PREDICTING HEALTH-RELATED QUALITY OF LIFE CHANGES AND ENDOCRINE
THERAPY UNDER-UTILIZATION IN BREAST CANCER

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ABSTRACT

Laura C. Pinheiro: Predicting Health-Related Quality of Life Changes and Endocrine Therapy
Under-Utilization in Breast Cancer
(Under the direction of Bryce B. Reeve)

Women with breast cancer (BC) experience HRQOL decrements following diagnosis,

which can extend into treatment and survivorship. Poorly managed HRQOL during primary

treatment is associated with under-utilization of adjuvant treatments. As such, preemptively

identifying women who are at risk for poor HRQOL and providing targeted management early in

the care continuum may support women to appropriately receive adjuvant therapies, thus

improving outcomes.

The objectives of this dissertation were to 1) identify HRQOL patterns after diagnosis

and treatments and determine predictors of patterns, 2) examine racial/ethnic differences in

HRQOL throughout the care continuum, and 3) assess if early HRQOL patterns were predictive

of under-utilization of endocrine therapy (ET) during survivorship. This dissertation used the

Carolina Breast Cancer Study, a population-based study including 3,000 women diagnosed with

BC from 2008-2013 across North Carolina.

In Aim 1, we identified four subgroups of women with BC who experienced different

HRQOL trajectories from 5- to 25-months post-diagnosis. We found younger age, lack of social

support, and having public insurance or being uninsured was associated with an increased

likelihood of poor HRQOL.

In Aim 2, we assessed if racial disparities existed between Non-Hispanic White and

Black women in physical, social, emotional, functional, and spiritual well-being, and BC specific

domains between 5- and 25-months post-diagnosis. At 5-months, White women reported better physical and functional HRQOL, but Blacks reported greater spiritual well-being. At 25-months, White women's HRQOL scores rebounded above U.S norms, but Blacks reported physical HRQOL scores below U.S. norms and their White counterparts.

In Aim 3, using HRQOL subgroups identified in Aim 1, we estimated associations between 5-month HRQOL and ET use among women with hormone-receptor positive tumors. Poor HRQOL was not significantly associated with a woman's likelihood of ET initiation, but was significantly associated with lower likelihood of adherence.

This dissertation's contributions have important implications for clinical practice, health policy and future research. Our findings provide insights on targeted HRQOL management for women with BC. We identified associations between poor HRQOL and under-use of adjuvant treatment. Developing more equitable approaches to managing HRQOL for women with BC has the opportunity to improve outcomes.

To my parents—for always being in my corner.

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LIST OF ABBREVIATIONS

AIC   Akaike Information Criterion

ANCOVA   Analysis of covariance

BC   Breast Cancer

BCC   Breast Cancer Concerns

BIC   Bayesian Information Criteria

CBCS   Carolina Breast Cancer Study

CI   Confidence Interval

CFI   Comparative Fit Index

COPD   Chronic Obstructive Pulmonary Disease

ET   Endocrine Therapy

EWB   Emotional Well-Being

FACT-B   Functional Assessment of Cancer Therapy for Breast Cancer

FACIT-SP   Functional Assessment of Chronic Illness Therapy for Spiritual Well-Being

FWB   Functional Well-Being

HER2   Human Epidermal Growth Factor Receptor 2

HR   Hormone Receptor

HR+   Hormone Receptor Positive

HRQOL   Health-related Quality of Life

HS   High School

IOM   Institute of Medicine

LP   Latent Profile

LPA   Latent Profile Analysis

LR   Likelihood Ratio

LSM	Least Square Means
LTA	Latent Transition Analysis
MLM	Multinomial Logit Models
OR	Odds Ratio
PWB	Physical Well-Being
PRO	Patient-Reported Outcome
RDE	Residual Direct Effect
RMSEA	Root Mean Square Error of Approximation
SEM	Structural Equation Modeling
SPWB	Spiritual Well-Being
SWB	Social Well-Being
TLI	Tucker-Lewis Index

CHAPTER 1: INTRODUCTION

Over 3 million women in the United States live with breast cancer (BC), yet this group

has poorly understood physical and psychosocial needs.[1, 2][3] As screening, diagnosis and

treatment strategies improve, we expect the number of women living with BC to increase.

Women with BC experience psychosocial and physical decrements in health-related quality of

life (HRQOL) throughout surivorship.[3] In fact, having BC or having had BC is a significant risk

factor for poor mental and physical well-being relative to the general population.[4, 5] Women

experience HRQOL decrements before, during, and after their BC treatments.[3, 6] Specific patient

concerns include fear of BC recurrence or death, lymphedema, fatigue, early menopause, and

difficulty returning to work [1, 4, 5, 7] Poorly managed HRQOL in the 36-months following a cancer

diagnosis may impact long-term HRQOL and increase the risk of mortality.[8] Incorporating non-

monetary costs to patients (i.e., decrements in expected HRQOL) into cancer treatment decisions

may help deliver more patient-centered BC care. Cancer care that reflects patient needs and

preferences is consistent with the national emphasis on patient-centered care.[9-11][12, 13]

Racial/ethnic gaps in HRQOL are known to exist in the cancer and general U.S

populations, but disparities are not uniform across cancers, age groups, and HRQOL domains.[14,]

[15] Understanding how racial groups, both young and old, are affected differently by cancer will

help researchers and clinicians to more equitably manage cancer's impact on HRQOL. Previous

research indicates Black women with BC report worse HRQOL than Whites.[3, 16-21] However, a

retrospective case-control study of nearly 2,000 Medicare beneficiaries found that while racial

disparities in HRQOL are prevalent among individuals before cancer diagnosis, gaps in certain

domains narrow following exposure to the cancer care system.[14] Specifically, pre-diagnosis differences in some domains were 10 points (with Whites having higher scores than Blacks) and following diagnosis/treatment gaps narrowed to 1 point or less.[14] A possible explanation for the narrowing gaps following cancer diagnosis/treatment is that minority groups such as Blacks may have more social support throughout cancer treatment, which helps to manage the impact of cancer on HRQOL.[22] Another potential explanation is that, in general, Blacks tend to have less access to health care than Whites.[23, 24] Thus, once Black women are diagnosed with BC and enter into the health care system, HRQOL differences between Blacks and Whites may narrow because Blacks previously unaddressed needs are now being met, which impacts their HRQOL. Through this dissertation, we gained a greater understanding of racial gaps in changes in HRQOL and potentials target for improving equity in HRQOL management for women with BC.[20] To date, no study has assessed racial disparities in changes in individual domains of HRQOL in a relatively younger (i.e., not exclusively Medicare), multi-payer, racially diverse BC population.

Nearly 80% of BC cases are hormone receptor positive (HR+), meaning tumors have receptors for estrogen or progesterone hormones.[25] To reduce risk of BC recurrence, women with HR+ BC are recommended to take endocrine therapy (ET) for 5 years after primary BC treatment.[26] Despite clear benefits associated with ET (e.g., 40% reduction in 5-year risk of BC recurrence and 30% reduction in BC-related mortality), up to 30% of HR+ women never initiate therapy and, among those who do, nearly 50% are non-adherent by 5 years.[27-31] Once women make it through primary treatment-induced side effects, it is challenging to begin and continue adjuvant treatments that may lead to more symptoms and potentially worse HRQOL.[32, 33] Poor HRQOL prior to ET initiation may be an indicator of future under-utilization of life-saving

adjuvant therapies, as women struggle to acclimate to "normal" life.[32-38] Under-utilization is defined as not initiating or not adhering to therapy.[39] Preemptively identifying women at risk for poor HRQOL allows for targeted HRQOL management from BC diagnosis, which may reduce HRQOL decrements throughout care.[40, 41] Targeted HRQOL support may increase the likelihood that women adhere to adjuvant treatments. Therefore, a better understanding of patient-level characteristics associated with HRQOL patterns in women with BC and of whether HRQOL profiles predict if women are less likely to initiate and adhere to ET can help improve quality of BC care in the United States.

Numerous studies have shown differences in both health care use and HRQOL by race.[3, 16, 18, 29, 42-48] Overall, Black women are less likely to receive appropriate primary and adjuvant BC treatments.[48] Under-utilization of ET has been shown to be associated with worse BC outcomes (survival and BC recurrence).[47] Racial disparities in ET use are known to exist with Black women being less likely to initiate and adhere to therapy.[36, 39, 47, 49] Previous work has also shown the presence of primary BC treatment side effects (especially related to chemotherapy) and HRQOL during ET may lead to discontinuation or non-adherence.[32, 50-53] It is possible that such symptoms may impact Black women differently than White women, thus increasing the likelihood of inappropriate ET use. To our knowledge, no studies have explored associations among race, pre-ET HRQOL and likelihood of initiation of and adherence to ET. Furthermore, previous work in this line of research was done in small samples of older, primarily White women, which may not be generalizable to many women with BC in the United States.[36, 53] Exploring associations between HRQOL and ET use in an age and racially diverse sample is especially important, as racial disparities in HRQOL are known to exist and may impact ET use differently.[3, 19, 43, 48, 53] A greater understanding of predictors of HRQOL and ET use throughout

the cancer care continuum offers valuable insights on how best to provide targeted care management for women most susceptible to HRQOL decrements.

The **overall objectives** of this work were to identify subsets of women experiencing different HRQOL patterns during the trajectory of diagnosis and treatment, determine demographic characteristics associated with HRQOL profiles, and assess whether pre-ET HRQOL patterns were predictive of under-utilization of ET. The **central hypothesis** was that patient-specific characteristics (e.g., age at diagnosis, race, socioeconomic status) could be used to preemptively identify subsets of women with BC who experience different HRQOL trajectories *and* that HRQOL profiles following diagnosis were significantly associated with ET initiation and adherence. This dissertation determined demographic predictors of HRQOL patterns as well as whether HRQOL was associated with ET initiation and adherence among nearly 3,000 women diagnosed with invasive BC from 2008 to 2013 in North Carolina through the following specific aims:

Aim 1

Identify profiles of women with BC who experience different HRQOL trajectories from 5 to 25-months post-diagnosis.

HRQOL is often presented as a global measure, but this traditional approach does not allow for an understanding of domain-specific decrements that may be experienced among women with BC. For example, a woman may not experience poor physical well-being throughout treatment, but her emotional well-being may suffer considerably. An overall score masks this important finding, and clinicians are unaware that patients experienced a HRQOL decrement. In fact, a systematic review of HRQOL among women with BC concluded that evaluating HRQOL as a single, global measure often leads clinicians to miss granular HRQOL decrements captured by individual domains.[3] This dissertation employed innovative structural

equation modeling techniques such as latent profile analysis (LPA) and latent transition analysis (LTA) to allow scores for each domain to be controlled for simultaneously. LPA is an appealing technique, as it allows us to consider scores on individual HRQOL domains, accounting for individual heterogeneity that may be masked by using a single score to represent multiple domains of HRQOL.[54] LPA is more patient-centered than traditional approaches to assessing HRQOL and identifying women that are most susceptible to decrements, as it takes individual HRQOL patterns into account rather than aggregating across HRQOL domains into a single index.[55] Through LPA, 5- and 25-month post-diagnosis HRQOL measures were used to identify HRQOL profiles of women with BC. The approach in Aim 1 allowed for a deeper understanding of whether specific limitations (e.g., functional mobility, body image concerns) were predictive of HRQOL profiles among women with BC. As each of the time points represents different points in the cancer care continuum, it was possible that women were in one HRQOL profile during active treatment and transitioned to another profile during adjuvant treatment or survivorship. To predict such transitions, LTA, a longitudinal extension of LPA, was also used. In addition, through multinomial logistic regression models, non-modifiable characteristics associated with membership in a HRQOL group and transition from one profile to another over time were identified.[54]

Aim 2

Determine whether racial disparities exist in changes in six HRQOL domains (i.e., physical, social, emotional, functional, and spiritual well-being, and breast cancer specific concerns) between 5 and 25-months post-diagnosis.

