estrogen receptor- or progesterone receptor-positive tumor
- **Exclude**: 1) cases in the cancer registries coded as autopsy- or death certificate-only cases; and 2) breast cancer cases coded as M8540-M8543 (Paget's disease for breast cancer), M9050-M9055 (mesotheliomas), M9140 (Kaposi sarcoma), M9590–M9989 (lymphohematopoietic malignancies), or M8520 (lobular).

N= 2,346

3) Check the CMS Medicare enrollment (using data from Medicare claims).

Include: patients who were continuously enrolled in Medicare Parts A and B from 2006 to 2008 or until death, and continuously enrolled in Medicare Part D from the first breast cancer diagnosis to the end of the observation (12/31/2008) or until death.
Exclude: patients who were enrolled in a Health Maintenance Organization or Medicare Advantage Program.

N= 1,022

4) Check the eligibility and definition of AET new users.

Include: patients who had primary treatment for breast cancer (mastectomy or breast conserving surgery) within 180 days after the diagnosis.
Exclude: 1) patients who had any AET prescription filled before receiving the primary treatment; and 2) patients who were not recommended to receive AET because of contraindications or who died prior to planned or recommended AET.

N= 963

5) Validate data quality by comparing the data from cancer registries and Medicare claims.

Exclude: cases that had mismatching information across data sources (e.g., gender, date of birth, geographic residence)

N=946 (Aim 1 final sample)

Then, we followed additional steps to identify **the final sample for Aim 2**:

1) From the final sample in Aim 1, choose a subset of subjects who were prescribed AET within one year following the diagnosis.

Include: patients who newly initiated AET within one year after diagnosis

N=450

2) Set follow-up days. (Note: the follow-up period was from the initiation of AET to 12/31/2008 or death.)

Include: patients with at least 6 months of follow-up data

N=428 (Aim 2 final sample)

3.2 Variable measures

3.2.1 Measurement of access to care

3.2.1.1 Potential access

3.2.1.1 .1 System-level characteristics (at the county level)

Socioeconomic status of counties: **The Appalachian Regional Commission's county economic status classification (2013)** is an index-based, area-level economic status classification system that describes and tracks the economic situation of Appalachian counties**.**[153] The index calculation is based on the average unemployment rate (2008-2010), the per capita market income (2009), and the average poverty rate (2006-2010) of each Appalachian county. The original index has five categories. Each represents a percentile group based on the national index values of all US counties: distressed (worst 10%), at risk (worst 10-25%), translational, competitive (best 10-25%), and attainment (best 10%). It is a validated, specific measure of the economic status of Appalachian counties and has shown to be related to late stage diagnosis of breast cancer among Appalachian women.[5] Its weakness may be the lack of a social component such as the family structure, wealth and home ownership, which may limit

its sensitivity to some potential area-based SES features that could lead to health disparities. In this particular study, this index was restructured into three classifications: economically distressed, at risk, and others.[5]

Educational attainment: ARC data reports were used to extract **the county-level percentage of residents aged 25 and above with less than a high school diploma and the percentage with at least a bachelor's degree (2007-2011).**[153]

Transportation barriers: We used the dummy variable of metropolitan and non-metropolitan defined by the 2013 NCHS Urban–Rural Classification Scheme for Counties to evaluate the geographic varying effects of these Appalachian counties**.**[154]

Community health risks: As per the Andersen's model,[142,143] infant mortality rates may reflect socioeconomic conditions, as well as the quality and effectiveness of a healthcare system,[12] and can be used to evaluate community health risks at the local level. In addition, cancer mortality rates may also reflect the availability of and access to quality cancer care in the community. We extracted **the 2007 infant mortality rates (reported as deaths per 1,000 births)** at the county level from the linked birth/infant death records (2007-2010) produced by the CDC and NCHS.[155] **The 2007-2011 average county-level cancer mortality rates** were identified from the United States Cancer Statistics data provided by the CDC and NCI, and were presented as the **annual age-adjusted, cancer-related death rates per 100,000 residents**.[156]

Healthcare provider resources: We identified the **Health Professional Shortage Area (HPSA)** designation, as defined by the U.S. Department of Health and Human Services, using data from the 2007–2009 Area Resources Files at the county level. Each

Appalachian county was categorized as being partially within a HPSA, entirely within a HPSA, or not within a HPSA.[5]

3.2.1.1 .2 Individual-level characteristics

- ***Predisposing factors***

Demographic information: The following demographic information were extracted from the cancer registries: 1) **Age at diagnosis** (in year 2007): 18–64, 65–74, 75-84, ≥85 years old; 2) **Race**: white or non-white; 3) **Marital status:** married or not married; 4) **Geographic residence:** state of residence at diagnosis (PA, OH, KY, or NC).

- ***Enabling factors***

Income: The 2007-2011 average estimates of **annual median household income** were extracted from the American Community Survey data using census block group codes.[157] We created a categorical variable of the four quartiles of median household income.

Health insurance benefits: 1) As discussed in Chapter 2, Medicaid and Medicare dual-eligible enrollees may have additional insurance benefits; therefore, we created a **dual Medicaid and Medicare eligibility indicator** (yes/no) to evaluate the effect of different health plans on patient access to AET and AET use. Patients ever at the dual-eligible status during the study time were considered "yes"; 2) the average monthly **out-of-pocket drug costs:** all payments paid by each patient for each drug claim in Medicare Part D were summed up, divided by follow-up days and then times 30 days**; 3) whether patients reached the out-of-pocket threshold and began to receive catastrophic**

coverage: Patients ever reaching the out-of-pocket threshold during follow-up were categorized as “yes”.

Travel time to receive care: The largely rural environment, geographic isolation, and substantial transportation barriers in the Appalachian region may result in poor access to care, which further contributes to cancer disparities. Travel time to mammography centers is one of the currently available validated measures of spatial access to care, which has been shown to relate to late-stage diagnoses of breast cancer.[158] Travel time is a direct, straightforward, and commonly-used measure of special access. It also has the strength of capturing distance decay, which is defined as the decrease of similarity as distance increases.[159,160] In other words, travel time can tell the distinctions between the mammography center close to the patient and the one at the opposite boundary edge to the patient. But it cannot take in account the supply of healthcare resources and demand of patients.[161] Nevertheless, our research group also compared different currently available validated spatial access measures and found that travel time to the closet mammography centers may be one of the best to predict the receipt of guideline-recommended AET (unpublished work), therefore we included this measure in this present study. We calculated **the estimated average travel time (in minutes) between the patient and the three closest mammography centers**. We geocoded the addresses of patients and mammography centers. Travel network distances were calculated from each patient to each mammography center. The shortest travel network path between the patient and mammography center was determined as the distance to the nearest mammography center.

Need factors

Cancer-related clinical information: We obtained information on **breast cancer stage** (I, II, III), **tumor size** (<1 cm, 1–2 cm, >2 cm, unknown), and **lymph nodal status** (negative or positive) from the cancer registries.

Comorbidities: 1) The **Charlson Comorbidity Index (CCI)** was used to assess overall health status based on Medicare claims data during the baseline period. The CCI is a composite score used to predict mortality; a higher score represents more comorbidities or more severe comorbidities. We calculated the Deyo CCI, which contains 17 condition diagnoses based on the ICD-9-CM codes[162], but we excluded the primary diagnosis of interest in this study—female breast cancer. Table 3.1 shows the detailed calculation and codes used; 2) we used **the number of hospitalizations over the baseline period** as a proxy for overall disease severity and burden.

3.2.1.2 Realized access

We designated the provider and affiliated facility with the most breast cancer-related Medicare claims after the diagnosis as the main provider and facility. We used NPI and UPIN to identify and link the provider and facility information.

3.2.1.2.1 Facility characteristics

Type, size and accreditation: 1) **The American College of Surgeons ─ Commission on Cancer (CoC)** provides accreditation for facilities to ensure high quality of cancer care**.** The CoC assigns each facility to a category based on its type, size, and case volume.[163] The CoC categories included in our sample were community cancer program

(14.9%), comprehensive community cancer program (35.8%), NCI-designated comprehensive cancer program (3.0%), network cancer program (0.5%), academic comprehensive cancer program (11.5%), no designation (31.4%), and unknown (2.9%). We created a variable with the following categories: CoC-accredited, not accredited, and unknown; 2) the CMS 2007 Medicare Provider of Service file was used to determine **number of beds** (<100 beds, 100-200 beds, >200 beds, or unknown)**, facility type, and ownership** (for-profit, government, not-for-profit, unknown).

3.2.1.2.2 Provider characteristics

Specialty and credential: We identified specialties and credentials using NPI and UPIN from Medicare claims data. Each healthcare provider was categorized as an oncologist, general practitioner, or other.

Graduation year: The provider's graduation year was used as a proxy for years of practice experience. It has shown to be associated with the receipt of guideline-recommended AET among Appalachian women in previous literature.[63] We categorized this variable into three groups: before 1980, the 1980s, and after 1989.

3.2.2 Measurement of care coordination

Number of breast-cancer-related follow-up visits: Most measurements of care coordination (88%) rely on survey instruments, and very few use administrative data.[164] Therefore, we attempted to create a measure that would capture the major components of care coordination among breast cancer survivors, including surveillance and prevention of recurrence, treatment-related long-term adverse effects, and overall

health.[165] We calculated the number of breast-cancer-related follow-up visits after the primary treatment until death or until the end of our observation (detailed codes are presented in Table 3.2), according to the breast cancer follow-up care recommendations from the ASCO.[55]

Timeliness of primary treatment initiation after the diagnosis: The timeliness with which a patient receives care may be affected by factors at the patient-, provider-, and healthcare system-levels[166]; timeliness may also be regarded as an indicator of quality of care and care coordination.[144] We calculated the number of days between the diagnosis of breast cancer and the initiation of surgery. Since a gap of more than 60 days is associated with worse survival outcomes,[166] we dichotomized the variable to timely primary treatment and delayed primary treatment using 60 days as the cut-off point.

3.2.3 Measurement of provider's decision making and behaviors

Two main measurements were chosen: 1) **type of breast cancer treatment received: surgery type** (breast-conserving surgery or mastectomy), **radiation therapy** (yes/no), and **chemotherapy** (yes/no); 2) if patients received AET, **the type of AET used** (tamoxifen, anastrozole, letrozole, and exemestane). We identified AET use using NDC codes and then classified patients into three groups: tamoxifen only, aromatase inhibitor (AI) only, and switching between tamoxifen and AI. Table 3.3 shows the specific procedure or drug codes used to identify breast cancer treatments.

3.2.4 Measurement of medication-related factors

The following medication-related factors were included: 1) **the number of unique prescription drugs co-administered** during the follow-up period, as a proxy measure of pill burden, was identified using NDC from the Medicare Part D claims data; 2) **the season at the initiation of AET (**spring, summer, fall, winter) was also included in analyses because the seasonal weather condition may have influences on travel and transportation, which in turn may affect patient behaviors of picking up their drugs. And the seasonal effects may be more phenomenal in a largely rural and mountainous environment such as Appalachia; 3) **AET associated side effects.** We utilized proxy measures for AET-associated side effects (e.g., osteoporosis, hot flashes/night sweats, arthralgia) using the indicators of the use of evidence-based pharmacological treatments (prescription drugs) for them. Dummy variables included whether or not patients used antidepressants (fluoxetine, paroxetine, venlafaxine, citalopram, gabapentin), bisphosphonates (zoledronic acid, alendronate, risedronate), and pain medications (opioids, gabapentin, pregabalin) during the follow-up period.

3.3 Aim 1: *Assess the relationship between access to cancer resources and the receipt of guideline-appropriate adjuvant endocrine therapy.*

3.3.1 Outcome measures

3.3.1.1 The receipt of guideline-recommended AET

To determine what constitutes guideline-recommended AET use, we referred to the NCCN and ASCO quality measures for breast cancer.[167] Therefore, we defined the

receipt of guideline-appropriate AET as whether AET was prescribed to eligible female breast cancer survivors with positive hormone receptors within one year of diagnosis.

3.3.2 Statistical analysis

We conducted descriptive analyses of access-related factors, type of breast cancer treatment, and the receipt of guideline-recommended AET. We reported the means of continuous variables and frequencies and percentages of binary and categorical variables. We also presented the percentage of patients who received guideline-appropriate AET, and of those patients, the respective percentages of patients who received tamoxifen, who received AI, and who switched between tamoxifen and AI. The logistic regression was utilized to assess the relationship between access to cancer care and the receipt of guideline-appropriate AET, and type of other breast cancer treatments were controlled. We utilized a robust standard error and tested the significance of the categorical variables in the model using the Wald test. The Hosmer-Lemeshow goodness-of-fit test, multicollinearity, c-statistic, linear predicted value and linear predicted value squared (the “linktest” command in Stata) were checked. Likelihood ratio tests and Akaike's information criterion (AIC) and Bayesian information criterion (BIC) were used for model selection.

3.3.3 Sensitivity analysis

Furthermore, to account for the potential random effects of clustered county- and state-level factors, we re-estimated the model above using the multilevel mixed effect logistic regression.

3.4 Aim 2: *Examine the associations between access to cancer care resources and adjuvant endocrine therapy (AET) adherence and persistence, as well as the effects of AET use outcomes on survival.*

3.4.1 Outcome Measures

3.4.1.1 Adherence

We calculated AET adherence for each individual using the Medication Possession Ratio (MPR). The MPR is a commonly used medication adherence measure using administrative claims data that has been adopted in a great deal of AET adherence research.[22,23] It is defined as the ratio of the amount of days for which the drug was dispensed divided by the number of days for which drug was needed,[168,169] which was determined in this study using the following equation[170,171]:

Medication possession ratio (MPR) = number of days' supply / (number of follow-up days ─ number of inpatient days)

Additionally, the MPR was truncated between 0 and 1.2, as well as dichotomized into adherence and non-adherence using the conventional cut-off point of 0.8 ($0 \leq MPR < 0.8$: non-adherence; $0.8 \leq MPR \leq 1.2$: adherence). For those who switched between tamoxifen and AI, we precluded any double-counting of the days when the patient took both tamoxifen and AI. The non-adherence rate refers to the percentage of patients who were not adherent.

3.4.1.2 Persistence

Medication persistence is defined as the act of complying with a provider's recommendations to use medications for a prescribed length of time.[130] It is also commonly operationalized in retrospective claims data studies as the discontinuation of drugs after exceeding a permissible gap.[130] In AET persistence research, the prescription fill gap has been defined as ranging from 45 to 180 days, based on the pharmacological characteristics of the drugs; legitimate delays in refills, such as hospitalization; and the length of follow-up period.[27,122,123,125,131–133] Taking all of the above into consideration, we decided to define AHT non-persistence as a minimum 60-day medication fill gap. Patients who switched drugs within 60 days were still considered persistent. The non-persistence rate (also referred to as early discontinuation rate) refers to the percentage of patients who were not persistent.

3.4.1.3 Survival

Overall survival was defined as the period from AET initiation until death. The follow-up period ended on December 31, 2008.

3.4.2 Statistical analysis

We conducted descriptive analyses of the access variables, medication-related factors, type of breast cancer treatment, and follow-up days using means for continuous variables and frequencies and percentages for binary and categorical variables. We assessed MPRs, adherence rates, and discontinuation rates among the three AET groups. We used the 2×2 contingency table and phi coefficient to assess the correlation

between AET adherence and persistence. Preliminary bivariate association analyses were conducted to find potential predictors of adherence, persistence, and survival. We conducted two-tailed t-tests for continuous predictors of adherence and chi-square tests for binary and categorical predictors of adherence. We used Kaplan-Meier survival curves and log-rank tests to assess the associations between each binary/categorical variable and persistence or survival time, as well as univariate Cox regression analyses to evaluate the relationships between each continuous variable and persistence or survival time. In particular, we utilized Kaplan-Meier survival curves and log-rank tests to assess the bivariate associations between AET adherence/persistence and overall survival.

3.4.2.1 Adherence

We conducted multivariate logistic regression to assess the relationship between access to cancer care and AET adherence. Other potential covariates included medication-related factors, type of breast cancer treatment, and follow-up days. We incorporated potentially significant predictors with a *p* value less than 0.25 in the bivariate association analyses into the final multivariate logistic regression model with a robust standard error. For the final logistic model of adherence, we also tested the significance of the categorical variables and checked the goodness-of-fit, multicollinearity, c-statistic, linear predicted value and linear predicted value squared (the “linktest” command in Stata). We also tested the potential random effects of clustered county- and state-level factors.

3.4.2.2 Persistence

We obtained multivariate-adjusted estimates of persistence time using the Cox proportional hazards (PH) model. We included in the final model only those predictors for which $p < 0.25$ in the bivariate association analyses. We checked the proportional hazard assumption of the variables in the final model. If a variable did not meet the assumption, we estimated a stratified model based on the variable.[121]

3.4.2.3 All-cause mortality

We conducted survival analyses to test the working hypothesis that, among breast cancer patients who received guideline-recommended adjuvant treatment, those who were adherent to and persistent with their adjuvant treatments had a lower risk of death. We plotted the Kaplan-Meier curves for overall survival to compare patients who were adherent to/persistent with AET with those who were not, and we used the log-rank test to compare these Kaplan-Meier curves. To allow for the multivariate comparison of these survival measures, we utilized the Cox PH regression model. In the models, we also adjusted the potential predictors with a *p*-value less than 2.5 in the bivariate association analyses. We checked the proportional hazard assumptions and goodness-of-fit.