Aim 2 used analysis of covariance models to assess racial variations in changes in HRQOL among women with BC. This dissertation specifically looked at differences between Non-Hispanic White (White) and Non-Hispanic Black (Black) women. Aim 2 evaluated each

HRQOL domain separately, in order to tease out domain-specific patterns, which have been shown to vary considerably by race.[14] As the approach in Aim 2 aggregated HRQOL as a single score for each domain, which is a more traditional method, conclusions were also compared to those from the innovative methods employed in Aim 1. Such a comparison informs the understanding of predictors of HRQOL in our sample. That is, it indicated racial variations in the impact of cancer on HRQOL.

Aim 3

Evaluate the association between pre-ET (within 9-months of diagnosis) HRQOL profiles and ET use following primary BC treatment among women with HR+ BC.

Understanding the relationship between pre-ET HRQOL and ET use allows us to identify women who are more likely to experience under-utilization. Aim 3 fills an important gap in the literature, offering a potential mechanism to identify women who may under-utilize ET based on HRQOL within 6-months of diagnosis. Aim 3 assessed whether a woman's HRQOL following diagnosis (i.e., HRQOL profile) was significantly associated with under-utilization of ET. Aim 3 built on Aim 1 analyses, as it used 5- month latent profiles identified in Aim 1 to determine if there was a link between active-treatment HRQOL and adjuvant treatment decisions. Logistic regression models (adjusting for demographic, treatment and tumor characteristics) were used to predict ET non-initiation and non-adherence separately. As non-initiation and non-adherence are less common, we selected these as our outcomes to minimized the degree to which odds ratios over-estimated risk. Results from Aim 3 offer a new way to identify women who might benefit from domain-specific HRQOL management, thus potentially increasing the likelihood of appropriate ET use. Using post-diagnosis HRQOL screening as an indicator for poor ET use is potentially inexpensive and easy to do with validated HRQOL instruments, which makes findings from Aim 3 particularly appealing.

Data for this dissertation came from the third phase of the Carolina Breast Cancer Study (CBCS-III), which was funded by The University Cancer Research Fund of North Carolina and the Susan G. Komen Foundation. Three datasets were combined for analyses: the CBCS-III baseline (within 9-months post-diagnosis) survey, medical record abstractions and CBCS-III 25-month follow-up (within 36-months of diagnosis) mail-in survey data. All three aims were restricted to women who completed both a 5-month and 25-month follow-up HRQOL survey. Aim 3 had two additional eligibility criteria: all women must have a HR+ tumor to ensure they were recommended to receive ET and they could not have initiated ET prior to their first CBCS-III survey.

Previous work in this field is limited, as studies were done in small samples of older, primarily White populations using generic HRQOL instruments (e.g., Short Form-36) and treating HRQOL domains independently. This dissertation used HRQOL measures from a BC-specific instrument: the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B), which was designed to be more sensitive to changes women with BC experience as well as a chronic disease instrument: the spiritual well-being domain from the Functional Assessment of Chronic Illness Therapy for Spiritual Well-Being (FACIT-SP).[56] Through this work, we gained a deeper understanding of specific demographic and clinic predictors of a composite measure of HRQOL among a large, age and racially diverse population of women with BC in North Carolina. The racial composition of the 3,000-person sample (i.e., 50% Black) offered an ideal platform to assess racial disparities in changes in HRQOL in hopes of informing strategies to more equitably manage cancer's impact on HRQOL among women with BC. As poorly managed HRQOL during primary treatment may lead to under-utilization of adjuvant treatment, preemptively identifying women at risk for poor HRQOL and providing targeted HRQOL

management early in the BC treatment process may support women to appropriately receive life-saving adjuvant therapies such as ET.[32-36, 38] This dissertation's contribution is significant, as it provides valuable insights on targeted HRQOL management for women susceptible to poor HRQOL.

This dissertation is organized as follows: Chapter 2 discusses the current peer-reviewed literature in BC on HRQOL, racial disparities and endocrine therapy utilization. Through our careful review, the gaps in the literature are clearly described and the unmet need that this dissertation fills is clearly explained. Chapter 3 outlines the overall methods used in this dissertation. For each aim, this includes study design, hypotheses, data source, study sample, power, and analytic approaches. Chapter 4, 5, and 6 are the manuscripts corresponding to the three aims of this dissertation, respectively. The study described in Chapter 4 has been published in *Breast Cancer Research and Treatment*. The studies in Chapters 5 and 6 All are currently under review in peer-reviewed journals for publication. Finally, Chapter 7 summarizes important findings from each aim, highlights clinical, health policy, and research implications of the work, notes limitations, and discusses potential opportunities for future research. Tables and figures are included at the end of each chapter. Cited references are numbered in order of their appearance in the text and are listed in the reference section at the end of the dissertation.

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

This comprehensive literature review summarizes peer-reviewed evidence on three topics related to this dissertation: breast cancer (BC), health-related quality of life (HRQOL) and racial disparities in health care. Literature for this review was identified from searches in PubMed, The Cumulative Index to Nursing and Allied Health Literature, Google Scholar, and PsycInfo. This review focuses on English-language publications in the United States written in the last 30 years. Each section below goes into detail regarding work within specific topic areas. The first section covers BC burden and biology as well as primary treatments and endocrine therapy (ET). The next section provides background regarding patient-centered care and HRQOL among women with BC. We then describe race as a social construct as well as how racial disparities are traditionally assessed in the health care disparities literature. Finally, this chapter outlines racial disparities in BC risk, screening, primary treatment patterns, HRQOL, and ET utilization. We discuss gaps in the current literature and how this dissertation fills an important unmet need by contributing to a greater understanding of predictors of change in HRQOL throughout the BC care continuum and determining whether HRQOL is associated with under-utilization of ET.

Breast Cancer

Burden

BC is the most common cancer in the world among women and is responsible for 29% of all female cancers.[57] In the United States, there were 246,660 new invasive female cases of BC and 40,890 BC-related deaths recorded in 2015.[57] Given that the 5- and 10-year BC survival rates in the U.S are 90% and 80%, respectively, the majority of women diagnosed with BC will

not die from their disease.[58, 59] As of January 1, 2014, there were over 3 million women in the

U.S living with BC or who had a history of BC.[60] With advancements in BC screening, diagnosis

and treatments, we anticipate the number of women living with BC will grow. In spite of the size

and growth of the population of women living with BC, this group does not have well

understood physical and psychosocial needs.[1, 2 3] A greater understanding of HRQOL patterns of

women with BC will inform care that is more in line with patient needs and values.

Biology

Within BC there are 21 histological and 4 molecular subtypes.[57]. Each clinical subtype

presents itself and responds differently to treatment modalities.[57] Four primary molecular

subtypes, identified through biological markers, which identify whether tumors have hormone

receptors (HR) or human epidermal growth factor receptor 2 (HER2), are used to direct

treatment selection.[57] The Luminal A subtype accounts for 74% of all BC and indicates that

tumors have positive receptors for either estrogen or progesterone hormones, but not for

HER2.[57, 61] Luminal A BCs are considered hormone receptor positive (HR+) and respond well to

endocrine therapy (ET), making them the subtype with the best prognosis for BC recurrence and

survival.[57, 61] The Luminal B subtype accounts for 10% of all BCs and, like Luminal A, also

includes tumors that HR+. Luminal B subtype tumors differ from Luminal A in that they can

also be HER2 positive.[57, 61] Luminal B subtypes are known to be more aggressive than Luminal

A, but they also respond well to ET.[57, 61] As such, Luminal A and Luminal B subtypes are often

grouped together as HR+ BCs and account for 80% of all BCs.[25] The third subtype is the HER2

enriched group, which includes tumors that do not have receptors for estrogen or progesterone,

but are HER2 positive.[57] This subtype accounts for 4% of all BCs, and has generally worse

prognosis compared to the Luminal A and B subtypes.[57] The fourth subtype is Triple Negative

tumors, which accounts for 12% of BCs and does not have receptors for estrogen, progesterone

or HER2.[57, 61] The Triple Negative subtype is twice as common among Black women in the U.S (compared to White women) and has the worst prognosis of all subtypes, as they do not respond to targeted therapies such as ET.[57]

Primary BC Treatments

Surgery is the most common primary treatment approach among women with BC. Surgical treatment modalities include lumpectomy, mastectomy without reconstruction, and mastectomy with reconstruction.[62] Breast conserving approaches such as lumpectomy with radiation have been shown to achieve the similar long-term survival rates as mastectomy.[63-66] There are conflicting conclusions regarding the impacts of breast conserving and mastectomy surgical approaches on HRQOL among women with BC.[4, 67] There are studies which conclude that there is no difference in HRQOL impact between the two approaches, while other studies find that women undergoing mastectomy have better or worse HRQOL compared to women who received a lumpectomy.[4, 67] These mixed conclusions highlight the need for additional research to understand how BC treatments contribute to HRQOL over time and how such treatments are impacted by patient-level characteristics such as age, race and socioeconomic status.

Through this literature review, we found evidence that HRQOL following primary treatment varies by whether a woman received radiation or chemotherapy. [68, 69] HRQOL has also been shown to vary by the type of radiation or chemotherapy received, which many previous studies neglect to account for in their analyses.[68, 69] Radiation therapy following lumpectomy is considered guideline recommended, as it reduces the risk of BC recurrence and mortality.[70, 71] Similarly, chemotherapy following primary BC treatments among women with HR negative disease has been shown to be associated with improved BC outcomes.[72] In the last two decades, novel BC treatments, such as Herceptin, have been developed and are now used in clinical

practice.[1] While previous work provides valuable insights into treatment-related impacts on HRQOL, they may not reflect current concerns for women with BC.[2] In addition, most work was done in small samples of primarily non-Hispanic White women, which may not be generalizable to all women with BC in the U.S. Furthermore, many published studies comparing BC treatments by HRQOL did not use a patient-reported outcome (PRO) measure that had been validated in a BC population, which limits the strength and interpretability of findings.[62, 73] In addition, we should not rely solely on these older publications to inform our perceptions of short and long-term treatment-related HRQOL among women with BC.[62]

Types of ET

Endocrine therapies (ET) for the prevention of BC-recurrence following primary BC treatment are widely used for HR+ BCs.[25] These adjuvant therapies work by either blocking estrogen production (Tamoxifen) or by inducing estrogen biosynthesis (aromatase inhibitors).[74] Numerous options exist including selective estrogen receptor modulators (SERMs), both non-steroidal and steroidal aromatase inhibitors (AIs), estrogen receptor antagonists, progestins, and luteinizing hormone-releasing hormones (LHRH) agonists.[75] ET options differ for premenopausal and postmenopausal women. Typically, premenopausal women take Tamoxifen and postmenopausal women take AIs.[36, 76] ET regimens are taken as daily pills for 5 years following completion of primary BC treatments.[76 36, 77]

Initiation of ET

ET is regarded as a highly effective adjuvant treatment strategy (i.e., 40% reduction in BC recurrence and 30% reduction in BC-related mortality) for women with HR+ disease.[27-31, 78] According to clinical practice guidelines, ET is indicated for all HR+ BC patients to reduce the risk of BC recurrence.[76] Despite the well-established benefits of ET, 10-30% of eligible women never initiate the therapy.[27-31] Studies conducted in more affluent populations have shown higher

rates of ET initiation (around 80%), but studies focused on low-income women have found rates of initiation below 70%. The difference in initiation rates in these studies indicates that low socioeconomic status may be a risk factor for lower likelihood of ET initiation.[79] Self-reported reasons for non-initiation vary with women reporting fear of side effects, personal decision or high costs.[36] An observational study focusing on low-income women on Medicaid found that receipt of chemotherapy, being married, and younger age at diagnosis were significant predictors for non-initiation of ET.[80] Among women on Medicaid, receipt of breast conserving surgery as well as not receiving radiation therapy have also been shown to decrease the likelihood that a woman initiates ET.[79]

ET Side Effects

ET does not come without meaningful side effects, as it is induces both short and long-term estrogen deprivation.[74] ET side effects and symptoms have been shown to impact a woman's HRQOL.[75] Tamoxifen, the most widely used SERM, has been associated with hot flashes, vaginal dryness, dyspareunia, and decreased interest in sexual activity.[74, 81] Studies have shown that these symptoms are more prevalent in younger women taking Tamoxifen.[74] AIs are also associated with similar side effects, but because postmenopausal women typically take AIs, early menopausal symptoms that bother younger women may be of less concern for older populations.[75] Though the type and severity of side effects associated with Tamoxifen vs. AIs vary considerably, two large clinical trials assessing HRQOL among women taking AIs versus Tamoxifen for adjuvant ET found no significant differences between the two types of ET at 2 and 5 years.[75, 82-84] ET-related side effects and HRQOL decrements may also be further exacerbated by receipt of chemotherapy, which has been shown to have severe short- and long-term impacts on HRQOL.[75] Poorly managed side effects may lead women to be non-adherent to their ET. A prospective study found that side effects were significantly associated with

inappropriate ET use.[32] That is, women who experienced side effects were more likely to discontinue use of ET.[32] One study found that unpleasant side effects accounted for nearly 40% of patient-reported reasons for non-adherence to ET.[78]

Adherence to ET

Non-adherence and non-persistence to ET treatment regimens are of great concern, as women who are inconsistent in medication use or do not take the therapy for the full five years will not realize the full benefits of ET.[31, 34, 78] That is, women who do not take ET for entirety of the time recommended are known to have worse BC outcomes (i.e., recurrence and survival) compared to women who take ET for the prescribed 5 years.[34, 85] Patient-reported rates of non-adherence in clinical trials range from 23-40%.[31, 32] This rate is expected to be higher in clinical practice with estimates of non-adherence ranging from 35% at 3.5 years to 50% by 5 years.[31, 34, 86] These high non-adherence rates highlight the need for efforts targeting women who are less likely to adhere in hopes of increasing the number of women who are able to realize the full benefits of ET. This dissertation examined rates of ET initiation and adherence in an age and racially diverse sample of women with BC in an attempt to identify an early indicator (i.e., HRQOL) of ET under-utilization.

Health-Related Quality of Life

The last decade has seen a nation-wide emphasis on patient-centered care.[87] The Institute of Medicine (IOM) defines patient-centered care as, "care that is respectful and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions."[88] Traditionally, medical encounters are represented from the clinician and payer perspectives.[89] Now, however, the patient perspective is increasingly being considered through the use of PROs in clinical practice.[89] A PRO is defined as, "a report of the status of a patient's health condition that comes directly from the patient without interpretation of the

patient's response by a clinician or anyone else."[90] The patient-centered movement has tremendous potential to improve the quality of care patients receive, as clinicians will be able to make treatment decisions that best reflect patient needs and values.[91, 92]

To ensure physicians understand patient preferences, information about patient experience must be collected directly from the patient. Collecting and utilizing PRO data is a way for patients to communicate their HRQOL to clinicians.[93] HRQOL is a multidimensional concept and is defined as "one's subjective sense of well-being in response to a major illness encompassing spiritual, functional, cognitive, emotional, psychological, physical and social well-being."[7 94] HRQOL is often presented as a global measure, but this traditional approach does not allow for an understanding of domain-specific decrements. For example, a patient may not experience poor physical well-being throughout treatment, but their emotional well-being may suffer considerably. An overall score masks this important finding, making it difficult for clinicians to realize that their patient has experienced a HRQOL decrement. In fact, a systematic review of HRQOL among women with BC concluded that evaluating HRQOL as a single, global measure often leads clinicians to miss granular HRQOL decrements captured by individual domains.[3] This dissertation assessed individual HRQOL domains separately as well as simultaneously in order to better understand the domain-specific decrements as well as identify patient-level factors that were associated with particular HRQOL domains.

HRQOL of Breast Cancer Survivors

Because BC impacts the breasts, which are a defining characteristic of the female body, the physical and psychosocial stresses related to a BC diagnosis and treatment are considered, "intimately associated with self-image, self-esteem, sexuality, femininity, and reproductive and nurturing capacity."[95] As such, 30% of women with BC report emotional and/or physical

function limitations following a BC diagnosis.[96] HRQOL concerns that arise following a diagnosis often continue to impact women for up to 20 years following the conclusion of BC treatments, especially if they are poorly managed.[96-98] Women with BC consistently report greater levels of physical and menopausal symptoms compared to healthy women their age.[99] These symptoms have been attributed to treatment regimens such as surgery, chemotherapy and ET.[99-101] Studies have also shown that having BC is a significant risk factor for poor mental well-being relative to the general population, and rates of depression are twice as high among individuals with cancer compared to adults without cancer.[4, 5, 102] As the number of women with BC grows and we aim to improve the quality of BC care, we must better understand and predict HRQOL impacts during cancer care, as HRQOL has been shown to significantly impact BC outcomes such as survival.

Physical and Functional Well-Being

Women with BC consistently report decrements in physical function during and after treatment.[103] Certain treatments, including mastectomy and chemotherapy, have been associated with particularly large declines in physical functioning.[100] Although physical well-being returns to pre-treatment levels in most women with BC within a few months of the conclusion of therapies, for some women physical well-being remains poor and may continue to worsen over time.[103, 104] Identifying predictors of worsening physical well-being among women with BC is critical, as poor physical well-being may negatively impact BC outcomes. One study found that physical functioning decrements in the two years following BC diagnosis are significantly associated with greater risk of 10-year mortality.[103] Another study concluded that functional limitations have been shown to be associated with worse overall survival among women with BC.[105] Physical and functional decline have also been shown to be significantly associated with greater risk of mortality in different race and age groups.[106] Thus, targeted support is needed for

women who are at risk for physical and functional well-being decrements during their cancer care.[99]

Mental Well-Being

Psychological stress is the most prevalent co-morbid condition reported by BC survivors following treatment.[107] Self-reported depression and anxiety have shown to be common conditions among women with BC.[108] However, emotional concerns impacting a woman's mental, emotional or social well-being are often not shared with physicians.[96] That is, women tend not to alert clinicians that they are experiencing decrements in psychosocial HRQOL and providers are less likely to ask patients about these types of symptoms. Obtaining this information and sharing it with providers may alert clinicians of patients who are experiencing particular decrements. Previous studies have found no significant differences in mental HRQOL among BC treatment groups, which may make it difficult to identify women based solely on treatments received.[100] For example, receipt of chemotherapy has been show to be significantly associated with worse HRQOL, but a longitudinal study comparing mental health by receipt of chemotherapy found no significant differences.[104] However, this study used the SF-36, a generic measure of HRQOL, which may not be sensitive to BC-specific decrements in mental well-being. Further work using appropriate HRQOL instruments is needed to better understand the mental health impacts associated with exposure to the cancer care continuum.

Although decrements in mental well-being following a BC diagnosis are common, some women also experience positive growth during cancer care, which may help ameliorate the impact of cancer on their mental health.[99] That is, some BC survivors have reported that, although BC diagnosis and treatment challenged them, it also gave their lives a new sense of meaning and purpose.[99] This is referred to as "posttraumatic growth (PTG)" and is defined as "positive changes in self-perception, interpersonal relationships or life philosophy following a

traumatic life event."[109, 110] PTG has been shown to mitigate the negative impacts of BC on mental well-being.[110, 111] Interventions supporting PTG among women with BC may help reduce mental HRQOL decrements associated with BC diagnosis and treatment.[111]

HRQOL Differences by Age

Most studies consider the cutoff between "younger" versus "older" women with BC to be age 50 years, as this is the average age when menopause begins in the U.S.[112] A systematic review of HRQOL in younger women with BC published in 2012 found that, overall, women with BC under age 50 years report worse HRQOL compared both to the general population as well as to women with BC over age 50 years.[112, 113] In general, HRQOL gaps between younger and older women were larger in mental well-being than in physical well-being.[112, 113] Some studies that indicated that older women experienced slightly worse physical well-being, while other studies found no significant differences between older and younger BC patients.[112, 113] Across studies reviewed, younger women experienced more frequent and severe treatment-related symptoms as well as psychosocial HRQOL decrements related to fear of recurrence, early menopause and infertility.[112] The most prevalent psychosocial concerns across articles were depression, stress and anxiety.[112]

A proposed explanation for age-related HRQOL differences is that, compared to older women with BC, younger women struggle more in adapting to life with BC.[114] That is, as younger women are more likely to work outside of the home, care for children, and have more financial responsibilities; they report higher levels of disruption of these activities compared to older women.[102, 114] Fertility complications and early menopause following treatments are also more concerning for younger women.[114-116] Such treatment-related side effects are considered "age-inappropriate" and have been shown to negatively impact mental health in women under age 50 years.[114] Mental well-being decrements (e.g., depression) in women experiencing such

age-inappropriate impacts of BC were even greater among women under age 35 years.[114] Younger women are also known to present with more aggressive BC and are more likely to undergo aggressive BC treatments in order to increase chance of survival, which may lead them to experience greater HRQOL impacts than older women.