3.4.3 Sensitivity analysis

Sensitivity analyses were conducted to reduce the potential errors or uncertainty caused by the definitions of adherence and persistence, as well as to achieve a better understanding of the relationships. AET adherence and persistence were redefined

using MPR cutoff points ranging from 0.6 to 0.9 and a 90-day medication fill gap, respectively.

For both study aims, the statistical significance level was set to $p < 0.05$. We utilized R 3.0.2 for general data management, ArcGIS 10.1 for geo-related data management, and Stata 13 for analyses.

Table 3.1 The ICD-9 codes and scores used in the calculation of the Charlson Comorbidity Index

Condition	Score	ICD-9 code
Myocardial Infarction	1	'410','412'
Congestive Heart Failure	1	'39891','40201','40211','40291','40401','40403','40411','40413','40491','40493', '4254','4255','4257','4258','4259','428'
Peripheral Vascular Disease	1	'0930','4373','440','441','4431','4432','4438','4439','4471','5571','5579','V434'
Cerebrovascular Disease	1	'36234','430','431','432','433','434','435','436','437','438'
Dementia	1	'290','2941','3312'
Chronic Pulmonary Disease	1	'4168','4169','490','491','492','493','494','495','496','500','501','502','503', '504','505','5064','5081','5088'
Connective Tissue Disease	1	'4465','7100','7101','7102','7103','7104','7140','7141','7142','7148','725'
Ulcer Disease	1	'531','532','533','534'
Mild Liver Disease	1	'07022','07023','07032','07033','07044','07054','0706','0709','570','571','5733','5734','5738','5739','V427'
Diabetes without complications	1	'2500','2501','2502','2503','2508','2509'
Hemiplegia or Paraplegia	2	'3341','342','343','3440','3441','3442','3443','3444','3445','3446','3449'
Moderate to Severe Renal Disease	2	'40301','40311','40391','40402','40403','40412','40413','40492','40493','582', '5830','5831','5832','5834','5836','5837','585','586','5880','V420','V451','V56'
Diabetes with End Organ Damage	2	'2504','2505','2506','2507'
Any Tumor	2	'140','141','142','143','144','145','146','147','148','149','150','151','152','153', '154','155','156','157','158','159','160','161','162','163','164','165','170','171','172','175','176','179','180','181','182','183','184','185','186','187','188', '189','190','191','192','193','194','195','200','201','202','203','204','205','206','207','208','2386'
Moderate to Severe Liver Disease	3	'4560','4561','4562','5722','5723','5724','5728'
Metastatic Solid Tumor	6	'196','197','198','199'
AIDS	6	'042','043','044'

Note: the disease of interest ─ female breast cancer diagnosis ─ was removed in “any tumor”

Table 3.2 Codes used for calculating the number of breast-cancer-related follow-up visits

	ICD-9-CM code (diagnosis)	ICD-9-CM code (procedure)	HCPCS/CPT code
General medical examination	174.0-174.9, V10.3	V70.0-V70.2, V72.62	99395, 99396, 99397, 99385, 99386, 99387
General counselling or preventive medicine counseling and/or risk factor reduction intervention(s)	174.0-174.9, V10.3	V65.3, V65.40, V65.41, V65.49	99201, 99202, 99203, 99204, 99205, 99212, 99213, 99214, 99215, 99241,99242,99243,99244,99245, 99341, 99342, 99343, 99344, 99345, 99347, 99348, 99349, 99350,99401,99402, 99403, 99404, 99411, 99412
Clinical breast cancer examination, mammography	174.0-174.9, V10.3	V76.11, V76.19	S0613, 77055, 77056, 77057, G0202,G0204, G0206, 77051(used with 77055 or 77056), 77052 (used with 77057 or G0202)
Pelvic examination	174.0-174.9, V10.3	V72.31, V76.2	57410, G0101
Genetic counseling	174.0-174.9, V10.3	V26.31, V26.32, V82.71, V82.79	

Table 3.3 List of procedure and drug codes used to identify breast cancer treatments

	ICD-9	CPT/HCPCS	SSC *
Surgery			
Breast conserving surgery	85.20-85.23,85.25	19120,19125,19126,19160,19162,19301,19302	10-29
Mastectomy	85.33-85.36,85.41-85.48	19220,19180,19182,19200,19240,19303,19304,19305,19306,19307,19340,19342	30-80
Radiation	V58.0, V66.1, V67.1, 92.20-92.29	77401-77418, G0174,G0178,G0179, 77520-77525, 77750-77790	
Chemotherapy	V58.1x, V66.2, V67.2, 99.25	95990, 95991, 96400 - 17, 96420,96440,96450,96520,96530, 96545, 96549, C9205, C9259, C9280,C9415, C9420, C9421,G0355,G0357, G0358,G0359, G0360, G0361,G0362,G0363, J0460, J0640, J1051, J2405, J8520,J8521,J8530,J8600, J8610,J8705,J8999, J9000, J9001, J9010,J9015,J9020, J9031,J9035,J9040,J9041,J9045, J9050, J9055, J9060,J9062,J9065,J9070, J9080,J9090,J9091,J9092, J9093, J9094, J9095,J9096,J9097, J9100,J9110,J9120,J9130,J9140, J9150, J9160, J9165,J9170,J9178, J9180,J9181,J9182,J9185,J9190, J9200, J9201, J9206,J9208,J9209,J9211,J9212,J9213,J9214,J9216, J9225, J9230, J9245,J9250,J9260, J9263,J9264,J9265,J9266,J9268, J9270, J9280, J9290,J9291,J9293, J9305,J9310,J9320,J9340,J9350, J9360, J9370, J9375,J9380,J9390, J9999, K0415,K0416, Q0083, Q0084, Q0085, Q2043,S0177,S0178,S0181, X7052, X7624, X7632, X7642, X7647, X7648	
NDC for endocrine therapy**			
Tamoxifen	605053035, 605053036, 636294413, 550452703, 637390269, 003780144, 003780274, 548683004, 548684287, 000930782, 000930784, 005912232, 005912233, 005912472, 005912473, 000544831, 000544834, 000548831, 000548834, 001725656, 001725657, 003100600, 003100604, 003100730, 003100731, 005550446, 005550904, 387790341, 515520838, 519272976, 545693765, 545695716, 545695857, 629911151, 633040600, 633040601, 661050832, 001791952, 003100446, 005550446, 005550904, 548683004, 548684287, 558870872, 662670873, 004800782, 530021032, 551600149, 551600150, 004800784, 260530044, 485816221, 485816222, 620370964, 625405656, 625405657, 511292622, 511294218, 511294662, 595640144, 001791299, 125810600, 511291952, 625840600, 637390269		
Aromatase inhibitors (AIs)	000097663, 000780249, 003100201, 122800346, 499990986, 545695714, 545695731, 548684151, 548685000, 548685261, 477810108, 000540080, 000095206, 597622858, 108297663, 001791657, 170881004, 422910373, 633230772, 000540269, 000937620, 003782071, 006034180, 167290034, 247240030, 519910759, 605053255, 683820363, 004807620, 422540243, 548686252, 551110646, 578842021, 621750888, 627560511, 658410744, 680840803, 001791889, 511291122, 353560270, 007815356, 422910105, 430630383, 510790323, 631870080, 633230129, 000540164, 000937536, 001151261, 003786034, 009046195, 009046229, 165710421, 167290035, 519910620, 636295269, 658410743, 680840448, 260530006, 604290286, 420430180, 602580866, 605052985, 636720015, 663360533, 664350415, 678770171, 680010155, 683820209, 001790068, 216950990, 422540161, 548686130, 551110647, 621750710, 627560250		

***codes used in cancer registries

** First 9-digit NDC

CHAPTER 4

DISSERTATION MANUSCRIPT ONE

ACCESS TO CANCER CARE AND ADJUVANT TREATMENT UTILIZATION AMONG BREAST CANCER SURVIVORS IN APPALACHIA

Abstract

Background: The Appalachia region of the U.S. experiences excess cancer mortality and a lack of access to cancer care resources. Current research on the reasons for breast cancer disparities in Appalachia mainly focuses on breast cancer prevention, screening, and primary treatment and does not include adjuvant treatment use disparities. This study aimed to investigate the utilization of adjuvant endocrine therapy (AET) among Appalachian female breast cancer survivors and to evaluate systemically the relationship between access to cancer care and AET use in this underserved region.

Methods: This was a retrospective cohort study from January 1, 2006 to December 31, 2008 of female breast cancer survivors who resided in the Appalachian counties of four states (PA, OH, KY, and NC). We analyzed a linked dataset from cancer registries, Medicare claims, and the U.S. census, as well as healthcare provider and facility information. We included Medicaid-enrolled adult women diagnosed with invasive, non-metastatic, hormone-receptor-positive breast cancer. The multivariate logistic regression was used to assess the relationship between access to cancer care and the receipt of guideline-appropriate AET.

Results: Only 450 of the 946 eligible patients (47.6%) received guideline-recommended AET; for these patients, the most commonly prescribed AET was aromatase inhibitors (74.7%), followed by tamoxifen (18.9%). 6.4% switched between these two drug classes. Logistic regression results revealed that the receipt of guideline-concordant AET was associated with shorter travel time to receive care, dual Medicare and Medicaid eligibility, being unmarried (vs. married), and living in Pennsylvania (vs. Ohio).

Conclusions: Geographic and socioeconomic factors such as travel time to receive care and healthcare plan type are important elements that could contribute to breast cancer treatment disparities in Appalachia. The findings may add to evidence for developing targeted intervention strategies to reduce cancer disparities in Appalachia.

Introduction

The Appalachian region of the United States (U.S.) is characterized by a largely rural environment, high poverty rates, poor access to adequate cancer care, and demographical homogeneity. Forty-two percent of the region's population is rural,[2] 83.9% is white,[1] 25.7% live in a high poverty area,[3] and 16.5% have less than a high school education.[1] All of these figures are higher than the respective national averages.

The National Cancer Institute (NCI) classifies the Appalachian population as a special population of interest due to the significant cancer outcome disparities for most common cancers .[4–6] Among Appalachian women, breast cancer is the most commonly diagnosed cancer and has the second highest mortality rate following lung and bronchus cancer.[7] In general, breast cancer mortality in the thirteen Appalachian states was about 7% higher than in the other thirty-seven states ($p < 0.05$).[106] Additionally, breast cancer mortality has declined in recent decades nationwide, but the breast cancer mortality decline in Appalachia has been only about half that of the non-Appalachian regions.[11] This significant disparity may be partly explained by the higher prevalence among Appalachian women of modifiable risk factors associated with breast cancer including inadequate fruit and vegetable consumption, lack of physical activity, and obesity,[7,8] as well as by the lower rates of receipt of guideline-recommended prevention (e.g., mammogram in women over 40[8,9]) and primary treatment (e.g., guideline-appropriate adjuvant radiation therapy after breast conserving surgery [BCS][10]). So far, however, research into the reasons for breast cancer outcome disparities in Appalachia has mainly concentrated on breast cancer prevention and screening, as well as primary cancer treatment, and not on adjuvant treatment use.

Among the factors that are likely contributing to cancer disparities in Appalachia, lack of access to adequate effective cancer care is critical. Rural residence, geographic isolation, lack of public transportation, underdeveloped telecommunication infrastructure, high poverty and unemployment rates, inadequate medical resources, a shortage of healthcare professionals, lower levels of educational attainment, and attitudinal and cultural factors in Appalachia may all result in poor access to care.[9,12–14]

Despite the substantial cancer disparities and the NCI's particular interest in Appalachia, there have been relatively few studies of cancer issues in this region, primarily for lack of data and of a well-represented study sample. Kimmick et al (2014),[63] a recently published article with a particular focus on Appalachian breast cancer patients, linked Medicare claims data with four Appalachian states' cancer registries to examine the treatment guideline concordance among women diagnosed with stage I-III breast cancer. The present study utilized the same dataset to further investigate the utilization of adjuvant endocrine therapy (AET) among female breast cancer survivors in this underserved region. In particular, the relationship between access to cancer care and AET use was evaluated systemically based on an integrated conceptual model.

Methods

1. Study design and data source

This was a retrospective cohort study from January 1, 2006 to December 31, 2008 of female breast cancer survivors who resided in the Appalachian counties of four states (PA, OH, KY, and NC), as defined by the Appalachian Region Commission (ARC).

Eligible patients had a primary breast cancer diagnosis with a positive histology, cytology, or microscopic confirmation in 2007. The study design comprised a baseline period that began one year before the diagnosis date, and patients were followed up with from the diagnosis date until death or until the end of the observation (12/31/2008). Two main datasets, Medicare claims data and cancer registries, were linked using patient identifiers including name, social security number, gender, and birthdate, a method validated in previous studies.[5,63] System-level characteristics were acquired using county names or codes from ARC data reports, the 2010 U.S. census, the Area Resource File, the National Center for Health Statistics (NCHS), the Centers for Disease Control and Prevention (CDC), and the NCI. Provider/facility characteristics were mainly identified using the Unique Physician Identification Numbers (UPIN) and National Provider Identifiers (NPI) from the Medicare Provider of Service files and the Medicare Physician Identification and Eligibility Records files.

Completely de-identified data were used for final analyses. The study was approved by the University of Michigan's Institutional Review Board (IRB), and data use was approved by the Centers for Medicare and Medicaid services (CMS) and each state's cancer registry.

2. Study population

The study sample was obtained based on a series of inclusion and exclusion criteria specified in Figure 4.1. Among the 17,074 adult women in the Appalachian counties who were diagnosed with primary breast cancer in the four states' cancer registries, we included those who were diagnosed with confirmed stage I-III, hormonal receptor (HR)

positive, primary breast cancer in 2007. Eligible patients were continuously enrolled in Medicare Parts A and B during the study time and in Part D from the time of the first breast cancer diagnosis. We excluded those who were enrolled in a Health Maintenance Organization (HMO) or Medicare Advantage Program due to the lack of claims data. Our study subjects were those who survived the primary breast cancer treatment (surgery) and were eligible for AET, but did not have AET before. Lastly, we verified the data and excluded cases with mismatching information across data sources.

3. Outcome measures

The National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology's (ASCO)'s recommendations and method[167] were used to determine what constitutes guideline-recommended AET use. Therefore, we defined the receipt of guideline-appropriate AET as whether AET was prescribed to eligible female breast cancer survivors with positive-HR status within one year of biopsy-confirmed diagnosis.

4. Covariate measures

We adapted the constructs from Andersen's behavioral model for health service use[142,143] as the theoretical background and integrated the findings of empirical work regarding AET medication use to guide this study. As per Andersen's model, the presence of characteristics or resources that enable patients to seek medical care can be classified into three categories: predisposing factors that are pre-existing characteristics of patients to predict the probabilities of using medical services or products, enabling factors that refer to the ways available to patients to use the services

or products, and need factors that generally indicate the severity of the disease and overall health status.[143] These can be assessed at both the system level and the individual patient level. These characteristics may impact patients' actual utilization of medical care. Realized access is often operationalized by assessing the features of healthcare providers or facilities and quality of care, such as care coordination. Taken together, these individual and provider characteristics may influence providers' decision-making and prescribing behaviors, and it is the combination of all of these factors that affects patient medication use pattern, which, subsequently, may also influence cancer health outcomes.

4.1 Measurement of access to care

4.1.1 Potential access

System level characteristics (at the county level): 1) The counties' socioeconomic status was measured using the Appalachian Regional Commission's 2013 county economic status classification system,[153] an index calculated based on the average unemployment rate (2008-2010), the per capita market income (2009), and the average poverty rate (2006-2010) of each Appalachian county. The index was utilized to sort counties into three groups: economically distressed, at risk, and others[5]; 2) The county-level educational attainment was assessed using ARC data reports and recorded the percentage of residents aged 25 and over with less than a high school diploma and the percentage with at least a bachelor's degree (2007-2011)[153]; 3) The urban–rural geographic residence was determined using the 2013 NCHS Urban–Rural Classification Scheme for Counties. The counties were classified as either part of a metropolitan area

or not[154]; 4) Community health risks were operationalized as infant and cancer mortality rates. We extracted the 2007 infant mortality rates (deaths per 1,000 births) at the county level from the linked birth/infant death records (2007-2010) produced by the CDC and the NCHS.[155] We identified the average annual age-adjusted, cancer-related death rates (deaths per 100,000 people, 2007-2011) from the United States Cancer Statistics data provided by the CDC and the NCI [156]; 5) Health Professional Shortage Area (HPSA) designations were drawn from the 2007–2009 Area Resources File at the county level. Each Appalachian county was categorized as being partially within a HPSA, entirely within a HPSA, or not within a HPSA.[5]

Individual level characteristics: 1) Predisposing factors: demographic information was extracted, such as age at diagnosis, race, marital status, and state of residence at diagnosis from the state cancer registries; 2) Enabling factors: the 2007-2011 average estimates of annual median household income were extracted from the American Community Survey data[157] using census block group codes, and a categorical variable of the four quartiles of median household income was created. In addition, we created a dual Medicaid and Medicare eligibility indicator to evaluate the effect of different healthcare benefits on patient access to AET. The estimated average travel time (in minutes) from the patient to the three closest mammography centers was also calculated. Travel time to mammography centers is one of the currently available validated measures of spatial access to care, which has been shown to relate to late-stage diagnoses of breast cancer.[158] We geocoded the addresses of patients and mammography centers and calculated travel network distances from each patient to each mammography center. The shortest travel network path between the patient and

mammography center was determined as the distance to the nearest mammography center; 3) Need factors: we obtained cancer-related information including breast cancer stage (I, II, III), tumor size (<1 cm, 1–2 cm, >2 cm, unknown), and lymph nodal status (negative or positive) from the cancer registries. Patients' comorbidities and overall health statuses were assessed using the number of hospitalizations over the baseline period and the Charlson Comorbidity Index (CCI). The CCI is a composite score used to predict mortality; a higher score represents more comorbidities or more severe comorbidities. Specifically, we utilized the Deyo CCI, which contains 17 condition diagnoses based on the ICD-9-CM codes,[162] but we excluded the primary diagnosis of interest in this study—female breast cancer.