Several studies showed that older women had mean scores across HRQOL domains that were not significantly different from non-cancer populations.[112, 113, 117] A potential explanation for this is that among older women, a BC diagnosis is not as surprising, as the risk of BC is known to increase with age.[102] Conversely, younger women do not often perceive themselves at risk for BC so their diagnosis may be rather emotionally disruptive.[102] Regardless of age, social support and optimism have been shown to help women cope with BC and have better HRQOL outcomes.[102, 108]

HRQOL and Chemotherapy Use

Chemotherapy is used following breast conserving surgery to prevent disease recurrence.[98] Chemotherapy is especially important with HR negative tumors, as these tumors do not respond to ET.[70] Although the clinical (e.g. survival and recurrence) benefits of chemotherapy make it quite appealing, women receiving chemotherapy may be at greater risk for HRQOL decrements compared to women who do not undergo this therapy.[98] Receipt of chemotherapy has been associated with long-term body image concerns, fear of recurrence and worse sexual functioning.[118] [101] A study of disease-free BC survivors found that women with no history of chemotherapy had significantly better overall HRQOL compared to women who had received chemotherapy.[119] That is, after adjusting for demographic, clinical and treatment characteristics, receipt of chemotherapy was a significant predictor of poorer long-term HRQOL.[119] Given the link between receipt of chemotherapy and poorer HRQOL, it is important to determine whether associations between HRQOL and ET use vary by receipt of

chemotherapy. Providing HRQOL support to women undergoing chemotherapy may help support these women to continue their chemotherapy regimens and to initiate and adhere to ET.

HRQOL and ET Initiation

Psychosocial decrements in HRQOL, which arise following BC diagnosis and during treatment, such as anxiety, depression and distress, have been shown to interfere with BC treatment decisions. [95, 108] These factors also impact a woman's ability to cope with and adjust to her disease.[108] Women identified at risk for HRQOL decrements should receive targeted HRQOL support to reduce the risk of inappropriate treatment decisions. Although several studies have collected and continue to collect data on side effects and HRQOL while women take ET, to our knowledge, no studies have examined whether HRQOL prior to ET initiation is associated with ET initiation. As such, this dissertation fills an important knowledge gap as it identifies a potential early indicator of inappropriate ET initiation in women with BC.

HRQOL and ET Adherence

Some work has been done examining the association between HRQOL and ET adherence. One study examined the association between pre-ET depression, anxiety, and physical functioning and ET adherence and found that the presence of these conditions was significantly associated with non-adherence.[50] However, this study only included 91 women with early-stage BC and did not use a validated BC-specific instrument to measure depression, anxiety or physical functioning.[50] Furthermore, only 3 of the women were "non-White", which does not lend itself to reliable examination of sub-group variation in ET use by HRQOL.[50] Another study examined the association between HRQOL and ET discontinuation and did not find significant associations.[35] However, this study collected HRQOL data following ET initiation so assessments may have been confounded by ET symptoms, which have been shown to be associated with non-adherence.[35, 75] Another study conducted in Australia examined the

association between pre-ET anxiety, depression, hot flashes, musculoskeletal pain, osteoporosis and vaginal atrophy (measured by prescriptions for drugs dealing with these conditions) and ET adherence.[120] This study did not find that pre-existing conditions were predictive of ET adherence.[120] However, the study did not collect any self-reported HRQOL information to identify psychosocial and physical limitations. Although conclusions from this study are informative, due to differences in health care system structure and treatment practices, conclusions from this study may not be generalizable to women with BC in the U.S. Finally, a recent study examined the association between psychosocial HRQOL and ET non-persistence and concluded that better HRQOL was significantly associated with lower likelihood of ET non-persistence.[121] This study also found that greater levels of distress were associated with non-persistence.[121] Findings from this study help inform this dissertation, as the study used the same HRQOL instrument (FACT-B), however, the study only included 601 older (50% over 60 years) women with HR+ BC, of which only 7% were Black.[121] Chapter 6 of this dissertation presents the first study to examine associations between ET use and pre-ET HRQOL (measured by a validated, BC-specific instrument) in a large, multi-payer cohort of women with BC. Given the age and racial diversity of this cohort, the findings of this study are more generalizable to women with BC across the U.S., compared with previous studies.

Racial Disparities in Health Care

The National Cancer Institute (NCI) defines health disparities as, "differences in the incidence, prevalence, mortality and burden of cancer and related adverse health conditions that exist among specific groups in the U.S."[122] In the disparities literature, there are four competing approaches to assessing racial disparities in health and health care.[123] Each of these approaches

has its strengths and limitations, which are discussed below.

Race as Biology

The first approach views race as biological category and believes that differences in health outcomes by race can be explained by biology.[123] However, research indicates there are no biological criteria that can be universally applied to assign persons to specific racial groups."[124, 125] That is, there is a great deal of biological heterogeneity within a particular racial group, therefore, assuming that everyone belonging to the same racial group has the same genetic characteristics is not reasonable.[124] As such, the health services research field has mostly abandoned the biological view of race.

Race As a Social Construct

In contrast to race as biology, race has been described as a "complex multidimensional construct reflecting the confluence of biologic factors and geographical origins, culture, economic, political and legal factors, as well as racism."[124] In essence, race functions as a form of social stratification, as it impacts one's access to both goods and services.[126, 127] In the U.S, racial categories are linked to various important societal factors that may impact health including: socioeconomic status, racism, culture, social and economic progress, discrimination, and identity.[124] Thus, race is considered a master social category, as it is a "central determinant of social identity and obligations, as well as of access to societal rewards and resources."[124] In this dissertation, the definition of race as a social construct will be used to frame the understanding of how race impacts HRQOL and health care utilization among women with BC.[124, 126] We assessed whether there were racial disparities in changes in HRQOL among women with BC.

The Residual Direct Effect of Race on Health Care

The residual direct effect (RDE) of race on health care is another approach to assessing racial disparities in health care that, to some extent, operationalizes race as a social construct.[128-130] The RDE approach controls for all other mediators of the relationship between race and the outcome (i.e., socioeconomic status, education) and allows one's "race" to represent the unmediated effect of race on health outcomes.[128] Typically the RDE approach compares the "race" coefficient in a model that does not control for socioeconomic factors to the "race" coefficient in model that does adjust for socioeconomic factors.[130] According to the RDE, if the differences between two racial groups disappears after adjusting for socioeconomic factors, a racial disparity does not exist, although disparities by socioeconomic groups may.[130] The race coefficient in the RDE approach would still encompass unmeasurable factors such as institutional racism, different care seeking behavior and access to health care networks that are not determined by insurant status and income. A strength of the RDE approach is that it isolates the independent effect of race (from other factors) on health outcomes.[130] However, critics of this approach have said the RDE does not account for the effects of race on health outcomes that are mediated by socioeconomic factors, which may offer potential opportunities for intervention through increased education, access and social support.[130]

Institute of Medicine Approach

The Institute of Medicine's (IOM) definition of racial disparities in health care, truly conceptualizes race as a social construct linked to a range of mediating factors, including socioeconomic staus.[123, 125] The motivation behind this third disparities approach is that minority groups are overrepresented in lower socioeconomic groups and if we adjust for both race and socioeconomics, we may underestimate racial differences in health outcomes.[123] For example, Blacks have more than double the poverty rate compared to Whites.[124] According to McGuire

and colleagues, the IOM defines a disparity as the "difference in treatment provided to members of different racial or ethnic groups that is not justified by the underlying health conditions or treatment preferences of patients." [128, 131, 132] That is, a racial disparity is the difference in quality of care between two racial groups that cannot be explained by either clinical differences (i.e., disease severity), health status (i.e., comorbid conditions) or patient preference.[128, 131] When determining if racial disparities in health outcomes exist, controlling for both race and socioeconomic status may lead us to "over control" for the "causal effect of race on health."[123, 133] This approach views race as preceding socioeconomic status on the casual pathway to health outcomes.[133] That is, socioeconomic factors such as income and education are considered mediators of racial disparities.[128, 131, 133] Although the framework does not assume that race causes lower income, it acknowledges that minority groups are more likely to be of lower socioeconomic status, thus leading them to consume lower levels of health services.[128] McGuire and colleagues implemented the IOM's definition of disparities in a previous study by only controlling for clinical characteristics and patient preferences (not socioeconomic factors) and assessing racial disparities in mental health service use. This study found larger racial disparities using the IOM's definition than the RDE, which controls for socioeconomic mediators of health service use.[128] This is not surprising, as the IOM's definition of disparities allows "race" to encompass all mediating factors of health care outcomes that are not explained by an individual's clinical characteristics, health status and preferences whereas the RDE controls for all socioeconomic mediators.[128, 132, 134] A limitation of the IOM definition is that it does not acknowledge that factors such as comorbidities, disease prognosis and patient preferences are often affected by socioeconomic factors such as income, education and insurance status. For example, rates of diabetes and hypertension (comorbid conditions) are known to be higher

among Blacks than Whites and this may be attributed to not only race, but also socioeconomic factors including income and insurance.

Race and Socioeconomic Interactions

Finally, the fourth approach to assessing racial disparities considers race and socioeconomic status as distinct constructs, which have both independent and interactive effects on health outcomes.[123] That is, socioeconomic status is on the causal pathway between race and health status and it moderates the association between race and health outcomes.[124] One might also argue that race moderates the association between socioeconomic status and health outcomes. When determining differences in health outcomes between two racial groups, one should not ignore the important contribution that differences in socioeconomic status contribute.[123, 125] In fact, racial gaps may actually be exacerbated among higher or lower socioeconomic groups.[124, 125] For example, the difference in low birth weight between Blacks and Whites may be larger or smaller depending on the mother's highest level of education, indicating that race and educational attainment may have an interactive effect on low birth weight.[123] A distinct difference between this approach to measuring racial disparities in health care and the other three approaches described above is that it supports the use of examining the interactive effects of race and socioeconomic factors on health outcomes. Given that socioeconomic factors and race are both associated with HRQOL, it is likely that each of these factors moderates the association between the other and HRQOL. As such, this is the primary approach implemented in the assessment of racial disparities in changes in HRQOL described in Chapter 5 of this dissertation.

Racial Disparities in BC

The risk and burden associated with BC has been shown to vary systemically between Black and White women in the U.S.[135] According to the American Cancer Society, although White women are more likely to be diagnosed with BC, Black women are more likely to die from the disease.[57] Among White women, the 5-year relative survival rate was 92%, but it was only 81% among Black women.[57, 59] The disproportionate burden of BC experienced by Black women can be partially explained by genetic risk factors, access to screening and treatment patterns.[48] As these factors are unable to explain all of the racial differences in BC outcomes, we aimed to better understand other factors, such as HRQOL, which may help inform more equitable cancer care management.

Biological Risk Factors

The overall association between BC and age is well-established, with risk of being diagnosed with BC increasing with each additional year of life.[136] Younger age at BC diagnosis is also significantly associated with more aggressive disease and increased risk of death.[136] Overall, the median age at diagnosis is 61 years, but this varies between Black and White women with medians of 58 and 62 years, respectively.[57, 59] Black women are more likely to be diagnosed at younger ages and with more aggressive BC tumors.[48, 137, 138] A large population-based study using NCI's Surveillance, Epidemiology, and End Results (SEER) data found that more than 33% of the Black women diagnosed with BC are diagnosed before age 50 years, compared to less than 25% of the White population.[138] This SEER study also found that there was a larger representation of Black women in advanced BC stages compared to White women.[138] The racial gap widens among younger ages, as the incidence and BC mortality rates are two and three times (respectively) greater among Black women under 35 years compared to White women.[48]

Relatedly, Black women are more likely to be diagnosed with BC subtypes such as triple negative BC that are less responsive to targeted therapies such as ET and have worse overall prognosis.[48, 138]

Disparities in Screening Practices

In the last two decades, efforts to improve BC awareness and screening have increased considerably, and the rates of mammography are now similar between White and Black women in the U.S.[24, 48, 139] Therefore, we assume that screening does not explain a large proportion of the racial gap in BC outcomes.[48] Although racial gaps in mammography appear to have narrowed, previous studies have identified widening gaps in screening between socioeconomic groups.[24, 135, 139] That is, low-income women (especially without health insurance) are significantly less likely to receive mammograms compared to higher-income women.[24, 135] As Blacks are overrepresented in low socioeconomic groups and present with more aggressive BC they may be impacted differently. This highlights the importance of evaluating both the independent and interactive effects of race and socioeconomic status on health outcomes.

Disparities in Primary Treatment Patterns

Delays in BC diagnosis and treatment initiation have been shown to be associated with worse survival.[140] A meta analysis found that treatment delays of 3-6 months (as compared to <3 months) from initial consultation to treatment initiation have been shown to be associated with a 12% reduction in rates of survival.[141] Treatment delays in BC are known to exist among women who are medically underserved.[140, 142] As Blacks are over-represented in lower socioeconomic groups, they may be more likely to experience barriers related to diagnosis and treatment delays.[46] A population-based study found that even after accounting for socioeconomic status (i.e., poverty index) and access to health care (i.e., insurance coverage) Black women experienced more treatment delays in both BC diagnosis and treatment initiation compared to

White women.[142] Another study found that after accounting for demographic and clinical characteristics, Black women were 3 times more likely than White women to experience a delay in surgery of 2 months or more.[140] As Black women tend to present with more advanced and aggressive disease, disparities in treatment delays are of particular concern.[46, 142-145]

Inappropriate use of chemotherapy and radiation following surgery are known to occur among Black women and may contribute to racial disparities in BC recurrence and mortality.[70, 72] However, evidence regarding which racial group is less likely to receive chemotherapy is mixed. Adjusting for clinical and tumor characteristics, several studies concluded that Black women were less likely than White women to receive adjuvant chemotherapy following surgery.[70, 72, 143] Another study found that Black are not less likely to receive chemotherapy.[146] Among women who do initiate chemotherapy, Black women are more likely to prematurely discontinue treatment, which is significantly associated with greater risk of death.[144] Black women have also been shown to be more likely to receive "suboptimal" chemotherapy (i.e., fewer cycles of chemotherapy than recommended), which is known to increase risk of mortality.[27, 147] A study examining racial disparities in dose and intensity of adjuvant chemotherapy concluded that Black women received lower doses of chemotherapy compared to White women.[70, 148] Two other studies confirmed that Black women were less likely than White women to receive recommended radiation therapy following breast-conserving surgery, which is considered guideline recommended.[147, 149] Black women were found to be less likely to receive surgery at "high-quality" hospitals, which authors defined as hospitals that have higher rates of radiation after breast-conserving surgery.[150] These systematic differences in treatments received by Black and White women with BC may help explain contemporary disparities in BC mortality.

Beyond delays and inappropriate care, there are also differences in the type of surgery that Black and White women receive, which may also impact outcomes. However, evidence regarding racial differences in treatment patterns vary based on year of study publication, age and socioeconomic composition of the sample and by type of insurance coverage. For example, a multi-payer study of young and old women published in 2015 found that, compared to White women, Black women were 18% more likely to receive breast conserving surgery and 6% less likely to have a mastectomy, but 21% more likely to experience surgical complications and have longer hospital stays.[151] Two other studies of elderly Medicare populations published in 2002 and 2003 found that Black women were less likely to receive both breast conserving surgery and radiation therapy.[152, 153] Patterns observed in these two Medicare studies were consistent with those in a non-Medicare study published in 2006 including both young and old women in SEER, which found that Black women were more likely to receive mastectomy, less likely to have lumpectomy, and even less likely to have lumpectomy with radiation.[154] Another study from 1997, which was also conducted in an elderly BC population, found Black women were 25% less likely to undergo any kind of definitive primary therapy.[150] Structural and organizational characteristics of the health care system may partially explain racial disparities in health care service use.[145]

This mix of evidence may reflect primary treatment practice changes that have occurred over the last two decades. A particular strength of this dissertation is that women in our dataset were diagnosed with invasive BC between 2008-2013, so treatment patterns should reflect contemporary trends in North Carolina. Much of the previous work done in this area was limited to single insurance providers, Non-Hispanic White women and older age groups (i.e., Medicare only populations). Through the availability of medical record abstraction data in the Carolina

Breast Cancer Study (used for this dissertation), we were able to account for both timing and receipt of all BC treatments received in a multi-payer (e.g., private, Medicare, Medicaid) cohort of age and racially diverse women with BC, making this dissertation innovative.

Disparities in HRQOL

Racial disparities present in diagnosis and treatment may extend into survivorship and impact both short and long-term HRQOL among women with BC.[155] Racial gaps in HRQOL are known to exist, but disparities are not uniform across cancer types or even HRQOL domains.[14, 15] On average, Black women experience greater socioecological burdens that are not as common among White women.[156] Financial stressor, job insecurity, and balancing multiple responsibilities (e.g., house, parental, job) make dealing with BC more difficult for Black women.[42, 44, 156] Following diagnosis, Black women continue to struggle with these challenges, further exacerbating HRQOL decrements associated with BC diagnosis and treatment.[42, 156] In addition, Black women are less likely to be married or partnered, which may contribute to HRQOL disparities due to lack of social support in the home. Understanding how racial groups, both young and old, are affected differently by BC will help researchers and clinicians to more equitably manage cancer's impact on HRQOL.

Physical Well-Being

Previous research has indicated that, overall, Black women tend to report worse HRQOL than White women.[3] [16-21] Physical and functional well-being among Black women with BC are particularly worse than their White counterparts.[42, 156] Functional limitations following BC treatments, such as trouble pushing/pulling objects or lifting less than 10 pounds, and difficulty walking half a mile are known to be more common and severe in Black women with BC.[106] One study assessing upper-body limitations in women with BC found that after adjusting for demographic and treatment characteristics, Black women were more likely to report limitations

than White women.[157] Such limitations are of particular concern as they may make activities of daily living (e.g., showering, bathing, getting dressed) more difficult.[157] Lack of energy is seen as a greater concern among Black women than among White women.[156] Black women with BC also tend to report lower levels of physical activity, which has been associated with better physical functioning and greater overall HRQOL.[3, 20, 158] Studies have also confirmed that although BC survivors report lower levels of physical activity compared to the general population, White women have higher levels of physical activity in comparison to Black.[20, 42, 156, 158] Increased physical activity has also been shown to be associated with better physical well-being and vitality.[20, 42, 156, 158]

Mental Well-Being

Compared to Black women without a BC diagnosis, Black BC survivors have been shown to report greater levels of fatigue, hot flashes and poorer sleep quality.[22] However, Black women with BC also report greater social support (with their church, communities and God) as well as positive growth following BC diagnosis/treatment compared to White women.[22, 159] Social support and positive growth may help mitigate depression that is often associated with a BC diagnosis and may reduce cancer-related stress.[22] Increased community support and positive growth experienced by Black women with BC may also help explain why this group tends to report fewer mental and emotional decrements compared to White women diagnosed with BC.[22, 42, 156] For example, a study of Medicare beneficiaries found that although Blacks had lower HRQOL across eight subscales in the Short Form 36 prior to cancer diagnosis, Blacks also experienced smaller declines in role emotional, mental health and social functioning domains compared to Whites.[14] In addition, there are some psychosocial concerns that have been shown to burden White women more than Black women.[44] For instance, a systematic review found that White women were more likely to experience fear of BC recurrence and issues with body image

compared to Black women.[44] Coping mechanisms may help explain the smaller decrements in mental well-being experienced by Black women following exposure to the cancer care continuum.[14, 22]

Spiritual Well-Being

Spirituality is defined as, "experiencing a meaningful connection to our core selves, others, the world and/or a greater power."[160, 161] Spirituality is considered distinct from religiosity, which is "structured worship and practice and theological beliefs."[160] Black women with BC consistently report the importance of spirituality in coping with their disease.[156, 160, 162] Spirituality may help mitigate the effects of BC on psychosocial well-being.[44] A systematic review found that across all studies evaluated, spirituality, faith and reliance on God were critical to coping,[44] spirituality and a perceived relationship with God were thought to provide hope and comfort for women struggling with BC diagnosis and treatment and also helped manage the psychosocial burden of the disease.[159] A limited body of evidence has also supported the association between spirituality and better health status among Blacks.[163, 164] Previous work in the area of spirituality of women with BC has recommended that clinicians promote the use of spirituality as a coping mechanism among Black women with BC.[159]

The richness of the dataset used for this dissertation makes it an ideal platform to better understand racial disparities in BC. To our knowledge, this is the first study to assess racial disparities in changes in individual domains of HRQOL in a large, relatively younger (i.e., not exclusively Medicare), multi-payer, racially diverse BC population. In doing so, we were able to tease out domain-specific decrements and determine whether Black or White women were more, less or equally susceptible to such decrements. By gaining a better understanding of racial gaps in changes in HRQOL, findings from this dissertation will help support more equitable HRQOL

management for women with BC.[20]

Disparities in ET Initiation

Previous work has identified racial disparities in adjuvant therapy initiation between Black and White women with BC.[72] Several studies have assessed disparities in adjuvant chemotherapy and radiation and some have examined disparities in ET initiation.[48, 72] Evidence on whether Black women are more, less or equally as likely as White women to initiate ET have been mixed and dependent on the population of women studied. For instance, a SEER study of women diagnosed with BC in 2005-2007 in Detroit and Los Angeles found that Black women were 3 times more likely to initiate ET compared to White women.[36] This was the only study that found that Black women were more likely to initiate ET than White women. Several studies reported no difference in ET initiation between Black and White women. In a low-income, Medicaid-insured population in North Carolina, unadjusted differences in ET initiation were found between Black and White women diagnosed in 2003-2007. Once demographic and clinical characteristics were adjusted for, however, no significant racial disparities were seen.[39] Another Medicaid-insured study of women in North Carolina diagnosed with BC between 1998-2002 also found that there were no significant differences in ET initiation between Black and White women.[80] The lack of differences in ET initiation by race was confirmed in a larger study of women on Medicaid.[79] A Medicare study evaluating the association between race and ET initiation also failed to find an association, but did find that insurance status and higher level of education were significantly predictive of ET initiation.[165] Another Medicare study published in February 2016 reported racial gaps in ET initiation with Black women being 30% less likely to initiate Tamoxifen than White women.[166] Finally, a study assessing racial disparities between Black and White, commercially insured women (under age 64 years) in North Carolina found

that Black women were 17% less likely to initiate ET compared to White women.[47] This study

stratified analyses by receipt of chemotherapy, as chemotherapy was significantly associated

with lower likelihood of ET initiation.[47]

The association between receipt of chemotherapy and lower likelihood of ET initiation

has been documented in other studies as well.[80] In chemotherapy-stratified models, the racial gap

in ET initiation was even more pronounced among women who received chemotherapy, but non-

significant among those not receiving chemotherapy.[47] As Black women tend to present with

more aggressive BC and may be more likely to receive chemotherapy, this important finding

highlights a need to address racial gaps in ET initiation among Black women undergoing

chemotherapy. As chemotherapy is associated with additional treatment burden, it may serve as a

barrier to ET initiation.[47, 80] Chemotherapy-related burdens include missed days of work, lack of

transportation to numerous appointments and additional costs.[47] Given the higher representation

of Blacks in lower socioeconomic groups, Black women with BC may be more vulnerable to

chemotherapy-related barriers to ET initiation.[167] As each of the previous studies examining

racial disparities in ET initiation looked at different insurance populations separately (i.e.,

Medicaid, Medicare and commercially insured), this dissertation fills an important knowledge

gap, as it examines racial disparities in ET initiation in an age-diverse, multi-payer group of

women in North Carolina.