4.1.2 Realized access

Facility characteristics: 1) The American College of Surgeons ─ Commission on Cancer (CoC) provides accreditation for facilities to ensure high quality of cancer care.[163] We created a variable using the categories of CoC-accredited, not accredited, and unknown; and 2) We acquired information on number of beds (<100 beds, 100-200 beds, >200 beds, or unknown), facility type, and ownership (for-profit, government, not-for-profit, unknown) from the CMS 2007 Medicare Provider of Service files.

Provider characteristics: 1) Specialty: Specialties were obtained using NPI and UPIN from Medicare claims data. Each healthcare provider was identified as an oncologist, a general practitioner, or others; 2) Graduation year: The provider's graduation year was used as a proxy for years of practice experience and may be associated with patients'

receipt of guideline recommended AET.[63] We categorized this variable into three groups: before 1980, the 1980s, and after 1989.

Care coordination: 1) We calculated **the number of breast-cancer-related follow-up visits** between primary treatment and death or the end of the observation period using the ASCO's recommended follow-up care guidelines for patients with breast cancer[55]; 2) We measured **timeliness of primary treatment initiation** using the number of days between diagnosis and the initiation of surgery. Because a gap of more than 60 days is associated with worse survival outcomes,[166] the variable was dichotomized to timely or delayed primary treatment using a cut-off point of 60 days.

4.1.3 Provider's decision making and behaviors

Two main measurements were chosen: 1) type of breast cancer treatment received: surgery type (BCS or mastectomy), radiation therapy (yes/no), and chemotherapy (yes/no); 2) if patients received guideline-recommended AET, we identified the type of AET used (tamoxifen and aromatase inhibitors [AIs] including anastrozole, letrozole, and exemestanes) using NDC codes.

5. Statistical analyses

We conducted descriptive analyses of access-related factors, type of breast cancer treatment, and the receipt of guideline-recommended AET. We reported the means of continuous variables, and the frequencies and percentages of binary and categorical variables. We also presented the percentage of patients who received guideline-

appropriate AET, and of those patients, the respective percentages of patients who received tamoxifen, who received AI, and who switched between tamoxifen and AI. The logistic regression model was utilized to assess the relationship between access to cancer care and the receipt of guideline-appropriate AET, and type of other breast cancer treatments were controlled. We utilized a robust standard error and tested the significance of the categorical variables in the model using the Wald test. The Hosmer-Lemeshow goodness-of-fit test, multicollinearity, c-statistic, linear predicted value and linear predicted value squared (the "linktest" command in Stata) were checked. We tested the interactions between the state of residence and county economic status, as well as the state of residence and HPSA designation. Likelihood ratio tests and Akaike's information criterion (AIC) and Bayesian information criterion (BIC) were used for model selection. Furthermore, to account for the potential random effects of clustered county- and state- level factors, the final model was re-estimated using the multilevel mixed effect logistic regression. The level of significance was set at $p < 0.05$ a priori. We utilized R 3.0.2 for general data management, ArcGIS 10.1 for geo-related data management, and Stata 13 for analyses.

Results

Our study included a total of 946 Medicare-enrolled adult women with invasive, non-metastatic breast cancer who lived in the 148 Appalachian counties of four states (KY, NC, OH, and PA). Table 4.1 and Table 4.2 show the descriptive statistics for county-, individual-, and facility/provider-level characteristics. Nearly half of the counties (45.3%) were economically distressed or at risk, and all of the economically competitive counties

were in Pennsylvania. Most counties were designated as non-metropolitan areas (68.2%), and only 22 of the 148 counties (14.9%) were not classified as health professional shortage areas (HPSA). In addition, these counties are disadvantaged compared to the national averages in terms of the percentage of the population aged 25 and over with less than a high school diploma (18.9% vs. 14.6%), the percentage of the population aged 25 and over with at least a bachelor's degree (15.7% vs. 28.2%), the infant mortality rate (7.2 vs. 6.8, measured as deaths per 1000 births), and the cancer mortality rate (197.5 vs. 175.1, measured as deaths per 100,000 residents).

We followed the study population for a period of 18 months, on average. The study population had a mean age of 75 years old, and almost all of the women were white (97%), underscoring the racial homogeneity of this region. Approximately 41.6% of patients were married; 18.4% were eligible for both Medicare and Medicaid. The average travel time to the closest three mammography centers was 16 minutes. The majority of patients were diagnosed with stage I or II breast cancer (90%) and with negative lymph nodes (72.9%). About two-thirds of patients were treated in CoC-accredited cancer programs (65.7%) and in large facilities with over 200 beds (64.6%). In addition, most patients sought breast-cancer-related follow-up care from general practitioners (60.6%); the mean number of breast-cancer-related follow-up visits was 2.16. In terms of breast cancer treatment, most received BCS (63.2%) vs. a mastectomy (36.8%); 63% did not receive radiation; half received chemotherapy (50.4%). Only 450 patients of the 946 final study subjects (47.6%) received guideline-recommended AET. Among those who received guideline-recommended AET, the most

commonly prescribed AET was an AI (74.7%), followed by tamoxifen (18.9%); only 6.4% of patients switched between these two drug classes.

Table 4.3 presents the results of multivariate logistic regression analysis of the receipt of guideline-recommended AET. We did not include race, facility ownership, or facility beds variables in the final model because of extreme small cell or multicollinearity issues. We found that geographic and enabling factors had important effects on access to guideline-concordant AET in Appalachia. Married women were less likely to receive guideline-recommended AET (*OR* = 0.63, *p* = 0.003). Breast cancer patients with dual Medicaid and Medicare eligibility had about four times greater odds of receiving guideline-recommended AET compared to those who with Medicare only (*OR* = 4.24, *p* < 0.001). Breast cancer patients with longer travel time to receive care were less likely to receive guideline-recommended AET (*OR* = 0.98, *p* = 0.02). Moreover, Ohio residents were less likely to receive guideline-recommended AET than Pennsylvania residents (*OR* = 0.60, *p* = 0.02). In addition, the interactions between the state of residence and county economic status as well as between the state of residence and HPSA designations were tested. But adding these interaction terms did not significantly improve our model based on the results of likelihood ratio tests, AIC and BIC, so we retained the model without interactions. In addition, the model was also re-estimated using multilevel mixed effect logistic regression with county- and state-level random effects. But the likelihood ratio tests showed no significant results, indicating no preference over regular logistic regression. Therefore, we chose the regular multivariate logistic regression as our final model.

Discussion

The lack of strong evidence regarding the relative importance of the multidimensional factors associated with access to quality care and standard treatment may limit our knowledge and ability to develop targeted interventions to reduce cancer disparities in Appalachia. Therefore, this study investigated AET utilization and associated multilevel access factors among Appalachian breast cancer survivors. To systemically evaluate access-to-care issues in Appalachia, we constructed a linked database by integrating various data sources under the guidance of a conceptual framework.

This study showed a low prevalence rate (47.6%) of guideline-recommended AET use among Appalachian breast cancer survivors compared to the average national rate (74%) for Medicare enrollees with Part D benefits according to the Surveillance, Epidemiology, and End Results (SEER) and Medicare data.[116] The difference may be due to undertreatment in our population, or it may be attributable to our study design: we included only new users who used endocrine therapy for adjuvant treatment purposes, not as chemoprevention or neoadjuvant therapy or for metastatic cases. Another study of new AET users enrolled in a commercial health plan in Massachusetts also found relatively low guideline-recommended AET use (58%).[117] Our results also showed more AI use than tamoxifen use in our population, which may have several explanations: 1) we had an older sample, so most women may have been postmenopausal at diagnosis. For these patients, AIs are the first-place adjuvant treatment as per clinical recommendations; 2) More and more evidence has emerged to support AI use since the start of the new century, and there seems to have been an increasing trend toward AI use around the late 2000s[116]; 3) Oncologists appear to prefer

prescribing AIs rather than tamoxifen to elderly women because of their efficacy and tolerability.[172] In addition, if we had a longer follow-up time, we might have seen more switching between drug classes.

The study findings corroborate the deficiencies in access to care in Appalachia. Our results suggested that the longer patients spent traveling to receive cancer care, the less likely they were to receive guideline-recommended adjuvant treatment. Previous research reached similar conclusions regarding the transportation barriers to receiving guideline-recommended breast cancer prevention care and primary treatment in Appalachia. Wheeler et al (2014), a study in North Carolina, found that urban/rural residence and travel distance to the radiation center could predict whether patients received radiation therapy.[110] A patient self-reported study in West Virginia found that having health insurance and being able to access medical care without delays due to transportation problems were significantly associated with better adherence to mammography screening guidelines.[107] Likewise, another qualitative study of Appalachian women's perspectives on breast cancer screening produced similar findings.[108]

Therefore, our findings further underscore the importance of reducing transportation barriers and improving geographic access to care among Appalachian breast cancer patients so as to reduce adjuvant treatment disparities. Moreover, nearly half of our study counties were economically distressed or at risk, and there were socioeconomic variations across states. Pennsylvania had the fewest economically distressed Appalachian counties and had no whole Appalachian county that was located in a HPSA, which may partly explain the higher likelihood of receiving guideline-

recommended AET in Pennsylvania. Kimmick et al (2014) also found that female breast cancer patients living in Pennsylvania were more likely to receive guideline-recommended endocrine therapy, chemotherapy, and radiation therapy than residents in North Carolina.[63] The treatment disparities across states may correlate to multiple factors including geographic environment, healthcare system, and state health policy, the investigation of which warrants further research efforts.[63] We did not find significant relationships between area-level SES or health professional shortage and receipt of guideline-recommended AET.

In addition to geographic, area-specific predictors, the receipt of guideline-recommended AET among Appalachian breast cancer survivors seem also to be related to individual SES factors such as type of healthcare plan benefits. We found that dually eligible beneficiaries were much more likely to receive guideline-recommended AET compared to their non-dual counterparts. Although dually eligible beneficiaries are generally more vulnerable in health, with more chronic and severe health conditions, and more economically distressed,[114] they are entitled to several additional health benefits such as automatic enrollment in Part D drug plans and no monthly premium or deductibles. Many states' Medicaid programs also help with copayments or out-of-pocket costs for the drugs that are not included in the Medicare Part D formulary. In addition, during the transition to Part D, many states developed contingency plans to help dually eligible beneficiaries retain drug coverage through Medicaid before they could access Part D drug benefits.[113] These differences in health benefits may mitigate patients' financial burden and difficulties with access to medications and drug utilization.

Our findings should be considered in the context of several limitations. First, because of the nature of our study design, we could not establish causal inference but could only show associations. Second, our study's duration and sample size limited our ability to determine differences in direct outcomes such as survival and breast cancer recurrence: survival differences resulting from AET use can usually be identified at 5-10 years [15,123]; at least 27 outcome events in each treatment arm are required.[173] Third, given the limited data availability and accessibility, our study lacked other detailed information such as individual-level educational attainment and household income, treatment facility location, prescriber information, accurate indications for the prescribed drugs, and data from the West Virginia residents. Although we attempted to use proxy measures to ascertain this information, it would be better if direct measures could be used. Lastly, the generalization of our results may be limited to initial oral AET use among elderly Appalachian women with invasive, non-metastatic, HR-positive breast cancer. We did not include those who used endocrine therapy as a primary treatment (no surgery) or who used ovarian suppression. Our population was also generally older than the typical breast cancer patient population; therefore, caution should be used when generalizing the results to other populations.

Conclusion

Despite these limitations, this study is among the first to examine the important question of how access to cancer care resources impacts AET utilization among Appalachian women with breast cancer. We found that geographic and socioeconomic factors such as travel time to receive care and type of healthcare plan contributed significantly to

breast cancer treatment disparities in Appalachia. The approach we established in this study may not only provide insights into cancer disparities in Appalachia but also have implications for investigating access-to-care disparities in other comparable underserved regions.

Figure 4.1 Flowchart of obtaining the final study sample

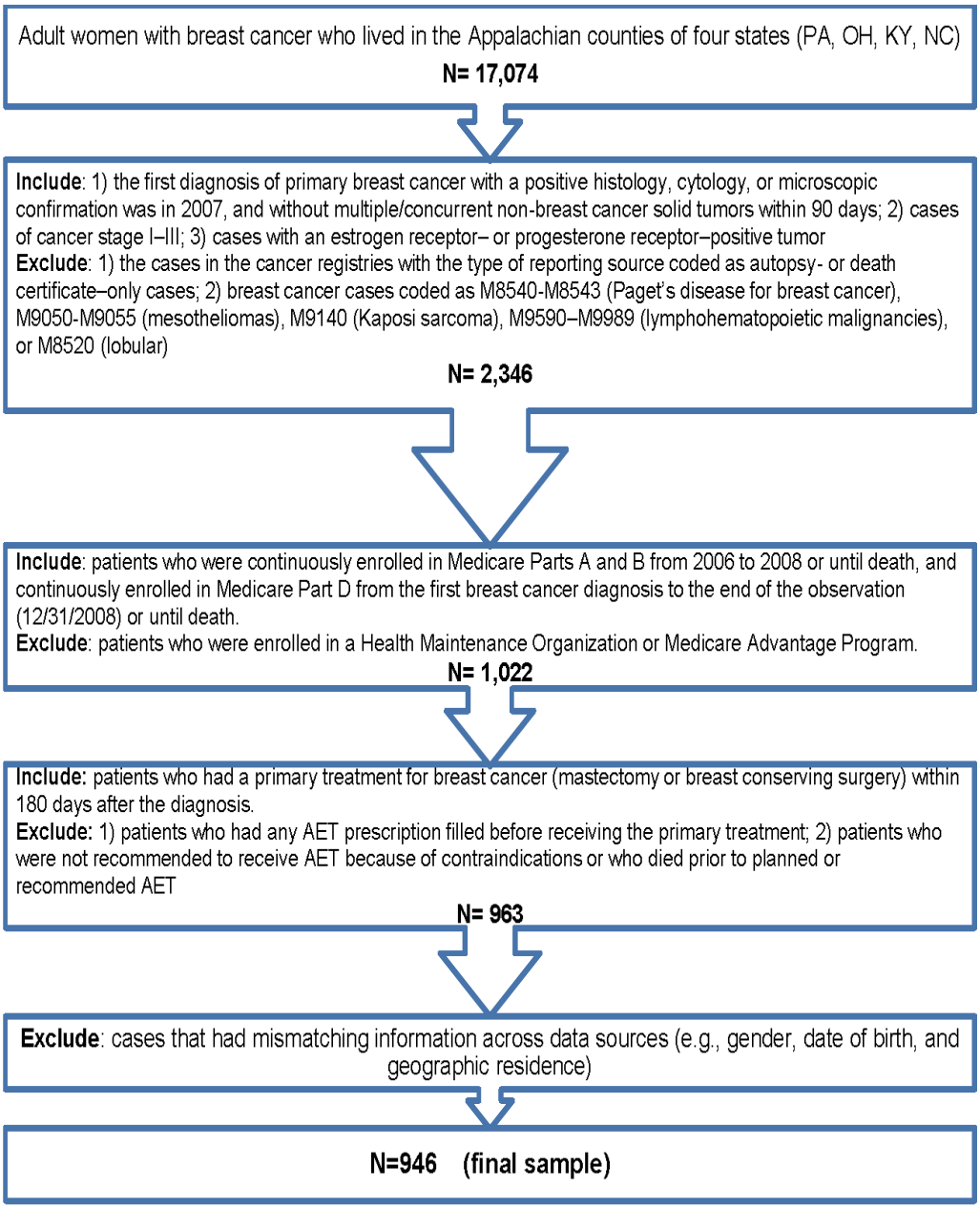


Table 4.1 Descriptive statistics of system-level characteristics (by county) (*N* = 148)

Variables	**Mean (SD)**
Percentage of less than high school graduate among persons aged 25 and over (%)	18.9 (7.6)
Percentage of at least a bachelor's degree among persons aged 25 and over (%)	15.7 (6.3)
Infant death rate per 1,000 births	7.2 (0.83)
Annual age-adjusted, cancer-related death rate per 100,000 population	197.4 (28.1)
	Frequency (%)
ARC's county economic status	
Distressed	36 (24.3%)
At risk	31 (21.0%)
Others	81 (54.7%)
Urban-rural classification	
Metropolitan	47 (31.8%)
Non-metropolitan	101 (68.2%)
Health Professional Shortage Area (HPSA) designation	
Whole county in HPSA	47 (31.7%)
Part county in HPSA	79 (53.4%)
Not in HPSA	22 (14.9%)

SD = Standard Deviation, ARC = Appalachian Region Commission

Table 4.2 Descriptive statistics of individual, facility and provider characteristics of final study population (*N* = 946)