Disparities in ET Adherence

Once a woman initiates ET, she will either take the medication diligently as intended

(adhere), not take the medication as prescribed (non-adherent), or stop taking the medication

entirely (discontinue). In this dissertation, we focus on non-adherence to ET, as across diseases,

poor adherence is associated with worse health outcomes.[168] Given data limitations, we

operationalize ET non-adherence and discontinuation as "non-adherence", but recognize that there are differences between discontinuation and non-adherence. Within BC, women with poor adherence are known to be at increased risk of death.[28] Adherence is often measured as the number of days of medication supplied divided by total days.[33] Traditionally, patients with adherence rates lower than 80% are considered "non-adherent".[33, 169] Patients vulnerable to poor adherence should be preemptively identified and provided additional support to ensure adherence.[31, 168] Part of identifying which patients are likely to be non-adherent is determining characteristics associated with non-adherence or discontinuation. Previous studies have attempted to identify demographic and clinical characteristics associated with non-adherence to ET and have had varying conclusions regarding racial disparities.[27, 30-33, 36, 45, 50, 53, 80, 170] A recent systematic review of racial disparities in ET adherence found that, in the majority of studies reviewed, racial disparities existed, with Black women being less likely to adhere than White women.[170] Looking closer at individual studies, some concluded that there was no evidence of racial differences in ET adherence, but noted differences by socioeconomics, age and other treatments received.[30, 33, 34, 36, 45, 80] Other studies found large and significant differences in ET adherence between Black and White women with BC.[27, 31] The mix of evidence of differences between races in ET adherence highlights an opportunity to assess associations between race and ET adherence in a multi-payer cohort with an over-representation of Black women in hopes of informing the literature on racial disparities in ET non-adherence.

Conclusion

Cancer care that considers HRQOL reflects patient needs and is consistent with the national emphasis on patient-centered care.[9-11 12, 13] As the number of women with BC in the U.S. continues to grow, understanding patient-level factors that are predictive of HRQOL trajectories throughout the cancer care continuum will help inform targeted HRQOL management for

women with BC. As discussed, there is a great deal of variation in HRQOL by demographic, socioeconomic and treatment characteristics as well as by HRQOL domain. In general, previous work reflects non-contemporary treatment patterns, uses generic HRQOL instruments, and focus on single payer groups of women that lacked large representations of Black women and/or women under age 50 years. A greater understanding of predictors of HRQOL and ET use throughout the cancer care continuum will offer valuable insights on how to provide targeted care management for women most susceptible to HRQOL decrements. The demographic diversity of the dataset used in this dissertation to assess racial disparities in HRQOL and identify an early screener for inappropriate ET use make this dissertation a departure from the status quo of research in HRQOL in BC.

CHAPTER 3: METHODS

A methodological approach that accounts for heterogeneity of women with BC while parsing out nuances using specific HRQOL domains contributes to a deeper understanding of patient-level factors explaining HRQOL across BC patients of different ages and races. Furthermore, determining if HRQOL can be used as a screener for future health behaviors such as initiating and adhering to ET offers an opportunity to intervene with women who are most susceptible to under-utilization of ET. Chapter 3 describes the various approaches taken in this dissertation to examine predictors of latent HRQOL sub-groups during active treatment and survivorship, assess racial disparities during these two distinct phases of BC care, and determine if HRQOL measured during active treatment is predictive of adjuvant therapy initiation and adherence. First, as the three aims employ the same conceptual framework, a discussion of the overall conceptual model guiding this dissertation is provided. The dissertation's study design, data source, sampling and eligibility, sample size and power, and key measures are described in detail. Then, each specific aim's research questions, hypotheses, descriptive statistics and analytic approaches are explained separately. Finally, limitations to the study design, data source and analytic approach are discussed. Figures and tables referenced in Chapter 3 can be found at the end of the chapter.

Conceptual Framework

The conceptual framework used to guide this dissertation was a modified version of Andersen's Behavioral Model (Figure 1).[171] Broadly, the framework postulates that individual characteristics and health behaviors influence outcomes.[171] Specifically, the framework suggests

how individual *predisposing* (e.g. race, age), *enabling* (e.g. marital status, level of education, income, insurance status) and *need* (e.g. comorbidities, tumor characteristics) factors impact *individual use of health services (e.g.,* treatments*).* Presumably, all of these factors and practices have effects on **health outcomes** (e.g., HRQOL), which can in turn influence future health service use.[171]

Predisposing Characteristics

Race has been considered a form of social stratification, as it may impact one's access to both goods and services.[126] In this dissertation, the definition of race as a social construct was used to frame the understanding of how race impacts HRQOL and use of health services.[124, 126] Numerous studies have shown differences in health care use by race.[3, 16, 18, 29, 42-48] Overall, Black women are less likely to receive appropriate primary and adjuvant BC treatments such as chemotherapy, radiation, and ET.[48] Under-utilization of ET has been shown to be associated with worse BC outcomes (e.g., survival and BC recurrence).[47] Racial gaps in HRQOL are also known to exist with White women generally reporting better HRQOL than Black women; however, the extent of such disparities in vary across age groups, cancer type, and HRQOL domain.[14, 15]

Age-related difference in BC treatment utilization and HRQOL are also well-documented in the literature.[4, 172-175] Specifically, older women are less likely to receive certain treatment modalities (e.g., breast conserving surgery) and chemotherapy, and also experience varying decrements in HRQOL compared with younger women with BC.[4, 172-174] In general, younger women report worse mental and emotional well-being, but better physical and functional well-being compared to older women with BC.[112, 113]

Enabling Resources

Enabling resources such as social support (i.e., marital status), highest level of education attained, insurance status, urban/rural residence, and family income may impact use of health services as well as HRQOL.[176, 177] As enabling resources temporally "occur" after predisposing factors (e.g., race), they are considered mediators of the relationship between race and HRQOL. Socioeconomic status is often captured with measures of income, education and occupational status.[126] Among other reasons, accounting for socioeconomic may be important because treatment delays in BC are known to exist among women who are medically underserved (e.g., lower income).[140, 142] As Blacks are over-represented in lower socioeconomic groups, they may be more likely to experience barriers related to diagnosis and treatment delays.[46] For example, Blacks are over represented in uninsured and Medicaid populations, and lack of insurance or underinsurance has been known to be associated with worse BC outcomes.[178] Lower socioeconomic status has also shown to be significantly associated with poorer HRQOL.[177, 179] In this dissertation, insurance status, family income, and highest level of education attained were used to account for enabling resources that reflect socioeconomic status. Marital status was also controlled for, as, among cancer patients, marital status, a measure of social support, has been shown to significantly impact physical and psychological health throughout the cancer care continuum.[40, 176, 179, 180] Furthermore, whether or not a woman resided in an urban or rural environment was also controlled for, to help account for cultural norms as well as access to care. For example, previous studies have reported that women residing in rural versus urban regions are less likely to receive certain recommended treatments or delay care.[181] Predisposing characteristics such as race and age may also impact enabling resources as shown in Figure 1.[123, 124] Racial gaps in HRQOL and use of health services may differ among higher or lower

socioeconomic groups; thus it is important to account for the impact of both predisposing and enabling factors when assessing changes in HRQOL.[124, 125]

Perceived and Evaluated Need

A woman's comorbid conditions (e.g., diabetes, heart disease, hypertension) as well as tumor characteristics (e.g., tumor stage, tumor size, tumor grade, nodal status, and hormone receptor status) affect her use of health services as well as her HRQOL.[176, 182] Within the BC disease group, there are a number of histological and molecular subtypes.[57]. Each clinical subtype presents and responds differently to treatment modalities.[57] Therefore, accounting for tumor characteristics such as tumor stage and grade, as well as hormone receptor status is essential to examining their influences on HRQOL and adjuvant treatment under-utilization. A previous study in women with BC found that comorbidities such as diabetes, mental health problems and hypertension were significantly associated with women receiving less aggressive BC treatments.[174] Certain comorbidities such as obesity are also known to be related to worse BC outcomes, as obesity is strongly associated with advanced BC stage among Black women.[183] Comorbid conditions and tumor characteristics are also impacted by predisposing characteristics and enabling resources. Specifically, compared to White women, Black women are more likely to be diagnosed with invasive BC at younger ages and with present with more aggressive tumors, making them less likely to receive breast-conserving treatments.[48] In addition, Black women are less likely to receive certain recommended treatments such as surgery, radiation and chemotherapy compared to their White counterparts.[48]

Use of Health Services

The types of treatment a woman with BC receives have both short and long-term impacts on BC recurrence, survival and HRQOL.[4, 67, 101] Although studies have shown differences in HRQOL by treatment modality and HRQOL domains, there is no overall consensus regarding

the effects of BC treatments on HRQOL, as different studies have yielded conflicting conclusions.[63, 67-69, 98, 175, 184-186] With respect to longer-term ET specifically, no studies have examined the association between pre-ET HRQOL and ET initiation and adherence in a large, age and racially diverse multi payer cohort of women with BC.

Health-Related Quality of Life

A patient-reported outcome (PRO) is defined as, "a report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else."[90] PROs are considered the gold standard for reporting a patient's HRQOL. Previous studies have shown that using PRO data in oncology settings can increase clinicians' awareness of symptoms and improve patient well-being.[11, 13, 92, 187] HRQOL is a multidimensional concept and is defined as, "one's subjective sense of well-being in response to a major illness encompassing spiritual, functional, cognitive, emotional, psychological, physical and social well-being."[7 94] HRQOL outcomes in this dissertation were measured by the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) and the Functional Assessment of Chronic Illness Therapy for Spiritual Well-Being (FACIT-SP). More detailed descriptions of the HRQOL measures used are included below.

BC Care Timeline

The median time from diagnosis to the initial survey among women in CBCS-III was 5.1 months, with 75% of women having their survey within 6.2 months of diagnosis and 91% completing the survey within 9 months.[46] "5-months post-diagnosis" represents a time period where women are typically in an active treatment phase (i.e., receiving surgery, radiation, chemotherapy). As this first assessment point occurs after diagnosis and likely after treatment initiation, many women will have experienced initial treatment-related decrements in HRQOL. Therefore, we anticipate that most women will experience a HRQOL rebound by their second

assessment point. That is, we anticipate that many women will experience improvements in HRQOL from the active to survivorship phases of assessment. "25-months post-diagnosis" indicates a time where most women have concluded active treatment and may be receiving longer-term adjuvant treatments such as ET, but may still be recovering from complex active treatment plans. This may also represents a time where women are in post-active treatment survivorship phases of care, which may include ongoing adjuvant endocrine therapy. As the second HRQOL assessment point occurs on average 25 months after BC diagnosis, we anticipate many women will experience improvements in HRQOL from the first assessment point Considering these two distinct time periods in the cancer care continuum for women with BC is important when conceptualizing the three aims for this dissertation.

<u>Study Design</u>

This dissertation was an observational longitudinal cohort study using existing, secondary data from the third phase of the Carolina Breast Cancer Study (CBCS). Data were collected at two time points with the first being on average 5 months after BC diagnosis and the second on average 25-months from BC diagnosis. For this study, all women had their first survey completed by 9 months from diagnosis and their second survey completed by 36 months from diagnosis. Since the average time to first survey was 5-months, we refer to this as the "5-month survey" and the average time to the follow-up survey was 25 –months we refer to this survey as the "25-month survey." Aim 1 used demographic, clinical, tumor, and HRQOL data from both time points to identify latent HRQOL subgroups of women with BC (via latent profile analysis) and determine predictors of subgroup membership as well as transitions between subgroups over time. Aim 2 assessed differences between Black and White women's HRQOL changes from 5 to 25-months following diagnosis, adjusting for demographic, clinical, and tumor characteristics from the first time point. Finally, Aim 3 used subgroups constructed from the HRQOL measures

at the first time point to predict use of health services (i.e. ET initiation and adherence) at the second time point, adjusting for demographic, clinical, and tumor characteristics from time one.

Data Source

Data for this dissertation came from the third phase of the Carolina Breast Cancer Study (CBCS-III) (funded by The University Cancer Research Fund of North Carolina and the Susan G. Komen Foundation). For my analyses, I compiled data from four distinct data sources: CBCS-III baseline (within 9-months of diagnosis), medical record abstraction, pathology report, and the 25-month follow-up telephone and mail-in survey.

CBCS-III includes 3,000 women diagnosed with invasive BC for the first time between 2008 and 2013 across 44 counties in North Carolina.[46] The study team collaborated with the North Carolina Cancer Registry to identify women across the state via rapid case ascertainment.[188] Women enrolled in CBCS-III were 20-74 years old North Carolina residents at the time of diagnosis with an incident, pathologically confirmed invasive BC.[46] To ensure representation of younger Black women, eligible women were sampled from four strata (sampling fractions indicated in parentheses): Black women under 50 years (100%), Black women 50 years and older (60%), Non-Hispanic White women under 50 years (40%), and White women 50 years and older (15%).[46] Through this sampling strategy, 50% of the overall cohort is composed of Black women. Women included in the CBCS-III are intended to represent women across North Carolina and, therefore, include women in rural and urban settings, privately and publically insured (and uninsured), of varying income levels and residing across 44 counties of the state.[46] Data were collected in-person by nurses within 9-months of diagnosis.[46, 189] Participants also completed a HRQOL questionnaire (FACT-B and FACIT-SP surveys) and consented for researchers to abstract their medical record data.[46, 188, 189] On average, 20 months after the first survey and 25-months after diagnosis, women completed a follow-up mail-in

survey, which included ET adherence questions, FACT-B and FACIT-SP surveys and a Disability of Arm, Hand and Shoulder (DASH) survey.

Sample and Eligibility Criteria

As this dissertation was focused on changes in HRQOL over time, all three study aims were restricted to women who completed both a 5-month and 25-month follow-up mail-in survey. A flow diagram of the exclusions made to construct the final study cohort is shown in Figure 2. Of the 2,998 women who completed an initial survey, 2,561 (85.4%) completed a 25-month follow-up mail-in survey. Of the 2,561 women who completed both surveys, 67 (2.6%) women were excluded because they identified as "other race." Since this dissertation was specifically focused on racial gaps between Non-Hispanic Black and Non-Hispanic White women, 30 women identifying as "Hispanic" were excluded leaving 2,464 women. Since women with distant stage BC made up a small proportion (<3%) of the cohort, these women were excluded so the cohort would be more homogenous in tumor and treatment characteristics. As such, there were 2,142 women eligible for analyses. The third aim includes two additional eligibility criteria. First, all women must have a HR+ tumor to ensure they would have been eligible to receive ET. This group was eligible for the ET adherence analyses. Second, women could not have initiated ET before their first survey so that taking ET, which is associated with worse HRQOL and side effects, would not confound the first HRQOL assessment. Of the 2,142 women included in Aims 1 and 2, 1,599 had HR+ disease, 1,114 initiated ET, and of these, 953 women did not initiate ET before their first CBCS survey. Of the 953 women who initiated after 5-months, 799 women initiated ET within 36 months and 154 did not. Thus, the cohort for the Aim 3 ET adherence analyses included 1,114 women who initiated ET and the Aim 3 ET initiation analyses included 953 women who initiated after 5-months.

Statistical Power

Sample size and statistical power requirements are not well established in the latent profile analysis literature.[190] A recent literature review of the 38 studies using latent profile analysis between 2007 and 2010, found that the median sample size was 377 individuals.[190] A key element to determining the correct sample size is the distance between latent profiles, which cannot be determined a priori. A review of the literature concluded that a sample size of at least 500 individuals is prudent for latent profile analysis.[190] For Aim 1, we included 2,142 women, which we assumed was a large enough sample to perform our analyses.

For Aim 2, there were 2,142 women (1,037 or 48% Non-Hispanic Black and 1,105 or 52% Non-Hispanic White) who met the eligibility criteria described above. Given the fixed sample size, with a significance level of 5%, we were powered at nearly 100% to detect effect sizes of 2-3 points (the meaningfully important differences for each of the six FACT HRQOL domains). For Aim 3, of the 953 women with HR+ disease who did not initiate ET by their first survey, 799 (84%) initiated ET by 36-months and 154 (16%) never initiated ET. With a sample size of 953 women and a significance level of 5%, we were powered at nearly 100% for Aim 3 ET initiation analyses. For the ET adherence analyses, we included all HR+ women who initiated ET (1,114 women) and were also powered at nearly 100%.

Key Variables and Measures

All variables listed in Table 1 for the three specific aims came from the CBCS-III 5-month post-diagnosis survey, 25-month telephone or mail-in follow-up survey, pathology report and medical record abstraction datasets.

HRQOL Measures

The two HRQOL instruments used in this dissertation were the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) and the Functional Assessment of Chronic Illness Therapy for Spiritual Well-Being (FACIT-SP). The FACT-B is a 37-item BC-specific instrument including 5 domains: physical (PWB), social (SWB), emotional (EWB), and functional well-being (FWB) and BC-specific concerns (BCC).[191] PWB includes 7 items, SWB 7 items, EWB 5 items, FWB 7 items and BCC 9 items.[56] The FACT-B has been previously validated and shown to be sensitive to change for women with BC, reliable and easy to use.[56] The FACT-B overall score ranges from 0 to 148 with higher scores indicating better HRQOL.[192, 193] The minimally important differences (MIDs) or the smallest difference that clinicians or patient perceive as clinically meaningful or important, for FACT-B domains are: BCC (2-3 points), PWB (2-3 points), EWB (2 points), and FWB (2-3 points).[194, 195] The SWB domain does not have a previously identified MID. [194, 195]

The FACIT-SP is a 12-item instrument specific to a chronic disease and includes the spiritual well-being domain (SPWB).[56] The FACIT-SP has also been previously validated and is the most commonly used instrument to measure spiritual well-being among individuals with cancer.[192, 196] The FACIT-SP includes three factors to measure overall SPWB: meaning, peace and faith, which have been shown to be independent predictors of HRQOL and not encompassed in the EWB and MWB domains.[193, 196, 197] The overall FACIT-SP ranges from 0 to 48 with higher scores representing better SPWB.[192] Each of the factors (meaning, peace, faith) range from 0 to 16.[192] As with the FACT-B, high scores on the FACIT-SP Higher scores on both the FACT-B and FACIT-SP indicate better HRQOL.[192, 193] The SPWB domain does not have an established MID.[194, 195]

Demographic Covariates

The self-reported demographic characteristics included in our analyses were age at diagnosis, race, smoking status, and body mass index (BMI), which were obtained from the CBCS-III 5-month survey. We also adjusted for a pre-specified list of comorbid conditions (e.g., diabetes, chronic obstructive pulmonary disease, obesity, hypertension, and heart disease), which came from the medical record abstraction dataset.

Socioeconomic Covariates

The socioeconomic covariates in Aims 1-3 include: marital status, level of education, and insurance status (all measured at 5-months). Given the high degree of collinearity between urban/rural residence, family income, insurance and education, socioeconomic covariates were ultimately limited to marital status, education and insurance status. Consistent with prior studies, the preliminary analyses suggested that the combination of education and insurance status was generally representative of socioeconomic status.[135] Furthermore, neither education nor insurance status exhibited missing values, whereas missing data were evident for the family income and urban/rural residence variables.

Treatment Covariates

We adjusted for surgery type (e.g., lumpectomy, mastectomy and mastectomy with reconstruction), and receipt of radiation, chemotherapy, and Herceptin. Treatment characteristic variables were obtained from the medical record abstraction dataset.

Tumor Covariates

In Aims 1 and 2, we examined unadjusted racial differences in tumor stage, tumor size, tumor grade, nodal status, and hormone receptor status (ER+, PR+, HER2+). However, due to high degrees of correlation between tumor stage, size, grade and nodal status, we only controlled for tumor stage and grade in our analyses. In addition, we constructed a "HR+" variable that

combined women who were ER or PR positive or borderline. Finally, because women who were HER2+ are often recommended to receive Herceptin, but all HER2+ women may not receive Herceptin, we only controlled for receipt of Herceptin in Aim 1-3 analysis since treatment rather than the marker itself would be more plausibly tied to the outcome of HRQOL. As Aim 3 only included women with HR+ disease, the tumor variables examined for this aim were tumor stage, tumor size, tumor grade and nodal status. Consistent with Aims 1 and 2, tumor stage and grade were included in Aim 3 analyses. Tumor stage and grade were obtained from the CBCS-III medical record abstraction and ER, PR and HER2 status came from the pathology report data.

Analytic Approach

The following section describes analytic approaches for Aims 1-3. For each aim, specific hypotheses tested, variables used in analyses, descriptive statistics, and models run are outlined. Aim 1 latent profile and latent transition analyses were performed in R. The multinomial logit models were performed in SAS Version 9.4. All Aim 2 and 3 analyses were performed in SAS version 9.4 with two-sided statistical tests and a significance level of 5%.