Variables	Mean (SD)
Average travel time to the three closest mammography centers (minute)	16.0 (10.0)
Baseline Charlson Comorbidity Index (CCI)	0.64 (1.1)
Baseline number of hospitalizations	0.39 (0.99)
No. of breast-cancer-related follow-up visits	2.16 (2.69)
	Frequency (%)
Age at diagnosis	
<65	66 (7.0%)
65 to 74	366 (38.7%)
75 to 84	404 (42.7%)
≥ 85	110 (11.6%)
Race	
White	918 (97.0%)
Non-white	28 (3.0%)
Marital status	
Married	394 (41.6%)
Not married	552 (58.4%)
State	
KY	113 (11.9%)
NC	190 (20.1%)
OH	176 (18.6%)
PA	467 (49.4%)
Annual median household income, quartile	
Low	237 (25%)
Second	236 (25%)
Third	237 (25%)
High	236 (25%)
Dual Medicare and Medicaid eligibility status	
Dual eligible	174 (18.4%)
Medicare only	772 (81.6%)
Stage	
Stage I	524 (55.4%)
Stage II	327 (34.6%)
Stage III	95 (10.0%)
Tumor size	
<1cm	189 (20.0%)
1-2cm	446 (47.1%)
>2cm	299 (31.6%)
Unknown	12 (1.3%)
Lymph nodal status	
Negative	690 (72.9%)
Positive	256 (27.1%)

	Frequency (%)
Commission on Cancer (CoC) accreditation	
Yes	622 (65.7%)
No	297 (31.4%)
Unknown	27 (2.9%)
Facility beds	
<100	129 (13.6%)
100-199	179 (18.9%)
≥ 200	611 (64.6%)
Unknown	27 (2.9%)
Facility ownership	
For profit	44 (4.6%)
Government organization	79 (8.4%)
Non-profit	791 (83.6%)
Others or unknown	32 (3.4%)
Provider's specialty	
Oncologist	250 (26.4%)
General practitioner	573 (60.6%)
Others	123 (13%)
Provider's graduation year	
Before 1980	361 (38.2%)
1980s	405 (42.8%)
After 1989	180 (19.0%)
Breast cancer surgery type	
Breast conserving surgery (BCS)	598 (63.2%)
Mastectomy	348 (36.8%)
Radiation therapy	
Yes	350 (37.0%)
No	596 (63.0%)
Chemotherapy	
Yes	477 (50.4%)
No	469 (49.6%)
Timeliness of primary treatment initiation	
Timely treatment (surgery within 60 days following diagnosis)	883 (93.3%)
Delayed treatment (surgery beyond 60 days after diagnosis)	63 (6.7%)

SD = Standard Deviation

Table 4.3 Predictors of receiving guideline-recommended adjuvant endocrine therapy (AET) among Appalachian women with breast cancer: multivariate logistic regression (*N* = 946)

Variable	Guideline-recommended AET Odds Ratio (95% CI)
Percentage of less than high school graduate among persons aged 25 and over (%)	1.04 (0.98, 1.10)
Percentage of at least a bachelor's degree among persons aged 25 and over (%)	1.01 (0.98, 1.04)
Infant death rate per 1,000 births	0.80 (0.57, 1.12)
Annual age-adjusted, cancer-related death rate per 100,000 population	1.00 (0.99, 1.02)
Average travel time to the three closest mammography centers (minute)	**0.98 (0.96, 0.99)***
Baseline Charlson Comorbidity Index (CCI)	0.92 (0.80, 1.06)
Baseline number of hospitalizations	1.02 (0.87, 1.18)
No. of breast cancer related follow-up visits	1.00 (0.93, 1.06)
ARC's county economic status	
Distressed	Reference
At risk	0.56 (0.28, 1.11)
Others	0.56 (0.26, 1.20)
Urban-rural classification	
Metropolitan	0.81 (0.55, 1.20)
Non-metropolitan	Reference
Health Professional Shortage Area (HPSA) designation	
Entirely within a HPSA	Reference
Partially within in a HPSA	0.88 (0.50, 1.57)
Not within a HPSA	1.12 (0.59, 2.14)
Age at diagnosis	
<65	0.79 (0.43, 1.47)
65 to 74	Reference
75 to 84	1.09 (0.80, 1.50)
≥ 85	1.05 (0.63, 1.75)
Marital status	
Married	**0.63 (0.46, 0.85)****
Not married	Reference
State	
KY	0.54 (0.25, 1.16)
NC	0.91 (0.32, 2.58)
OH	**0.60 (0.39, 0.94)***
PA	Reference
Annual median household income, quartile	
Low	Reference
Second	1.00 (0.68, 1.49)
Third	1.12 (0.75, 1.68)
High	0.97 (0.64, 1.48)
Dual Medicare and Medicaid eligibility status	
Dual eligible	**4.24 (2.76, 6.53)****
Medicare only	Reference

Variable	Guideline-recommended AET Odds Ratio (95% CI)
Stage	
Stage I	1.35 (0.55, 3.31)
Stage II	1.16 (0.67, 2.02)
Stage III	Reference
Tumor size	
<1cm	Reference
1-2cm	1.23 (0.84, 1.78)
>2cm	0.94 (0.50, 1.78)
Unknown	0.41 (0.11, 1.53)
Lymph nodal status	
Negative	Reference
Positive	1.18 (0.70, 1.96)
Commission on Cancer (CoC) accreditation	
Yes	0.90 (0.66, 1.25)
No	Reference
Unknown	0.62 (0.24, 1.54)
Provider's specialty	
Oncologist	1.19 (0.85, 1.67)
General practitioner	Reference
Others	1.07 (0.68, 1.70)
Provider's graduation year	
Before 1980	0.92 (0.67, 1.27)
1980s	Reference
After 1989	1.06 (0.72, 1.55)
Breast cancer surgery type	
Breast conserving surgery (BCS)	Reference
Mastectomy	1.17 (0.83, 1.65)
Radiation therapy	
Yes	1.19 (0.84, 1.69)
No	Reference
Chemotherapy	
Yes	1.05 (0.78, 1.41)
No	Reference
Timeliness of primary treatment initiation	
Timely treatment (surgery within 60 days)	Reference
Delayed treatment (surgery beyond 60 days)	0.86 (0.47, 1.54)

95% CI = 95% confidence interval, ARC = Appalachian Regional Commission
*$p < 0.05$, **$p < 0.01$

CHAPTER 5

DISSERTATION MANUSCRIPT TWO

MEDICATION USE OUTCOMES ASSOCIATED WITH ADJUVANT ENDOCRINE THERAPY (AET) AMONG APPALACHIAN BREAST CANCER SURVIVORS

Abstract

Background: There is a paucity of literature systemically examining the effects of access to cancer care resources on AET use behaviors, especially in underserved regions such as the Appalachian region in the United States, where gaps in healthcare access are well documented. The objectives of this study were to explore AET adherence and persistence in Appalachia, delineate the effects of access to care cancer on adherence/persistence, and evaluate the influences of adherence and persistence on overall survival.

Methods: We linked female breast cancer patients identified in cancer registries from the Appalachian counties in four states (KY, NC, OH, and PA) to 2006-2008 Medicare claims data. We included patients with invasive, non-metastatic, hormone-receptor-positive breast cancer who received guideline-recommended AET. Eligible patients were followed from the initiation of AET until death or the end of the observation period. Medication adherence was defined as corresponding to a Medication Possession Ratio (MPR) ≥ 0.8 and logistic regression was utilized to assess predictors of adherence. Medication non-persistence was defined as the discontinuation of drugs after exceeding

a 60-day medication gap, and multivariate adjusted estimates of non-persistence were obtained using the Cox proportional hazards (PH) model.

Results: About 31% of the total 428 patients were not adherent to AET, and 30% were not persistent over an average follow-up period of 421 days. Tamoxifen, relative to aromatase inhibitors, was associated with higher odds of adherence (OR = 2.82, $p < 0.001$) and a lower risk of non-persistence (HR = 0.40, $p < 0.001$). Drug-related side effects like pain may be an important factor leading to non-adherence and early discontinuation. In addition, AI adherence and persistence were significantly influenced by out-of-pocket drug costs, dual eligibility status, and coverage gaps. Non-adherence to and non-persistence with AET were associated with higher risks of all-cause mortality, after controlling for other factors.

Conclusion: Our findings of suboptimal AET adherence/persistence in Appalachia as well as positive associations between AET adherence/persistence and overall survival outcomes further underscore the importance of ensuring appropriate AET use in this population to reduce breast cancer mortality disparities. Our findings also suggest that intervention strategies focusing on individualized treatment and medication-related factors may improve adjuvant treatment use.

Introduction

Currently, surgery remains the primary treatment modality for breast cancer, but recent marginal gains in survival may be largely attributable to the adjuvant therapy that usually follows primary therapy,[15–17] including adjuvant radiation, chemotherapy, targeted therapy, and endocrine therapy. With the growing number of breast cancer survivors, breast cancer care should not only provide active treatment but also survivorship care such as post-treatment monitoring and risk-reducing maintenance behaviors.

Adjuvant endocrine therapy (AET) is a secondary prevention therapy recommended for use among hormone-receptor (HR) positive breast cancer survivors for a period of five to ten years after surgery to reduce recurrence and improve survival.[18–21] Additionally, patient adherence to and persistence with AET are critical in maximizing treatment benefits; this has been identified as a significant issue in clinical practice, with non-adherence and non-persistence rates as high as 59% and 73%, respectively.[22,23] There is increasing recognition in the literature that greater effort should be made to improve adjuvant treatment use to pursue better cancer outcomes.

The current literature showed a broad range of adherence and early discontinuation rates ranging from 41% to 95.7% and 12% to 73%, respectively.[22,23] Variations in adherence and persistence in these studies may be attributable to heterogeneity in methodology and study population. There is no gold standard method for measuring adherence and persistence of AET in clinical practice, nor is there a good biomarker available to measure the use of tamoxifen or aromatase inhibitors (AIs).[124] Therefore, almost all relevant studies used indirect methods to measure adherence and

persistence, namely pharmacy claims/medical records data, or physician report/patient self-report data. In general, studies that used physician report or patient self-report data showed better results, with adherence rates ranging from 77% to 94.7%[125–127] and non-persistence rates ranging from 21% to 31%.[118,125,128,129] Most studies on AET adherence and persistence analyzed medical and pharmacy claims data. In these retrospective claims data studies, adherence was usually defined as Medication Possession Ratio (MPR) ≥80%, while non-persistence/discontinuation was operationalized as the discontinuation of drugs after exceeding a permissible gap,[130] which ranged from 45 to 180 days depending on the study.[22] The discrepancies in persistence definitions may result in variations in discontinuation rates.

In addition, factors that were consistently shown to be negatively associated with AET adherence or persistence included extreme age, increasing out-of-pocket costs of AET, seeing a general practitioner vs. an oncologist during follow-up care, switching between drugs, and treatment-associated side effects.[22,23,140] However, there are very few studies that systemically examine the effects of access to cancer care resources on AET use behaviors, especially in underserved regions where patients suffer from the deficiencies of access to care, such as the Appalachian region. Additionally, in clinical practice, the literature regarding direct therapeutic outcomes associated with AET adherence and persistence remains underdeveloped. Most available studies controlled for individual-level characteristics such as demographics and cancer clinical status. Given the existing cancer disparities, relatively poor access to care, and lack of adjuvant cancer treatment use research on Appalachia's cancer patient population, it becomes important to investigate the relationship between AET adherence/persistence and

cancer survival among Appalachian breast cancer survivors, after controlling for access factors. In this way, we can better understand the marginal effects of AET use outcomes on cancer survival after teasing out the influences of poor access to care on survival. Therefore, the objectives of this study were to: 1) describe the prevalence of adherence to and persistence with AET among Appalachian breast cancer survivors; 2) assess the effects of access to cancer care resources on AET adherence and persistence; 3) evaluate the influences of AET adherence and persistence on survival after controlling for access factors.

Methods

1. Study design and data source

To achieve the study objectives, we conducted a retrospective cohort study among female breast cancer survivors living in the Appalachian counties of four states (PA, OH, KY and NC). The study time was from January 1, 2006 to December 31, 2008. The overall study design comprises three main periods: the baseline period (one year before the first breast cancer diagnosis), the diagnosis-to-AET period (the interval between the first diagnosis and the initiation of AET), and the follow-up period (from the date of the first AET prescription filled until death or the end of the observation period, 12/31/2008). Multiple data sources were integrated for final analyses: individual characteristics from cancer registries and Medicare claims data; system-level characteristics from the Appalachian Regional Commission (ARC) data reports, the 2010 U.S. census, the Area Resource File, the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), and the National Cancer Institute (NCI); and

provider/facility characteristics mainly from Medicare Provider of Service files and Medicare Physician Identification and Eligibility Records files. First, we linked women who were diagnosed with breast cancer during 2006-2008 and tracked in the four states' cancer registries to Medicare claims data using patient identifiers including name, social security number, gender, and birthdate. Then, the cross-link was established between patient data and system-level characteristics using county codes. The Unique Physician Identification Numbers (UPIN) and National Provider Identifiers (NPI) were utilized to link patient claims to provider/facility factors. The time frame of these data sources was in accordance with our study time period. The final dataset for statistical analyses had completely de-identified information. Data use was approved by the Centers for Medicare and Medicaid services (CMS) and cancer registries, and the study was approved by the University of Michigan's Institution Review Board (IRB).

2. Study population

We included adult women who lived in the Appalachian counties of the four states and were diagnosed with confirmed stage I-III, hormonal receptor (HR) positive, primary breast cancer in 2007. Other inclusion criteria were continuous enrollment in Medicare Parts A, B and D, recorded history of primary breast cancer treatment, eligibility for AET, and no AET use before the primary breast cancer treatment. Patients who were enrolled in a Health Maintenance Organization (HMO) or Medicare Advantage Program or had conflicting information across data sources were excluded from the study. Then we extracted a subset group of subjects who received guideline-recommended AET, which referred to the receipt of AET within one year following diagnosis.[167] To facilitate the

measurement of medication adherence and persistence, we ensured that we followed patients for a period of at least 6 months. Our final study sample comprised 428 subjects.

3. Outcome measures

3.1 Adherence

We calculated AET adherence for each individual using the MPR. The MPR is a commonly used medication adherence measure using administrative claims data that has been adopted in a great deal of AET adherence research.[22,23] It is defined as the ratio of the amount of days for which the drug was dispensed divided by the number of days for which drug was needed,[168,169] which was determined in this study using the following equation[170,171]:

Medication possession ratio (MPR) = number of days' supply / (number of follow-up days ─ number of inpatient days)

Additionally, the MPR was truncated between 0 and 1.2, as well as dichotomized into adherence and non-adherence using the conventional cut-off point of 0.8 ($0 \leq MPR < 0.8$: non-adherence; $0.8 \leq MPR \leq 1.2$: adherence). For those who switched between tamoxifen and AI, we precluded any double-counting of the days when the patient took both tamoxifen and AI. The non-adherence rate refers to the percentage of patients who were not adherent.

3.2 Persistence

Medication persistence is defined as the act of complying with a provider's recommendations to use medications for a prescribed length of time[130] and is commonly operationalized in retrospective claims data studies as the discontinuation of drugs after exceeding a permissible gap.[130] In AET persistence research, the prescription fill gap has been defined as ranging from 45 to 180 days, based on the pharmacological characteristics of the drugs; legitimate delays in refills, such as hospitalization; and the length of the follow-up period.[27,122,123,125,131–133] Taking all of the above into consideration, we decided to define AHT non-persistence as a minimum 60-day medication fill gap. Patients who switched drugs within 60 days were still considered persistent. The non-persistence rate (also referred to as early discontinuation rate) refers to the percentage of patients who were not persistent.

3.3 Survival

Overall survival was defined as the period from AET initiation until death. The follow-up period ended on December 31, 2008.

4 Covariate measures

The access factors examined in this study included county economic status, county-level educational attainment (percentages of persons with less than high school education and at least a bachelor's degree), urban or rural geographic residence, county-level infant and cancer mortality rates, Health Professional Shortage Area (HPSA) designation, age at diagnosis, marital status, state of residence, four quartiles

of annual median household income (at the census block group level), dual Medicare and Medicaid eligibility indicator, average travel time from the patient to the three closes mammography centers, breast cancer stage, tumor size, lymph nodal status, patients' comorbidities, treatment facility's Commission on Cancer (CoC) accreditation status, number of beds, facility type, ownership, the provider's specialty and graduation year, the number of breast-cancer-related follow-up visits, and timeliness of primary treatment initiation. We also assessed the type of breast cancer treatments received such as surgery type, radiation therapy and chemotherapy, as well as the type of AET received (tamoxifen, AIs, or switching between tamoxifen and AIs). We included commonly used AIs in this study, which were anastrozole, letrozole, and exemestanes.

For a better assessment of the adherence/persistence issue, we also included the average monthly out-of-pocket drug costs, whether patients reached the out-of-pocket threshold and began to receive catastrophic coverage, and the following medication-related factors: 1) **the number of unique prescription drugs co-administered** during the follow-up period, as a proxy measure of pill burden, was identified using NDC from the Medicare Part D claims data; 2) **the season at the initiation of AET (**spring, summer, fall, winter) was also included in analyses because the seasonal weather condition may have influences on travel and transportation, which in turn may affect patient behaviors of picking up their drugs. And the seasonal effects may be more phenomenal in a largely rural and mountainous environment such as Appalachia; 3) AET-associated side effects: we utilized proxy measures for AET-associated side effects (e.g., osteoporosis, hot flashes/night sweats, arthralgia) using the indicators of the use of evidence-based pharmacological treatments (prescription drugs) for them. As

per clinical recommendations for managing AET associated side effects,[174–176] we created dummy variables indicating whether or not patients used antidepressants (fluoxetine, paroxetine, venlafaxine, citalopram, gabapentin), bisphosphonates (zoledronic acid, alendronate, risedronate), and pain medications (opioids, gabapentin, pregabalin) during the follow-up period.

5 Statistical analyses

5.1 Descriptive analyses and bivariate association analyses

We conducted descriptive analyses of the access variables, medication-related factors, type of breast cancer treatment, and follow-up days using means for continuous variables and frequencies and percentages for binary and categorical variables. We assessed MPRs, adherence rates, and discontinuation rates among the three AET groups. We used the 2×2 contingency table and phi coefficient to assess the correlation between AET adherence and persistence. Preliminary bivariate association analyses were conducted to find potential predictors of adherence, persistence, and survival. We conducted two-tailed t-tests for continuous predictors of adherence and chi-square tests for binary and categorical predictors of adherence. We used Kaplan-Meier survival curves and log-rank tests to assess the associations between each binary/categorical variable and persistence or survival time, as well as univariate Cox regression analyses to evaluate the relationships between each continuous variable and persistence or survival time. In particular, we utilized Kaplan-Meier survival curves and log-rank tests to assess the bivariate associations between AET adherence/persistence and overall survival.

5.2 Multivariate analysis of AET adherence

Multivariate logistic regression was used to assess the relationship between access to cancer care and AET adherence. For the sake of parsimony, we incorporated potentially significant predictors with a *p* value less than 0.25 in the bivariate association analyses into the final multivariate logistic model with a robust standard error. For the final logistic model of adherence, we also tested the significance of the categorical variables and checked the goodness-of-fit, multicollinearity, and c- statistic. Model selection was based on likelihood ratio tests, Akaike's information criterion (AIC) and Bayesian information criterion (BIC). The potential random effects of clustered county- and state-level factors were also tested by using the multilevel mixed-effects logistic regression.

5.3 Multivariate analysis of AET persistence

We obtained multivariate adjusted estimates of non-persistence (discontinuation) using the Cox proportional hazards (PH) model. We included in the final model only those predictors for which $p < 0.25$ in the bivariate association analyses. We utilized the Efron method to handle ties. We checked the proportional hazard assumption of the variables in the final model by using the Schoenfeld and scaled Schoenfeld residuals. If a variable did not meet the assumption, we estimated a stratified Cox model based on the variable.[121]

5.4 Multivariate analysis of all-cause mortality

We utilized Cox PH models to assess whether AET adherence and persistence influence all-cause mortality among our study population. In the models, we also

adjusted the potential predictors with a *p* value less than 2.5 in the bivariate association analyses. We checked the proportional hazard assumptions by using the Schoenfeld and scaled Schoenfeld residuals and the goodness-of-fit by using the Cox-Snell residuals.

5.5 Sensitivity analyses

Sensitivity analyses were also conducted to reduce the potential errors or uncertainty caused by the definitions of adherence and persistence, as well as to achieve a better understanding of the relationships. AET adherence and persistence were re-defined using MPR cutoff points ranging from 0.6 to 0.9 and a 90-day medication fill gap, respectively.

The statistical significance level was set to $p < 0.05$. We used R 3.0.2 for general data management, ArcGIS 10.1 for geo-related data management, and Stata 13 for analyses.

Results

Our final study sample consisted of 428 Medicare-enrolled women with breast cancer living in the 125 Appalachian counties of four states (KY, NC, OH, and PA) who initiated AET within one year after the breast cancer diagnosis. Eligible patients were followed for a period of 181 to 706 days, with a mean of 421 days and a median of 411 days. The mean MPR for all subjects was 0.83, and approximately 69.4% were considered adherent to AET (shown in Table 5.1). The average AET persistence time was 347.6 days, and the early discontinuation rate was about 30.1%. The tamoxifen group had

better adherence and persistence than the AI group (mean MPR: 0.86 vs. 0.82; mean persistence time: 370.8 days vs. 338.9). AET adherence and persistence were found to be highly correlated (Phi coefficient = 0.81). In addition, when medication adherence was re-defined using MPRs ranging from 0.6 to 0.9, adherence rates varied from 83.2% to 55.1%, with the largest differences at the cutoff points of 0.7 and 0.9. The adherence rates at the cutoff points of 0.7 and 0.9 were 78.5% and 55.1%, respectively. If a 90-day medication fill gap was used to define non-persistence, the difference in the mean persistence times was moderately small (347.6 days for the 60-day fill gap *vs*. 366.4 days for the 90-day fill gap).

Table 5.2 describes county-level characteristics. The results confirmed the deficiencies in access to care in Appalachia including economically distressed or at risk populations (43.2%), largely rural environments (67.2%), and healthcare professional shortages (88%), as well as community educational levels and infant and cancer mortality rates that were worse than national averages. Bivariate association analyses showed that adherent and persistent patients were more likely to live in counties with a lower infant mortality rate (p = 0.048 and p = 0 .245, respectively). But, overall, we did not find bivariate associations with strong significance between county-level factors and adherence/persistence.

Table 5.3 presents the descriptive analysis results of individual, facility/provider, and medication-related characteristics. During the follow-up period, eligible patients had 2.25 breast-cancer-related follow-up visits, on average. Patients seem to suffer from substantial pill burdens. An average of approximately 11.6 prescription drugs was co-administered to patients during follow-up; the estimated average monthly out-of-pocket

drug costs were about $50.00. Approximately 26.4% of the population even reached the catastrophic coverage threshold. Moreover, the use rates of antidepressants, bisphosphonates, and pain medications that can treat AET-associated side effects were about 9.1%, 21.5%, and 10%, respectively. Dual eligibility status, catastrophic coverage, lymph nodal status, and use of pain medications had significant bivariate associations with AET adherence and persistence ($p < 0.05$).

Table 5.4 and Table 5.5 show factors significantly associated with AET adherence and discontinuation: AET drug class, catastrophic coverage, and use of pain medications. Please note that because dual eligibility status and provider specialty did not meet the proportional hazard assumption, our final Cox PH model of AET discontinuation was stratified by these two variables (see in Table 5.5). Patients receiving catastrophic coverage benefits had about three-fold odds of adhering to AET (*OR* = 3.25, $p = 0.001$) and a 44% lower risk of discontinuing AET (*Hazard Ratio* = 0.56, $p = 0.03$). Co-administration of pain medications was associated with 68% reduced odds of adherence to AET (*OR* = 0.32, $p = 0.003$) and an estimated 2.5 times increased risk of AET non-persistence (*Hazard Ratio* = 2.47, $p = 0.002$). Tamoxifen was associated with greater likelihood of adherence (*OR* = 2.82, $p = 0.003$) and a lower risk of non-persistence (*Hazard Ratio* = 0.40, $p = 0.002$) than AIs.

In addition, to better evaluate the factors associated with adherence and persistence, we stratified our population into those who took tamoxifen and those who took AIs and re-estimated the models. We found that increased out-of-pocket costs were associated with reduced likelihood of adherence in the AI group (*OR* = 0.99, $p = 0.008$), but the results were not significant in the tamoxifen group. Those dual-eligible enrollees who

qualified for low-income subsidies (LIS) did not experience the drug coverage gap experienced by Medicare-only enrollees; we did not find that receiving catastrophic coverage benefits significantly affected AET adherence or persistence among these dual-eligible enrollees. For Medicare-only enrollees, however, receiving catastrophic coverage significantly improved AI adherence (*OR* = 6.20, *p* = 0.001) and persistence (*Hazard Ratio* = 0.31, *p* = 0.01) but did not have significant impacts on tamoxifen use. In terms of side effects, we found that using pain medications was significantly associated with poor adherence (*OR* = 0.41, *p* = 0.03) and persistence (*Hazard Ratio* = 1.94, *p* = 0.05) to AI but not to tamoxifen.

The results of using differing definitions of adherence and persistence in our sensitivity analyses showed that AET drug class and catastrophic coverage were robust predictors of AET adherence while AET drug class and the use of pain medication were stable predictors of AET persistence. Moreover, when we used a 0.9 cut-off point to define adherence, the provider's specialty and primary treatment type became significantly correlated with adherence, as well. And if a 90-day medication gap was used to determine persistence, positive lymph nodal status was significantly associated with a lower risk of early discontinuation (*HR* = 0.47, *p* = 0.015).

During the study period, all-cause death occurred in 15 patients (3.5% of our sample). Figures 5.2 and 5.3 show the Kaplan-Meier survival curves by AET medication adherence and persistence. From the graphs, we can see that patients who were not adherent to or persistent with AET had a higher risk of death, both with significant log rank test results (*p* = 0.04 and 0.01, respectively). Multivariate adjusted Cox PH models also supported these findings (shown in Tables 5.6 and 5.7). Other significant factors

associated with increased risk of all-cause death were increased age and being treated in non-CoC accredited facilities. The conclusions did not differ if we changed the definitions of adherence and persistence.

Discussion

Our study is among the first to delineate the manner in which multidimensional determinants of access to cancer care affect patient medication use behaviors, specifically, adherence to and persistence with adjuvant treatments, in Appalachia. The AET adherence rate and early discontinuation rate in the first two years among Appalachian women with invasive, non-metastatic, hormone-receptor-positive breast cancer were 69% and 30%, respectively. We found that adherence rates in previous studies using US pharmacy claims data were in the range of 70%-80%,[116,117,138,139] and the discontinuation rates were fairly consistent at around 20%.[27,28,117,123] There were only two extreme results: one was a 60% adherence rate among Medicaid enrollees in North Carolina, one of the Appalachian states[27]; the other was a 90% adherence rate among patients using mail-order pharmacy services.[28] Overall, AET adherence and persistence seems to be lower in Appalachia compared to the rest of the US.

Our findings suggested that adherence to and persistence with AET were primarily related to the medication-related factors. Our results consistently showed that tamoxifen was associated with better medication use outcomes than AIs, which may be attributable to different adverse effect profiles and drug costs. The use of pain medications, presumably to treat AI-related musculoskeletal pain, was significantly correlated with poor adherence and persistence, which may partially explain the worse

medication use outcomes associated with AIs. Other research showed that AET-induced side effects like musculoskeletal pain may increase physical burden on patients, cause misbeliefs about AET use, and adversely affect patients' intentions to adhere to the medication.[177,178] Our study supports this conclusion and highlights the need to develop interventions that focus on individualized side-effect management and better patient education about AET use.

In addition, tamoxifen generally involves lower costs to both patients and third-party payers than AIs, so it may be associated with reduced financial burden in the long run. We found a negative relationship between out-of-pocket costs and adherence among patients who used AIs only (*OR* = 0.99, *p* = 0.008) but did not find a significant relationship among those who used tamoxifen only. The relationship may be influenced by several factors: type of Medicare healthcare plan, dual eligibility status that can determine the qualification for LIS, whether patients enter the coverage gap, and whether patients receive catastrophic coverage benefits beyond the out-of-pocket threshold. Riley et al (2011) found that adherence rates did not differ much between patients with and without LIS in the tamoxifen group, but adherence to AIs was significantly improved if patients received LIS.[116] In the present study, however, we did not establish a similar significant interaction between AET drug class and dual eligibility status to predict adherence or persistence. Previous research found that AET adherence declined when Medicare-only patients without LIS entered in the coverage gap compared to pre-coverage gap[116]; our study further found that AI adherence and persistence improved significantly after these patients got out of the coverage gap and

received catastrophic coverage benefits, but we found no significant changes in tamoxifen adherence and persistence in the same circumstances.

To our knowledge, our study is also one of the first to assess the effects of AET adherence and persistence on survival in an underserved region like Appalachia. Even with the constraints of small sample size and short follow-up time, we found significant positive relationships between non-adherence/non-persistence to AET and all-cause mortality. Hershman et al (2011) found that non-persistence and non-adherence to AET were significantly associated with increased hazard of all-cause death by 26% and 49%, respectively.[122] Similarly, McCowan et al (2008) identified a 10% increase in the hazard of all-cause mortality among those who were not adherent to tamoxifen, compared to those who were adherent, as well as a significantly lower risk of death associated with use of tamoxifen over a longer duration.[137] These findings may imply the importance of ensuring appropriate AET use in the pursuit of additional gains in survival. It is also noteworthy that AET adherence and persistence may have different influences on survival. By definition, AET persistence emphasizes more on the recommended length of time, which was determined by clinical evidence of benefits in breast cancer outcomes.[24,25] AET adherence focuses on whether patients can use AET everyday as recommended to keep a steady drug level that is warranted to maximize the drug effectiveness and improve clinical outcomes. However, long follow-up time that can cover the whole recommended clinical course of AET may be needed to differentiate the effects of AET adherence and persistence on breast cancer outcomes.

This study had several limitations. First, given the inherent characteristics of retrospective cohort studies, we could not establish causality. Second, the relatively

short length of the follow-up period and the small sample size limited our ability to conduct further analyses. For example, an adequate number of death cases would allow us to study breast-cancer-related survival, while a longer study period would give us the opportunity to look at changes in adherence and persistence over the whole recommended clinical course of AET (5 to 10 years). Third, we did not include some detailed information and important potential confounders, such as accurate drug indications, drugs used in hospice settings, prescribers' characteristics, pharmacy type, and patient attitudes and beliefs about long-term AET use. Fourth, when using administrative claims data to assess medication adherence/persistence, we assumed that the claims were billed in an accurate and timely manner, AET was obtained only through Medicare Part D, and the medication was actually taken by the patients. These assumptions may not always be true under all circumstances, which may cause measurement errors. For example, patients might obtain AET from other sources than through Medicare Part D, which may not be captured in our dataset especially when in the coverage gap. Dually eligible patients may receive additional benefits from their Medicaid programs to help with their out-of-pocket money, which were not considered in our calculation of out-of-pocket drug costs. Finally, our target population was Medicare enrollees with breast cancer who lived in the Appalachian region and was first-time users of tamoxifen and AIs, which were used only for adjuvant treatment purposes. We did not study ovarian suppression/ablation, or the use of tamoxifen or AIs as primary treatments or neoadjuvant therapy for breast cancer, or AET use in a general breast cancer patient population, which is typically younger than our study population. These

may limit the generalizability of our study findings and suggest the need for future research efforts.

Conclusion

AET adherence and persistence are suboptimal in Appalachia. They differ between drug classes possibly as a result of distinct adverse effect profiles and differences in patient affordability stemming from drug costs and health plan benefits. Additionally, we confirm the substantial benefits of adherence to and persistence with AET in achieving the advancement of overall survival. Therefore, this study suggests the value of adding a component focusing on medication management related to AET use to current cancer care models in Appalachia with the ultimate goal of reducing breast cancer mortality disparities.

Table 5.1 Prevalence of adjuvant endocrine therapy (AET) adherence and persistence among Appalachian women with invasive, non-metastatic, hormone-receptor positive breast cancer

Group	MPR, mean (SD)	Adherence rate, n (%) [£]	Persistence time (day), mean (SD)	Discontinuation rate, n (%) [£]
All subjects (*N* = 428)	0.83 (0.24)	297 (69.4%)	347.6 (165.5)	129 (30.1%)
Tamoxifen group (*N* = 80)	0.86 (0.26)	63 (78.8%)	370.8 (168.9)	15 (18.8%)
Aromatase inhibitor group (*N* = 319)	0.82 (0.24)	212 (66.5%)	338.9 (163.0)	105 (32.9%)
Switching group (*N* = 29)	0.85 (0.20)	22 (75.9%)	378.8 (179.1)	9 (31.0%)

SD = Standard Deviation, MPR = Medication Possession Ratio
[£] The denominator of the percentage was the number of patients in the specific subgroup.

Table 5.2 Descriptive statistics of system-level characteristics (by county) (*N* = 125)

Variables	**Mean (SD)**
Percentage of less than high school graduate among persons aged 25 and over (%)	18.8 (7.7)
Percentage of at least a bachelor's degree among persons aged 25 and over (%)	15.9 (6.4)
Infant death rate per 1,000 births	7.2 (0.85)
Annual age-adjusted, cancer-related death rate per 100,000 population	197.7 (28.8)
	Frequency (%)
ARC's county economic status	
Distressed	30 (24.0%)
At risk	24 (19.2%)
Others	71 (56.8%)
Urban-rural classification	
Metropolitan	41 (32.8%)
Non-metropolitan	84 (67.2%)
Health Professional Shortage Area (HPSA) designation	
Whole county in HPSA	40 (32.0%)
Part county in HPSA	70 (56.0%)
Not in HPSA	15 (12.0%)

SD = Standard Deviation, ARC = Appalachian Region Commission

Table 5.3 Descriptive statistics of individual, facility/provider, and medication-related characteristics of final study population (*N* = 428)

Variables	Mean (SD)
Average travel time to the three closest mammography centers (minute)	15.9 (10.2)
Baseline Charlson Comorbidity Index (CCI)	0.63 (0.95)
Baseline number of hospitalizations	0.38 (0.97)
No. of breast-cancer-related follow-up visits	2.25 (2.44)
Average monthly out-of-pocket costs (US dollar)	50.0 (64.2)
No. of unique prescription drugs co-administered	11.6 (6.24)
Follow-up time (day)	421.2 (116.3)
	Frequency (%) [#]
Age at diagnosis	
<65	35 (8.2%)
65 to 74	155 (36.2%)
75 to 84	187 (43.7%)
≥ 85	51 (11.9%)
Marital status	
Married	140 (32.7%)
Not married	288 (67.3%)
State	
KY	61 (14.3%)
NC	77 (18.0%)
OH	75 (17.5%)
PA	215 (50.2%)
Annual median household income (US dollar), quartile	
Low ($9,768 - $31,408.5)	107 (25%)
Second ($31,408.5 - $ 41,552)	107 (25%)
Third ($41,552 - $51,577.5)	107 (25%)
High ($51,577.5 - $15,0625)	107 (25%)
Dual Medicare and Medicaid eligibility status	
Dual eligible	121 (28.3%)
Medicare only	307 (71.7%)
Catastrophic coverage indicator	
Yes	113 (26.4%)
No	315 (73.6%)
Stage	
Stage I	239 (55.8%)
Stage II	149 (34.8%)
Stage III	40 (9.4%)
Tumor size	
<1cm	84 (19.6%)
1-2cm	215 (50.2%)
>2cm	129 (30.1%)
Lymph nodal status	
Negative	312 (72.9%)
Positive	116 (27.1%)
Commission on Cancer (CoC) accreditation	
Yes	272 (63.6%)
No	156 (36.4%)
Facility beds	
<100	70 (16.4%)
100-199	91 (21.3%)
≥ 200	267 (62.4%)

	Frequency (%) [#]
Facility ownership	
Non-profit	364 (85.0%)
Others	64 (15.0%)
Provider's specialty	
Oncology	116 (27.1%)
General practitioner	259 (60.5%)
Other	53 (12.4%)
Provider's graduation year	
Before 1980	163 (38.1%)
1980s	186 (43.5%)
After 1989	79 (18.5%)
Breast cancer surgery type	
Mastectomy	166 (38.8%)
Breast conserving surgery (BCS) + radiation	139 (32.5%)
BCS, no radiation	123 (28.7%)
Chemotherapy	
Yes	215 (50.2%)
No	213 (49.8%)
Timeliness of primary treatment initiation	
Timely treatment (surgery within 60 days)	398 (93.0%)
Delayed treatment (surgery beyond 60 days)	30 (7.0%)
Use of antidepressants	
Yes	39 (9.1%)
No	389 (90.9%)
Use of bisphosphonates	
Yes	92 (21.5%)
No	336 (78.5%)
Use of pain medications	
Yes	43 (10.0%)
No	385 (90.0%)
Season at the initiation of AET	
Spring	97 (22.7%)
Summer	103 (24.1%)
Fall	103 (24.1%)
Winter	125 (29.2%)

SD = Standard Deviation, AET = adjuvant endocrine therapy

Note that the percentages of some variables may not add up to 100% due to rounding errors.

Table 5.4 Predictors of adherence to adjuvant endocrine therapy (AET) among Appalachian women with breast cancer: multivariate logistic regression (*N* = 428)

Variable	Adherence to AET, Odds Ratio (95% CI)
Percentage of at least a bachelor's degree among persons aged 25 and over (%)	0.997 (0.957, 1.039)
Infant death rate per 1,000 births	1.16 (0.66, 2.04)
Annual age-adjusted, cancer-related death rate per 100,000 population	1.01 (0.99, 1.02)
Baseline Charlson Comorbidity Index (CCI)	1.08 (0.83, 1.40)
Average monthly out-of-pocket costs (US dollar)	0.997 (0.993, 1.001)
Health Professional Shortage Area (HPSA) designation	
Whole county in HPSA	Reference
Part county in HPSA	1.19 (0.49, 2.91)
Not in HPSA	1.26 (0.45, 3.55)
State	
KY	0.39 (0.14, 1.13)
NC	0.43 (0.07, 2.60)
OH	0.66 (0.30, 1.42)
PA	Reference
Dual Medicare and Medicaid eligibility status	
Dual-eligible	1.26 (0.59, 2.68)
Medicare-only	Reference
Catastrophic coverage indicator	
Yes	**3.25 (1.67, 6.33)****
No	Reference
Lymph nodal status	
Negative	Reference
Positive	1.51 (0.86, 2.66)
Commission on Cancer (CoC) accreditation	
Yes	0.89 (0.53, 1.50)
No	Reference
Provider specialty	
Oncology	1.25 (0.73, 2.16)
General practitioner	Reference
Other	0.54 (0.26, 1.10)
Breast cancer surgery type	
Mastectomy	Reference
Breast conserving surgery (BCS) + radiation	0.74 (0.40, 1.35)
BCS, no radiation	0.66 (0.36, 1.21)
Use of bisphosphonates	
Yes	1.39 (0.78, 2.46)
No	Reference
Use of pain medications	
Yes	**0.32 (0.15, 0.67)****
No	Reference
AET drug class	
Tamoxifen	**2.82 (1.42, 5.64)****
Aromatase inhibitor (AI)	Reference
Switching between two drug classes	2.20 (0.85, 5.66)

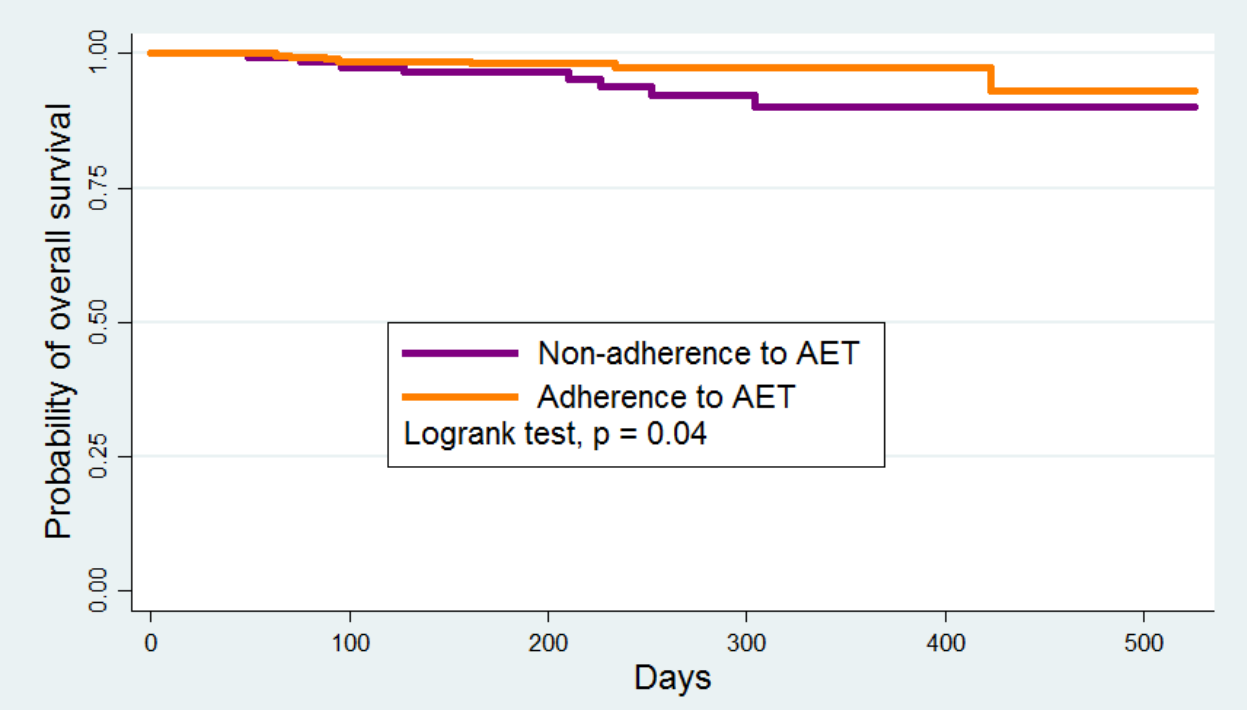
95% CI = 95% confidence interval ***p* < 0.01

Table 5.5 Factors associated with discontinuation of adjuvant endocrine therapy (AET) among Appalachian women with breast cancer: Cox proportional hazards (PH) model, stratified by the provider's specialty and the patient's dual eligibility status (*N* = 428)

Variable	AET discontinuation, Hazard Ratio (95% CI)
Percentage of at least a bachelor's degree among persons aged 25 and over (%)	0.99 (0.96, 1.02)
Infant death rate per 1,000 births	1.08 (0.90, 1.31)
Annual age-adjusted, cancer-related death rate per 100,000 population	1.00 (0.99, 1.01)
Baseline Charlson Comorbidity Index (CCI)	0.96 (0.77, 1.19)
Age at diagnosis	
<65	0.47 (0.16, 1.36)
65 to 74	Reference
75 to 84	1.10 (0.73, 1.66)
≥ 85	1.17 (0.63, 2.19)
Marital status	
Married	1.13 (0.76, 1.69)
Not married	Reference
Annual median household income (US Dollar), quartile	
Low ($9,768 - $31,408.5)	Reference
Second ($31,408.5 - $ 41,552)	1.26 (0.73, 2.17)
Third ($41,552 - $51,577.5)	1.06 (0.61, 1.85)
High ($51,577.5 - $15,0625)	1.25 (0.71, 2.20)
Catastrophic coverage indicator	
Yes	**0.56 (0.33, 0.95)***
No	Reference
Lymph nodal status	
Negative	Reference
Positive	0.69 (0.43, 1.10)
Commission on Cancer (CoC) accreditation	
Yes	1.22 (0.76, 1.94)
No	Reference
Facility beds	
<100 beds	1.20 (0.65, 2.21)
100-199 beds	0.75 (0.44, 1.28)
>=200 beds	Reference
Breast cancer surgery type	
Mastectomy	Reference
Breast conserving surgery (BCS) + radiation	1.14 (0.70, 1.86)
BCS, no radiation	1.50 (0.94, 2.40)
Use of bisphosphonates	
Yes	0.75 (0.46, 1.20)
No	Reference
Use of pain medications	
Yes	**2.47 (1.41, 4.33)****
No	Reference
AET drug class	
Tamoxifen	**0.40 (0.22, 0.71)****
Aromatase inhibitor (AI)	Reference
Switching between two drug classes	0.86 (0.41, 1.80)

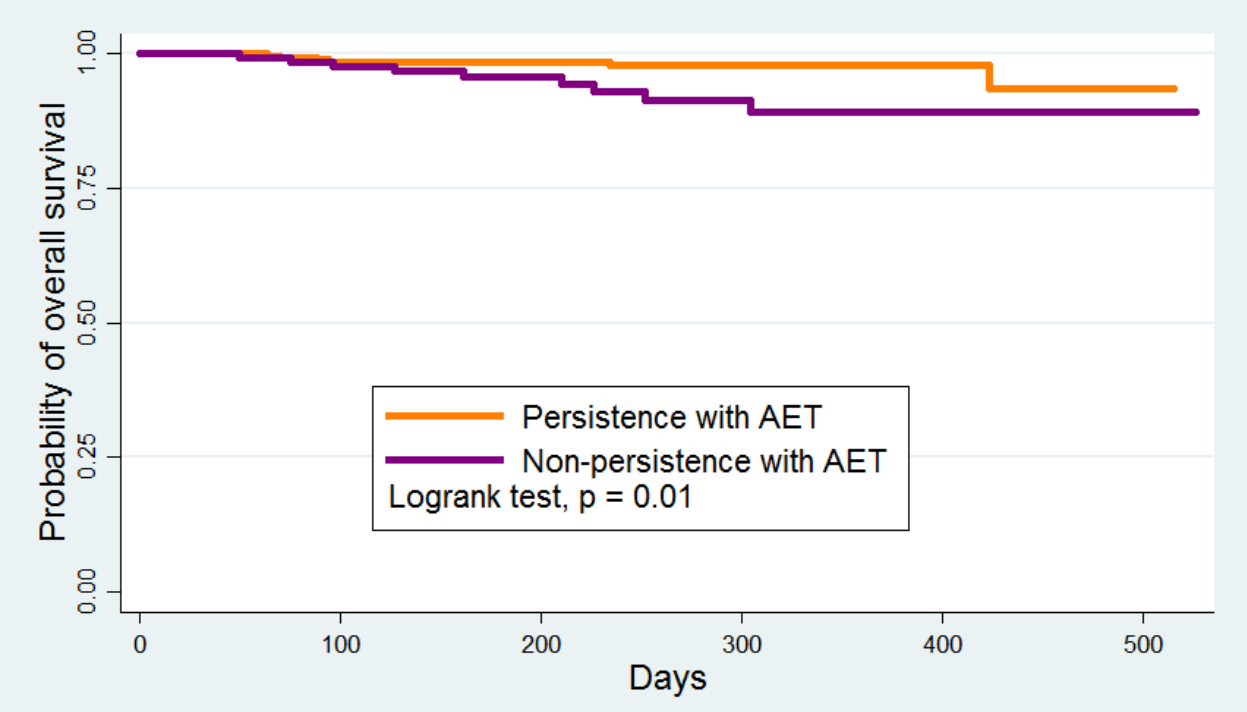
95% CI = 95% confidence interval
*$p < 0.05$, **$p < 0.01$

Figure 5.1 Kaplan-Meier curves of overall survival by adjuvant endocrine therapy (AET) adherence



Note: The start time of survival analysis was 180 days after the initiation of AET because our study design only included patients who were alive for at least 180 days after the initiation of AET.

Figure 5.2 Kaplan-Meier curves of overall survival by adjuvant endocrine therapy (AET) persistence



Note: The start time of survival analysis was 180 days after the initiation of AET because our study design only included patients who were alive for at least 180 days after the initiation of AET.

Table 5.6 The association between adjuvant endocrine therapy (AET) non-adherence and all-cause mortality among Appalachian women with invasive, non-metastatic and hormone receptor positive breast cancer, using Cox proportional hazards (PH) model (*N* = 428)

Variable	All-cause mortality, Hazard Ratio (95% CI)
Adherence to AET	
Yes	Reference
No	**9.15 (2.11, 39.62)****
Age at diagnosis (year)	**1.14 (1.04, 1.25)****
Marital status	
Married	1.75 (0.26, 11.57)
Not married	Reference
Dual Medicare and Medicaid eligibility status	
Dual eligible	3.07 (0.76, 12.41)
Medicare only	Reference
Stage	
Stage I	Reference
Stage II	1.46 (0.20, 10.40)
Stage III	1.25 (0.10, 16.05)
Tumor size	
<1cm	Reference
1-2cm	0.20 (0.02, 1.57)
>2cm	0.46 (0.04, 4.60)
Commission on Cancer (CoC) accreditation	
Yes	**0.12 (0.02, 0.72)***
No	Reference
Facility beds	
<100 beds	1.54 (0.29, 8.08)
100-199 beds	3.07 (0.56, 16.64)
>=200 beds	Reference
Breast cancer surgery type	
Mastectomy	Reference
Breast conserving surgery (BCS)	0.47 (0.12, 1.92)
Baseline number of hospitalizations	0.99 (0.65, 1.49)
No. of breast-cancer-related follow-up visits	0.56 (0.30, 1.07)
No. of unique prescription drugs co-administered	0.97 (0.88, 1.07)

95% CI = 95% confidence interval
**p* < 0.05, ***p* < 0.01

Table 5.7 The relationship between adjuvant endocrine therapy (AET) non-persistence and all-cause mortality among Appalachian women with invasive, non-metastatic and hormone receptor positive breast cancer, using Cox proportional hazards (PH) model (*N* = 428)

Variable	All-cause mortality, Hazard Ratio (95% CI)
Persistence with AET	
Yes	Reference
No	**9.48 (2.14, 41.95)****
Age at diagnosis (year)	**1.12 (1.02, 1.22)***
Marital status	
Married	1.35 (0.22, 8.43)
Not married	Reference
Dual Medicare and Medicaid eligibility status	
Dual eligible	2.79 (0.67, 11.57)
Medicare only	Reference
Stage	
Stage I	Reference
Stage II	1.22 (0.17, 8.92)
Stage III	1.17 (0.09, 14.59)
Tumor size	
<1cm	Reference
1-2cm	0.23 (0.03, 1.71)
>2cm	0.42 (0.04, 4.39)
Commission on Cancer (CoC) accreditation	
Yes	**0.11 (0.02, 0.72)***
No	Reference
Facility beds	
<100 beds	1.47 (0.29, 7.54)
100-199 beds	2.17 (0.45, 10.37)
>=200 beds	Reference
Breast cancer surgery type	
Mastectomy	Reference
Breast conserving surgery (BCS)	0.31 (0.07, 1.45)
Baseline number of hospitalizations	0.95 (0.62, 1.46)
No. of breast-cancer-related follow-up visits	0.55 (0.30, 1.01)
No. of unique prescription drugs co-administered	0.97 (0.88, 1.07)

95% CI = 95% confidence interval
**p* < 0.05, ***p* < 0.01

CHAPTER 6

OVERALL CONCLUSION

This study used a large dataset that integrated cancer registries, Medicare claims, area population data, and facility/provider information to examine AET utilization and use behaviors among breast cancer survivors in four states of Appalachia. It is innovative in terms of establishing an approach to systemically evaluate the relationships between AET utilization, adherence and persistence with determinants of access to cancer care in an underserved region like Appalachia in which significant deficiencies of access to care exist. It is also significant in the sense of further exploring whether and to what extent adjuvant treatment use disparities could result in breast cancer survival disparities in Appalachia. There are several major findings in this study that may contribute to current evidence of this issue in the literature.

6.1 Major findings

First, we found that the Appalachian region has disadvantaged AET utilization and use behaviors. The prevalence of receiving guideline-appropriate AET among invasive, non-metastatic, and HR-positive breast cancer survivors was only 47.6% in our Appalachian population, which was much lower than the national average rate (74%) identified in a nationwide Medicare population with Part D benefits by using the SEER and Medicare data.[116] The large discrepancy may be, in part, due to significant adjuvant treatment disparities in Appalachia, or because of our study design that included new users who

used endocrine therapy for adjuvant treatment use only. Therefore, to better delineate this problem, future research comparing the prevalence rates in Appalachian counties with non-Appalachian counties in these states is definitely warranted. Moreover, the two-year AET non-adherence and early discontinuation rates in the Appalachian breast cancer patient population were 31% and 30%, respectively, which also seem to be inferior to the rates in non-Appalachian populations in the U.S.[27,28,116,117,123,138,139] Overall, AET use is found to be a vital and pressing issue among Appalachian breast cancer survivors, which calls for effective, targeted interventions to alleviate adjuvant treatment use disparities in this region.

Second, inadequate medical and drug insurance coverage may be a critical barrier to AET access and use in the Appalachian breast cancer population. We found that the dual eligibility of Medicare and Medicaid determining the qualification of receipt of LIS was a significant factor contributing to AET use. Some breast cancer patients may not be poor enough to qualify for Medicaid, but the high expenses associated with cancer care and treatments may still be a significant financial burden to the patients and their families, which may make cost one of the most important determinants of access to and utilization of these treatments. Needless to say, there is a large indigent population in Appalachia. In addition, we found that adherence to and persistence with AIs were more likely than with tamoxifen to be influenced by out-of-pocket drug costs, dual-eligible status, and whether in the coverage gap. We speculate that the higher drug costs associated with AIs than with tamoxifen was one of the primary causes of better adherence and persistence with AIs than with tamoxifen in our population. The implementation of Part D has offered important opportunities for Medicare beneficiaries

to have better access to medications[116] and reduced cost-related medication non-adherence.[112] Yet there may still be barriers for breast cancer patients to access and maintain using high-cost cancer treatments, which warrants joint efforts from different stakeholders to improve guideline-appropriate medication access and use.

Third, other than the fact that insurance status and coverage can impact both AET access and use behaviors, we found that individual level potential access such as socioeconomic and geographical factors can exert significant influences on the receipt of AET but not on AET adherence and persistence. In fact, AET adherence and persistence may still be matters of medication-related characteristics. Appalachian breast cancer patients who travelled longer to receive cancer care were significantly less likely to receive guideline-recommended AET. And, patients who lived in Pennsylvania were more likely to get access to guideline-recommended AET than those who did not, which also supplemented the findings from previous studies of superior breast cancer screening and treatment use in Pennsylvania compared with other Appalachian states.[5,63] These findings may imply significant geographic variations of adjuvant treatment use in Appalachia, which may be crucial for resource allocation and leverage in such a largely rural and economically distressed region with limited resources available. On the other hand, non-adherence and early discontinuation with AET may be more driven by factors such as drug-related adverse effects. For instance, we found that pain may be an important factor causing AI non-adherence and non-persistence. We primarily assessed symptomatic, common side effects associated with AET, but rare, severe adverse effects or fear of these side effects may also relate to patient use behaviors of AET. The importance of treatment choice and medication-

related factors may have some implications for helping design the mechanism of effective interventions to improve AET use behaviors in Appalachia.

Finally, we identified significantly positive influences of AET adherence and persistence on overall survival among Appalachian breast cancer survivors. Along with the findings among patients in other regions,[122,137] our confidence is further increased concerning the positive link between AET adherence/persistence and overall survival among HR-positive, non-metastatic breast cancer. Although the current literature, including this study, does not have adequate sample size and follow-up time to identify the effects of AET adherence and persistence on other direct cancer outcomes such as breast cancer recurrence and breast-cancer-specific survival, existing evidence still suggests the benefits of improving AET adherence and persistence in achieving more marginal gains in cancer survival among breast cancer survivors.

6.2 Study implications

Our results showed the value of improving AET adherence and persistence in benefiting survival and the unsatisfactory AET use outcomes in Appalachia, which implies the importance of ensuring appropriate use of AET to potentially reduce breast cancer mortality disparities that continuously exist in this region. However, developing evidence-based interventions to directly advance AET use behaviors is a continuous challenge for breast cancer survivorship care.[178–180] To our knowledge, there has been no effective intervention available to promote AHT utilization and use behaviors. Our study findings may help build on the current knowledge of the potentially effective intervention strategies for this purpose. We found that patient access to and utilization

of AET may be largely attributable to logistical barriers in Appalachia, which implies that an intervention aiming to reduce access barriers and disparities in underserved regions may work. Patient navigation, which has played a critical role in cancer care, was originally proposed as a means of improving timely access to screening, follow-up, diagnosis, and treatment in underserved populations.[181] The patient navigator is a specially trained person (e.g., healthcare professional, social worker, trained lay person, etc.) whose fundamental role is to assess and reduce barriers to care. Traditional patient navigation models focus on instrumental or informational support or reducing logistical barriers associated with areas such as finance, insurance, transportation, coordination, and communication with healthcare providers.[182] However, the well-established patient navigation model in cancer care has been successfully applied to various aspects of the breast cancer disease trajectory, but not to medication adherence.[183] According to our findings that AET adherence and persistence were significantly influenced by medication-related factors such as drug-related side effects, we feel an important component targeting medication management may be missing in current patient navigation models in breast cancer care. Adding Medication Therapy Management (MTM) services to the patient navigation model may be an effective solution to this challenge. MTM refers to the medical services provided by pharmacists or qualified providers to optimize therapeutic outcomes via improving medication use.[184,185] It has been shown to reduce non-adherence and healthcare expenditures across various chronic diseases.[186] Core elements of MTM services in this model may include[187]: 1) medication therapy reviews (e.g., assessing patients' medication use behaviors, identifying potential drug-related issues); 2) a personal medication record

(e.g., medication reconciliation); 3) a medication related action plan (e.g., identifying barriers to and facilitators of AET adherence, encourage patients to make family members get involved in the treatment process); 4) intervention and referral (e.g., offering informational or technical support for AET use, referring patients to medication assistance programs); and 5) documentation and follow-up (e.g., documenting the services and communicating to patients' other health care providers, following up with patients at a regular basis if needed). The target population of the MTM component may be those breast cancer survivors who had poor AET adherence/persistence or other medication-related issues. One important targeted strategy worth noting in the MTM component is to monitor and manage AET-associated side effects. Alleviating the symptomatic side effects (e.g., vasomotor symptoms, musculoskeletal pain) through both provider management and patient self-management may help patients adhere to and persist with AET. Close monitoring is warranted for severe side effects (e.g., endometrial cancer and thromboembolism that are associated with tamoxifen, cardiovascular disease, and osteoporosis for AIs). Another important targeted strategy as part of patient navigator responsibilities is to help patients, especially elderly patients, choose a drug plan that could minimize out-of-pocket costs to reduce barriers to AET use. Although we found that insurance status and coverage were highly related to AET access and use, there is still significant room to improve in patient decision making in choosing optimal insurance benefits.[116,188–190] Navigators may help them better understand their prescription drug plans and find the one that could minimize out-of-pocket costs based on the individual patient's situation.

6.3 Testing the conceptual model

The conceptual model we proposed and tested was based on the Donabedian's structure-process-outcome framework[141], Andersen's behavioral model for health service use[142,143] and an extension of the Andersen's model proposed by Pam Short and Roger Anderson (unpublished work), Hendren and colleagues' cancer health disparity model,[144] and the findings of published empirical work regarding AET medication use. In light of our results, constructs from the Andersen's model such as predisposing factors (e.g., marital status and geographic residence) and enabling factors (e.g., travel time to receive care and dual Medicaid and Medicare eligibility) were related to the receipt of guideline-recommended AET. In other words, Appalachian breast cancer patients with superior individual level potential access were more likely to get access to appropriate adjuvant treatments. On the other hand, AET adherence and persistence were primarily associated with medication-specific characteristics such as side effects and drug costs. We did not find significant impacts of system-level potential access and realized access (facility/provider characteristics and care coordination) on AET utilization, adherence and persistence. We also identified the positive associations between AET adherence/persistence and overall survival. Overall, the conceptual model was generally informative and appropriate to guide the analyses of this study, but incorporating more psycho-behavioral factors may advance the prediction of AET use behaviors. Additionally, this study was not able to test several important constructs in the Hendren and colleagues' cancer health disparities model[144] such as patients' medical and medication knowledge/beliefs, patient activation, and providers' cultural competency, which warrants future research efforts.

6.4 Study limitations

Next, the main limitations of the study are briefly reiterated. First, the retrospective claims study design prevented causal inferences; the assumptions of using claims data to study medication use behaviors may not always hold in reality, which may induce potential measurement errors or bias. In addition, the Medicare Part D claims data we used may also have some limitations. For instance, when patients were in the coverage gap, they might obtain AET from other sources than Medicare Part D, which may not be captured in our dataset. In addition, patients with dual eligibility may receive additional subsidies from their Medicaid programs to help with their out-of-pocket money, which were not able to be included in our calculation of out-of-pocket drug costs. Second, because of limited data accessibility and availability, we were not able to include some important, detailed information in our analyses, such as individual-level educational attainment and household income, treatment facility location, prescriber's information, pharmacy type, accurate drug indications, and drugs used in the hospice setting. Third, the limited sample size and length of follow-up time may refrain us from detecting significant differences in some variables. For this reason, we were not able to assess the effects of AET adherence/persistence on some other direct breast cancer outcomes such as breast-cancer-specific survival. Lastly, the generalization of our results may be limited to Medicare enrollees living in Appalachia who are slightly older than the typical breast cancer population.

6.5 Future research and overall conclusion

Based on the current literature, including this study, we find that the following areas may be warranted for future research: 1) the role of different healthcare plans on AET access and use behaviors; 2) geographic variations of AET use in Appalachia; 3) the effects of AET adherence/persistence in a long run, in a general breast cancer population with all age groups, on different health outcomes including breast cancer recurrence and survival, as well as patient-centered outcomes such as health-related quality of life (HRQoL).

In conclusion, despite the significant survival benefits from AET use and adherence among breast cancer survivors with positive HR, the prevalence of receiving guideline-recommended AET as well as its adherence and persistence is unacceptably low in Appalachia. Interventions that combine logistical barrier reduction and medication management may be effective to improve AET use in this population.

APPENDIX A
Exemption from the Institution Review Board (IRB) regulation

Health Sciences and Behavioral Sciences Institutional Review Board • 540 East Liberty Street, Suite 202, Ann Arbor, MI 48104-2210 • phone (734) 936-0933 • fax (734) 998-9171 • irbhsbs@umich.edu

To: Rajesh Balkrishnan

From:

Richard Redman

Cc:

Rajesh Balkrishnan
Sofia Merajver
Amy Kilbourne
Jennifer Griggs

Subject: Notice of Determination of "Not Regulated" Status for [HUM00062883]

SUBMISSION INFORMATION:
Title: Pharmacotherapy Evaluation Tools for Improving Breast Cancer Outcomes in Rural Appalachia
Full Study Title (if applicable): Pharmacotherapy Evaluation Tools for Improving Breast Cancer Outcomes in Rural Appalachia
Study eResearch ID: HUM00062883
Date of this Notification from IRB: 4/4/2012
Date of IRB Not Regulated Determination : 4/4/2012

IRB NOT REGULATED STATUS:

Category	Description	Sort Order
Other		16

UM is not engaged in human subjects research.

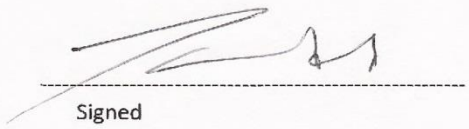
Richard Redman
Chair, IRB HSBS

APPENDIX B
Centers for Medicare and Medicaid services (CMS) data use agreement

Agreement to use CMS data for the "Breast Cancer Research" Project:

I Xi Tan unique name tanxi agree to the following:

1. Use is limited to your specific (your IRB approved proposal) project in collaboration with your mentor.
2. These data cannot be placed or stored on a portable device or personal computer. (see 3 and 8)
3. Data must be stored and used on a departmental centralized server that sits behind a firewall intended to protect sensitive personal information. This folder is on the Research Drive and is called *Breast Cancer Project*. None of the data may be stored on the C drive or any other network locations.
4. Data should not be stored on removable media without permission from Dr. Anderson.
5. You will not permit others to use or view the raw data (except your faculty mentor).
6. There can be no emailing of the data.
7. All computers will be protected with an automatic screen lock and password re-entry.
8. The use of a personal laptop as a remote desktop will only be acceptable if you do not transfer files from your remote session onto your local C drive in the laptop.
9. You must take the HIPAA and Security Awareness Training per Data Use Agreement 25507. https://maislinc.umich.edu/maislinc/app/taxonomy/learnerSearch/LearnerSearch.aspx?RootNodeID=-1&NodeID=195&UserMode=0 Print out the certificate of competition and attach.
10. If you suspect any unauthorized access or use of the data -- you will report to your supervisor and Pharmacy ITS
11. The user of the data has read the Data Use Agreement 25507 and agrees to those terms.
12. This document will be resubmitted each year.



Signed

9/13/2014

Date

To be placed in Departments Personnel file

APPENDIX C1

Manuscript 1: testing the interactions in the multivariate logistic regression models of receiving guideline-recommended adjuvant endocrine therapy (AET)

Model 1: Interaction between the state of residence and county economic status	**Odds Ratio (95% CI)**	**Model 2: Interaction between the state of residence and HPSA**	**Odds Ratio (95% CI)**
ARC's county economic status		HPSA designation	
Distressed	1.13 (0.66, 1.93)	In the HPSA	**0.48 (0.25, 0.94)***
Not distressed	Reference	Not in the HPSA	Reference
State		State	
PA	**1.58 (1.04, 2.40)***	PA	0.38 (0.12, 1.23)
Other states	Reference	Other states	Reference
State × county economic status	1.05 (0.05, 21.36)	State × HPSA designation	**4.60 (1.42, 14.81)***

Notes:

1. 95% CI = 95% confidence interval, ARC = Appalachian Regional Commission, HPSA = Health Professional Shortage Area
2. *$p < 0.05$
3. Covariates in these models included: county-level educational attainment (percentages of persons with less than high school education and at least a bachelor's degree), urban or rural geographic residence, county-level infant and cancer mortality rates, age at diagnosis, marital status, four quartiles of annual median household income (at the census block group level), dual Medicare and Medicaid eligibility indicator, average travel time from the patient to the three closes mammography centers, breast cancer stage, tumor size, lymph nodal status, patients' comorbidities, treatment facility's Commission on Cancer (CoC) accreditation status, the provider's specialty and graduation year, the number of breast-cancer-related follow-up visits, and timeliness of primary treatment initiation.

APPENDIX C2

Manuscript 1: sensitivity analysis results from the multilevel mixed effect logistic regression of receiving guideline-recommended adjuvant endocrine therapy (AET)

Variable	Guideline-recommended AET Coefficient (95% CI)
Percentage of less than high school graduate among persons aged 25 and over (%)	0.03 (-0.02, 0.08)
Percentage of at least a bachelor's degree among persons aged 25 and over (%)	0.01 (-0.03, 0.04)
Infant death rate per 1,000 births	-0.19 (-0.40, 0.01)
Annual age-adjusted, cancer-related death rate per 100,000 population	0.002 (-0.009, 0.014)
Average travel time to the three closest mammography centers (minute)	-0.02 (-0.04, 0.0003)
Baseline Charlson Comorbidity Index (CCI)	-0.09 (-0.23, 0.05)
Baseline number of hospitalizations	0.02 (-0.13, 0.17)
No. of breast cancer related follow-up visits	-0.001 (-0.06, 0.06)
ARC's county economic status	
Distressed	Reference
At risk	-0.55 (-1.27, 0.17)
Others	-0.41 (-1.25, 0.42)
Urban-rural classification	
Metropolitan	-0.20 (-0.61, 0.20)
Non-metropolitan	Reference
Health Professional Shortage Area (HPSA) designation	
Entirely within a HPSA	Reference
Partially within in a HPSA	-0.13 (-0.63, 0.36)
Not within a HPSA	0.11 (-0.55, 0.76)
Age at diagnosis	
<65	-0.28 (-0.91, 0.35)
65 to 74	Reference
75 to 84	0.10 (-0.22, 0.42)
≥ 85	0.07 (-0.44, 0.59)
Marital status	
Married	**-0.49 (-0.80, -0.18)****
Not married	Reference
Annual median household income, quartile	
Low	Reference
Second	0.01 (-0.40, 0.42)
Third	0.12 (-0.28, 0.53)
High	-0.04 (-0.46, 0.39)
Dual Medicare and Medicaid eligibility status	
Dual eligible	**1.43 (1.00, 1.87)****
Medicare only	Reference
Stage	
Stage I	0.30 (-0.62, 1.22)
Stage II	0.14 (-0.42, 0.70)
Stage III	Reference

Variable	Guideline-recommended AET Coefficient (95% CI)
Tumor size	
<1cm	Reference
1-2cm	0.20 (-0.17, 0.58)
>2cm	-0.05 (-0.70, 0.59)
Unknown	-0.88 (-2.26, 0.49)
Lymph nodal status	
Negative	Reference
Positive	0.18 (-0.36, 0.72)
Commission on Cancer (CoC) accreditation	
Yes	-0.14 (-0.47, 0.20)
No	Reference
Unknown	-0.52 (-1.43, 0.39)
Provider's specialty	
Oncologist	0.17 (-0.17, 0.52)
General practitioner	Reference
Others	0.07 (-0.37, 0.51)
Provider's graduation year	
Before 1980	-0.08 (-0.40, 0.24)
1980s	Reference
After 1989	0.05 (-0.34, 0.44)
Breast cancer surgery type	
Breast conserving surgery (BCS)	Reference
Mastectomy	0.15 (-0.20, 0.50)
Radiation therapy	
Yes	0.17 (-0.19, 0.54)
No	Reference
Chemotherapy	
Yes	0.06 (-0.23, 0.36)
No	Reference
Timeliness of primary treatment initiation	
Timely treatment (surgery within 60 days)	Reference
Delayed treatment (surgery beyond 60 days)	-0.15 (-0.73, 0.43)

95% CI = 95% confidence interval, ARC = Appalachian Regional Commission

**$p < 0.01$

Likelihood ratio test (vs. logistic regression): χ^2=0.88, $p = 0.17$

APPENDIX D1

Manuscript 2: predictors of adherence to aromatase inhibitors (AI): multivariate logistic regression (*N* = 319)

Variable	Adherence to AI, Odds Ratio (95% CI)
Percentage of at least a bachelor's degree among persons aged 25 and over (%)	1.01 (0.97, 1.06)
Infant death rate per 1,000 births	1.21 (0.54, 2.70)
Annual age-adjusted, cancer-related death rate per 100,000 population	1.00 (0.99, 1.02)
Baseline Charlson Comorbidity Index (CCI)	1.08 (0.80, 1.48)
Average monthly out-of-pocket costs (US dollar)	**0.994 (0.990, 0.998)****
Health Professional Shortage Area (HPSA) designation	
Whole county in HPSA	Reference
Part county in HPSA	0.74 (0.26, 2.12)
Not in HPSA	0.73 (0.20, 2.57)
State	
KY	0.42 (0.12, 1.52)
NC	0.17 (0.02, 1.58)
OH	0.72 (0.29, 1.79)
PA	Reference
Dual Medicare and Medicaid eligibility status	
Dual-eligible	0.96 (0.41, 2.25)
Medicare-only	Reference
Catastrophic coverage indicator	
Yes	**3.99 (1.86, 8.56)****
No	Reference
Lymph nodal status	
Negative	Reference
Positive	1.75 (0.92, 3.33)
Commission on Cancer (CoC) accreditation	
Yes	0.73 (0.39, 1.37)
No	Reference
Provider specialty	
Oncology	1.54 (0.83, 2.84)
General practitioner	Reference
Other	0.79 (0.34, 1.82)
Breast cancer surgery type	
Mastectomy	Reference
Breast conserving surgery (BCS) + radiation	0.56 (0.28, 1.10)
BCS, no radiation	0.57 (0.28, 1.19)
Use of bisphosphonates	
Yes	1.51 (0.77, 2.98)
No	Reference
Use of pain medications	
Yes	**0.41 (0.18, 0.93)***
No	Reference

95% CI = 95% confidence interval
**p* < 0.05 ***p* < 0.01

APPENDIX D2

Manuscript 2: factors associated with discontinuation of aromatase inhibitors (AI): Cox proportional hazards (PH) model, stratified by the provider's specialty and the patient's dual eligibility status (*N* = 319)

Variable	AET discontinuation, Hazard Ratio (95% CI)
Percentage of at least a bachelor's degree among persons aged 25 and over (%)	0.98 (0.95, 1.02)
Infant death rate per 1,000 births	**1.27 (1.01, 1.59)***
Annual age-adjusted, cancer-related death rate per 100,000 population	0.997 (0.986, 1.008)
Baseline Charlson Comorbidity Index (CCI)	1.02 (0.81, 1.29)
Age at diagnosis	
<65	0.66 (0.22, 2.02)
65 to 74	Reference
75 to 84	1.20 (0.77, 1.87)
≥ 85	0.98 (0.48, 2.02)
Marital status	
Married	1.17 (0.76, 1.82)
Not married	Reference
Annual median household income (US Dollar), quartile	
Low ($9,768 - $31,408.5)	Reference
Second ($31,408.5 - $ 41,552)	1.09 (0.60, 1.96)
Third ($41,552 - $51,577.5)	0.97 (0.53, 1.78)
High ($51,577.5 - $15,0625)	0.99 (0.53, 1.84)
Catastrophic coverage indicator	
Yes	**0.49 (0.27, 0.88)***
No	Reference
Lymph nodal status	
Negative	Reference
Positive	0.69 (0.41, 1.16)
Commission on Cancer (CoC) accreditation	
Yes	1.14 (0.66, 1.94)
No	Reference
Facility beds	
<100 beds	1.04 (0.51, 2.15)
100-199 beds	0.57 (0.31, 1.04)
>=200 beds	Reference
Breast cancer surgery type	
Mastectomy	Reference
Breast conserving surgery (BCS) + radiation	1.22 (0.72, 2.07)
BCS, no radiation	1.45 (0.85, 2.47)
Use of bisphosphonates	
Yes	0.72 (0.42, 1.23)
No	Reference
Use of pain medications	
Yes	1.92 (0.98, 3.75)
No	Reference

95% CI = 95% confidence interval

*$p < 0.05$

APPENDIX D3

Manuscript 2: predictors of adherence to tamoxifen: multivariate logistic regression (*N* = 80)

Variable	Adherence to AI, Odds Ratio (95% CI)
Percentage of at least a bachelor's degree among persons aged 25 and over (%)	0.85 (0.72, 1.01)
Infant death rate per 1,000 births	0.58 (0.14, 2.41)
Annual age-adjusted, cancer-related death rate per 100,000 population	1.04 (0.99, 1.10)
Baseline Charlson Comorbidity Index (CCI)	1.70 (0.73, 3.96)
Average monthly out-of-pocket costs (US dollar)	0.999 (0.978, 1.020)
Health Professional Shortage Area (HPSA) designation	
Whole county in HPSA	Reference
Part county in HPSA	11.19 (0.13, 964.68)
Not in HPSA	12.66 (0.17, 939.63)
State	
KY	0.15 (0.002, 10.36)
NC	154.95 (0.51, 47266.84)
OH	0.12 (0.008, 2.02)
PA	Reference
Dual Medicare and Medicaid eligibility status	
Dual-eligible	2.59 (0.07, 90.00)
Medicare-only	Reference
Catastrophic coverage indicator	
Yes	1.83 (0.17, 19.67)
No	Reference
Lymph nodal status	
Negative	Reference
Positive	0.06 (0.001, 2.75)
Commission on Cancer (CoC) accreditation	
Yes	4.97 (0.54, 45.53)
No	Reference
Provider specialty	
Oncology	0.21 (0.02, 1.88)
General practitioner	Reference
Other	**0.11 (0.02, 0.72)***
Breast cancer surgery type	
Mastectomy	Reference
Breast conserving surgery (BCS) + radiation	0.61 (0.02, 23.18)
BCS, no radiation	0.27 (0.01, 6.96)
Use of bisphosphonates	
Yes	0.39 (0.05, 3.14)
No	Reference
Use of pain medications	
Yes	0.16 (0.02, 1.32)
No	Reference

95% CI = 95% confidence interval
*$p < 0.05$

APPENDIX D4

Manuscript 2: factors associated with discontinuation of tamoxifen: Cox proportional hazards (PH) model, stratified by the provider's specialty and the patient's dual eligibility status (*N* = 80)

Variable	AET discontinuation, Hazard Ratio (95% CI)
Percentage of at least a bachelor's degree among persons aged 25 and over (%)	1.12 (0.97, 1.30)
Infant death rate per 1,000 births	0.48 (0.16, 1.42)
Annual age-adjusted, cancer-related death rate per 100,000 population	1.06 (0.96, 1.16)
Baseline Charlson Comorbidity Index (CCI)	3.96 (0.63, 24.93)
Age at diagnosis	
<65	
65 to 74	Reference
75 to 84	0.02 (0.0002, 1.56)
≥ 85	0.11 (0.0009, 13.82)
Marital status	
Married	0.86 (0.04, 16.42)
Not married	Reference
Annual median household income (US Dollar), quartile	
Low ($9,768 - $31,408.5)	Reference
Second ($31,408.5 - $ 41,552)	0.83 (0.01, 46.55)
Third ($41,552 - $51,577.5)	3.48 (0.11, 106.64)
High ($51,577.5 - $15,0625)	
Catastrophic coverage indicator	
Yes	2.39 (0.03, 190.23)
No	Reference
Lymph nodal status	
Negative	Reference
Positive	2.57 (0.03, 192.30)
Commission on Cancer (CoC) accreditation	
Yes	2.02 (0.19, 21.83)
No	Reference
Facility beds	
<100 beds	4.86 (0.23, 103.64)
100-199 beds	1.06 (0.03, 36.05)
>=200 beds	Reference
Breast cancer surgery type	
Mastectomy	Reference
Breast conserving surgery (BCS) + radiation	1.22 (0.72, 2.07)
BCS, no radiation	1.45 (0.85, 2.47)
Use of bisphosphonates	
Yes	
No	Reference
Use of pain medications	
Yes	0.54 (0.007, 40.15)
No	Reference

95% CI = 95% confidence interval

*$p < 0.05$, **$p < 0.01$

Note that we did not present the results in a very small cell or with an extremely large standard deviation.

APPENDIX D5

Manuscript 2: sensitivity analyses of predictors of adherence to adjuvant endocrine therapy (AET): multivariate logistic regression (*N* = 428)

Variable	Adherence to AI, Odds Ratio (95% CI)		
	0.6 cut-off point	**0.7 cut-off point**	**0.9 cut-off point**
Percentage of at least a bachelor's degree among persons aged 25 and over (%)	0.96 (0.92, 1.01)	0.97 (0.93, 1.02)	1.01 (0.97, 1.04)
Infant death rate per 1,000 births	0.80 (0.44, 1.46)	1.09 (0.62, 1.92)	1.37 (0.84, 2.21)
Annual age-adjusted, cancer-related death rate per 100,000 population	1.01 (0.99, 1.02)	1.01 (0.99, 1.02)	1.00 (0.99, 1.02)
Baseline Charlson Comorbidity Index (CCI)	0.94 (0.69, 1.27)	0.96 (0.72, 1.28)	1.00 (0.78, 1.26)
Average monthly out-of-pocket costs (US dollar)	0.999 (0.994, 1.004)	0.997 (0.992, 1.001)	0.999 (0.995, 1.003)
Health Professional Shortage Area (HPSA) designation			
Whole county in HPSA	Reference	Reference	Reference
Part county in HPSA	1.56 (0.58, 4.19)	1.14 (0.46, 2.84)	1.00 (0.46, 2.18)
Not in HPSA	1.06 (0.31, 3.64)	0.93 (0.30, 2.86)	1.42 (0.54, 3.78)
State			
KY	0.36 (0.11, 1.18)	0.36 (0.12, 1.10)	0.58 (0.22, 1.52)
NC	1.36 (0.19, 9.67)	0.44 (0.07, 2.67)	0.29 (0.06, 1.33)
OH	0.59 (0.24, 1.46)	0.51 (0.23, 1.17)	0.92 (0.45, 1.84)
PA	Reference	Reference	Reference
Dual Medicare and Medicaid eligibility status			
Dual-eligible	0.99 (0.44, 2.22)	0.88 (0.42, 1.86)	1.26 (0.69, 2.33)
Medicare-only	Reference	Reference	Reference
Catastrophic coverage indicator			
Yes	**3.95 (1.63, 9.60)****	**5.24 (2.30, 11.92)****	**2.93 (1.66, 5.20)****
No	Reference	Reference	Reference
Lymph nodal status			
Negative	Reference	Reference	Reference
Positive	1.34 (0.66, 2.72)	1.40 (0.75, 2.63)	1.40 (0.84, 2.32)
Commission on Cancer (CoC) accreditation			
Yes	1.40 (0.76, 2.61)	1.07 (0.60, 1.90)	0.89 (0.55, 1.43)
No	Reference	Reference	Reference
Provider specialty			
Oncology	1.38 (0.71, 2.68)	1.31 (0.71, 2.42)	0.95 (0.58, 1.58)
General practitioner	Reference	Reference	Reference
Other	1.63 (0.63, 4.20)	0.83 (0.38, 1.85)	**0.36 (0.18, 0.73)****
Breast cancer surgery type			
Mastectomy	Reference	Reference	Reference
Breast conserving surgery (BCS) + radiation	0.65 (0.31, 1.36)	0.97 (0.50, 1.88)	0.78 (0.44, 1.35)
BCS, no radiation	0.64 (0.32, 1.31)	0.80 (0.42, 1.52)	**0.49 (0.29, 0.84)***
Use of bisphosphonates			
Yes	1.14 (0.57, 2.27)	1.19 (0.63, 2.25)	1.38 (0.83, 2.32)
No	Reference	Reference	Reference
Use of pain medications			
Yes	0.47 (0.20, 1.10)	0.53 (0.24, 1.19)	**0.41 (0.19, 0.87)***
No	Reference	Reference	Reference
AET drug class			
Tamoxifen	**2.16 (1.00, 4.68)***	**2.80 (1.35, 5.82)****	**3.22 (1.77, 5.84)****
Aromatase inhibitor (AI)	Reference	Reference	Reference
Switching between two drug classes	2.31 (0.64, 8.36)	2.50 (0.80, 7.83)	1.48 (0.63, 3.45)

95% CI = 95% confidence interval
**p* < 0.05 ***p* < 0.01

APPENDIX D6

Manuscript 2: sensitivity analyses of factors associated with discontinuation of adjuvant endocrine therapy, using the 90-day medication fill gap (*N* = 428)

Variable	AET discontinuation using the 90-day medication fill gap, Hazard Ratio (95% CI)
Percentage of at least a bachelor's degree among persons aged 25 and over (%)	0.98 (0.94, 1.01)
Infant death rate per 1,000 births	1.22 (0.98, 1.52)
Annual age-adjusted, cancer-related death rate per 100,000 population	0.99 (0.98, 1.005)
Baseline Charlson Comorbidity Index (CCI)	0.95 (0.74, 1.21)
Age at diagnosis	
<65	0.65 (0.21, 1.98)
65 to 74	Reference
75 to 84	0.97 (0.59, 1.61)
≥ 85	1.29 (0.63, 2.62)
Marital status	
Married	0.98 (0.60, 1.60)
Not married	Reference
Annual median household income (US Dollar), quartile	
Low ($9,768 - $31,408.5)	Reference
Second ($31,408.5 - $ 41,552)	0.92 (0.47, 1.78)
Third ($41,552 - $51,577.5)	0.82 (0.42, 1.60)
High ($51,577.5 - $15,0625)	1.44 (0.74, 2.78)
Catastrophic coverage indicator	
Yes	0.60 (0.32, 1.14)
No	Reference
Lymph nodal status	
Negative	Reference
Positive	**0.47 (0.26, 0.87)***
Commission on Cancer (CoC) accreditation	
Yes	0.97 (0.55, 1.72)
No	Reference
Facility beds	
<100 beds	0.95 (0.45, 2.01)
100-199 beds	0.65 (0.35, 1.22)
>=200 beds	Reference
Breast cancer surgery type	
Mastectomy	Reference
Breast conserving surgery (BCS) + radiation	0.97 (0.54, 1.74)
BCS, no radiation	1.25 (0.71, 2.20)
Use of bisphosphonates	
Yes	0.62 (0.34, 1.13)
No	Reference
Use of pain medications	
Yes	**1.94 (1.01, 3.73)***
No	Reference
AET drug class	
Tamoxifen	**0.43 (0.22, 0.83)***
Aromatase inhibitor (AI)	Reference
Switching between two drug classes	0.43 (0.15, 1.24)

95% CI = 95% confidence interval, *$p < 0.05$

APPENDIX D7

Manuscript 2: selected results of sensitivity analyses of the associations between adjuvant endocrine therapy (AET) non-adherence/non-persistence and all-cause mortality, using Cox proportional hazards (PH) models (*N* = 428)

Model	Variable	All-cause mortality, Hazard Ratio (95% CI)
Model 1	Non-adherence to AET, defined as MPR < 0.6	**6.32 (1.61, 24.86)****
Model 2	Non-adherence to AET, defined as MPR < 0.7	**9.53 (2.19, 41.41)****
Model 3	Non-adherence to AET, defined as MPR < 0.9	**8.60 (1.92, 38.66)****
Model 4	Non-persistence with AET, defined as at least 90-day medication fill gap	**3.71 (1.03, 13.37)***

95% CI = 95% confidence interval, MPR = Medication Possession Ratio

**p* < 0.05, ***p* < 0.01

Covariates in these models included: age at diagnosis, marital status, marital status, dual Medicare and Medicaid eligibility indicator, breast cancer stage, tumor size, treatment facility's Commission on Cancer (CoC) accreditation status, facility beds, type of breast cancer surgery, baseline number of hospitalizations, the number of breast-cancer-related follow-up visits, and no. of unique prescription drugs co-administered.

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