Aim 1

Hypotheses

The structural equation modeling (SEM) approaches used in Aim 1 analyses were exploratory in nature, as they identified latent sub-groups of women who experienced different HRQOL trajectories during their exposure to the cancer care continuum. Before conducting our analyses, we were unsure of exactly how many latent profiles would arise at each time point. However, given our thorough literature review, we formulated several hypotheses for what we expected to see in our analyses.

These *a priori* hypotheses are described below.

Hypothesis 1: Non-modifiable characteristics including age at diagnosis, race, and socioeconomic status will be *significantly* associated with membership in HRQOL profile groups.

Hypothesis 1a: *Older age at diagnosis (older than 50) will be significantly related to profiles associated with better emotional, social and spiritual well-being, but worse physical and functional well-being HRQOL profiles.*[173]

Hypothesis 1b: *White race (compared to Black race) will be significantly associated with better physical and functional well-being HRQOL profiles.*[19]

Hypothesis 1c: *Black race (compared to White race) will be significantly associated with better emotional, social, and spiritual well-being HRQOL profiles.*[155]

Hypothesis 1d: *Lower socioeconomic status will be significantly associated with worse physical, functional, social and emotional well-being HRQOL profiles.*[177, 198]

Dependent Variables

The dependent variables for the latent profile analyses in Aim 1 were the six HRQOL domains (FACT-B and FACIT-SP): physical, social, emotional, functional, and spiritual well-being and BC-specific concerns. For the latent transition analyses in Aim 1, the categorical variable constructed from latent profiles at the second time point was used as the dependent variable in our models.

Key Independent Variables

Key independent variables for Aim 1 were non-modifiable patient-level factors including age at diagnosis, race and socioeconomic factors (e.g., education, insurance status, marital status) shown in Table 1. For the latent transition analysis, the key independent variable was the categorical variable constructed from the latent profile at the first time point.

Descriptive Statistics

First, we examined the overall distribution of demographic, socioeconomic, tumor and treatment characteristics within our cohort. Then we compared unadjusted mean HRQOL scores for each domain by non-modifiable patient-characteristics (e.g., age at diagnosis, race, education level attained, urban/rural community, income, marital status).

Cluster Analysis in Cancer

Studies using cluster analysis of symptoms to identify groups of patients at increased risk of poor outcomes were first published in the field of chronic pain, with the expectation of tailoring treatment choices to better meet patient needs.[40] Years later, cluster analysis was extended to cancer by a handful of studies, identifying patient subgroups based on coping strategies, psychosocial well-being, symptoms, and quality of life.[40, 41, 199-201] Overall, studies concluded that meaningful, distinct subgroups of patients could be identified and clinical interventions might actually have improved outcomes if they considered an individual's HRQOL status or coping strategy.[40, 41] For example, women who were in an emotionally unhealthy cluster could have been supported with therapy sessions following BC diagnosis to ameliorate the emotional impact of cancer and help them cope with their diagnosis and treatment.[40, 41] Preemptive identification of women who were at risk for decrements in mental and physical well-being during cancer care could allow clinicians to provide more patient-centered care.

More recent work used cluster analysis to identify symptom clusters and assess the impact of cluster membership on HRQOL and other health outcomes among women with BC.[202-204] Findings from such studies were quite valuable, as HRQOL has been shown to be significantly associated with cancer survival.[54] However, these studies only focused on two or three symptoms and most did not extend cluster analyses to measures of HRQOL, which can be more representative of an individual's overall well-being than isolated symptoms.[203] Of the

studies that did focus on identifying clusters of women with BC using HRQOL measures, several

combined multiple cancer types together, many were conducted outside of the U.S, most were

cross sectional and all had sample sizes of fewer than 200 women. Previous work concluded that

the next step in this line of work is to explore associations between specific patient clusters and

treatment decisions (i.e., ET use).[40] As such, this dissertation extends this novel methodology to

identify latent HRQOL sub-groups of women with BC in a large, population-based cohort.

Latent Variables

Latent variables are unobserved constructs that are represented by two or more observed

variables.[205, 206] Visually, latent variables are represented by ovals or circles.[205] The observed

measures are also referred to as indicators of the latent construct.[205] In this dissertation, the

observed measures were the individual domains on the FACT-B and FACIT-SP such as PWB,

SWB, EWB, FWB, BCC and SPWB (described above). The specific questions that make up

each domain are referred to as domain indicators.[205] Conceptually, latent variable models assume

that the HRQOL domain items measure the latent constructs, but do not cause them.[205, 206]

Latent Profile Analysis

Building on traditional cluster analyses, latent profile analysis (LPA) is a latent variable

model that uses continuous observed measures (i.e., PWB, SWB, EWB, FWB, BCC, SPWB) to

identify categorical clusters of women who experience distinct HRQOL patterns and group them

together as a "HRQOL profile" at each of the two time points.[54, 190, 205, 207] This type of approach

is optimal for identifying latent patterns within large, heterogeneous groups of individuals.[190]

Because LPA takes individual HRQOL patterns into account rather than aggregating across

individuals, it is considered more patient-centered than traditional approaches for assessing

HRQOL and identifying women who are most susceptible to HRQOL decrements.[55, 205]

Approaches that compare means and standard deviations have been criticized for not truly

representing HRQOL experienced by individuals.[75] Simply looking at changes in mean HRQOL

scores leads us to miss individuals who experience decrements, as a group's average score may

mask small decrements.[75] That is, small changes tend to disappear when comparing mean scores

and outliers who may be of interest to researchers are often ignored.[75] Unlike regression

techniques that model mean trend across the entire sample, LPA allows us to account for

heterogeneity in HRQOL among women with BC.[41, 199]

Latent variable models such as LPA or latent class analysis (used for categorical

observed measures) have also been used to address limitations in using single indices to

represent abstract, multidimensional concepts such as HRQOL.[208] HRQOL is often presented as

a single measure, but this approach does not allow for an understanding of domain-specific

decrements that may be experienced among women with BC. Recent work criticized the

evaluation of HRQOL as a single, global measure as it leads clinicians to miss decrements in

individual domains.[3] For example, a woman may not experience poor physical well-being

throughout treatment, but her emotional well-being may suffer considerably. An overall score

would not allow us to glean this important finding, and clinicians would be unaware that their

patient experienced a HRQOL decrement.   LPA considers scores on individual domains that

could be masked by using a single score to represent the multiple domains of HRQOL, making it

a strong approach to studying HRQOL in women with BC.[54, 208]

LPA Assumptions

There are some assumptions that must be satisfied in order to use LPA. First, we assume

that individuals within a latent profile are generally homogenous in their HRQOL distributions

or that there is homogeneity within each profile.[205, 209] Homogeneity is important because it

implies that patterns observed within a profile are characteristic of that particular profile, which

helps us to identify distinct patterns in the data.[205] We must also assume that variances are

homogenous across latent profiles, but this assumption can be violated and addressed through weighting and transformations.[190] Another assumption is that of local or conditional independence within latent profiles.[190, 209] The premise for this assumption is that after adjusting for an individual's latent profile membership, the values of the indicators within a particular latent profile are assumed to be independent (i.e., the errors are not correlated).[190, 209] While this assumption is necessary for latent class models, it can be relaxed somewhat for LPA models.[190] Finally, we also assume that there is latent profile separation or that item-response probabilities allow us to clearly differentiate between profiles.[205] When there is latent profile separation, if one conditions on a specific latent profile membership, a particular item-response pattern should be much more likely among one latent profile than among another latent profile.[205] That is, one profile should be more likely to have high HRQOL across all 6 observed measures than another profile if one conditions on being in the "high HRQOL profile." Latent profile separation or the "distance" between latent profiles is difficult to quantify a priori, but can be visually assessed when comparing item-response probabilities across latent profiles.[190]

LPA Model Selection

As LPA is an inherently exploratory research method, a combination of the underlying theory and model fit indices must be used to guide the selection of the best model and the ideal number of latent profiles at each time point.[205] To compare models and determine the appropriate number of profiles, we initially considered traditional fit indices including the Likelihood Ratio Test (LR Test), Akaike Information Criterion (AIC), Bayesian Information Criteria (BIC), Tucker-Lewis Index (TLI), Comparative Fit Index (CFI), and Root Mean Square Error of Approximation (RMSEA) [54] The fit indices were used to evaluate the various LPA model solutions (with increased number of profiles). For the AIC and BIC, models with lower values for these indices suggest better model fit.[205] For the TLI and CFI indices, a threshold of 0.90 was

set for good fitting models. A RMSEA below 0.05 as well as an insignificant p-value (i.e., above 0.05) for the likelihood ratio test were also used to determine models with good fit.

Consistent with the literature, the BIC was considered the most important index to determine the optimal model and thus, number of latent profiles.[190] The BIC is the most commonly used fit index across the LPA literature.[190] The BIC is calculated by using the following formula: $-2LL + m*\ln(n)$, which translates to (-2) multiplying the log-likelihood of the estimated model, m denotes the number of estimated parameters in the model and n is the number of observations.[190] By multiplying the number of estimated parameters by the natural log of the number of observations, the BIC penalizes over fitting models to improve fit.[190] Models with lower BICs were considered as fitting the data better.

We also used the BIC to compare the fit of models with different covariance structures. The covariance structures evaluated are shown in Table 2.[210] The most restrictive covariance structure is denoted by the letter "E" and assumes equal variances.[210] This structure is also referred to as K-means. The additional models allowed variance (E), volume (V) and orientation (I) to vary across profiles.[210] Ultimately, we selected the covariance structure and number of profiles with the lowest BIC.

In addition to the fit indices, we also considered the theory behind the LPA and the number of profiles that we anticipated would exist at each time point. As such, we used the number of women in each latent profile to help determine the appropriate number of profiles. That is, when there were too few women in a profile, we collapsed profiles together to facilitate interpretability of the results. Decisions to collapse groups were made carefully and in consultation with a breast oncologist.

Once the model with the best fit was selected, we calculated latent status prevalence for each time point. Latent status prevalence is the proportion of women with BC who we expected to be in a profile at a given time.[55, 205] We also computed mean scores for each of the 6 HRQOL domains in order to tease out which specific domains were most important to the particular profile. That is, we wanted to determine if particular profiles could be characterized with lower or higher mean HRQOL scores on certain FACT-B and FACIT-SP domains. Examining mean HRQOL domains in each profile allowed us to characterize the profile and better identify the HRQOL patterns experienced by individuals within a profile.

Latent Transition Analysis

After identifying the latent profiles at each time point, we used a latent transition analysis (LTA) to assess the probability of a woman remaining in the same latent HRQOL profile or transitioning to another HRQOL profile from 5- to 25-months after diagnosis.[54] LTA is considered a longitudinal application of LPA or latent class analysis (used for categorical observed measures) with two or more time points.[55] This type of approach allows us to conceptualize how individuals change over time and what characteristics are associated with change.[205] LTA is a type of latent Markov model and uses full information maximum likelihood estimation with the time 2 latent profile variable as the dependent variable and the time 1 latent profile variable as the explanatory variable.[54, 205] In order to determine the best model, we ran both models that constrain slope parameters to be equal at the two time points as well models that freely estimated parameters at both time points.[54] As described above, we used fit indices (LR test, AIC, BIC, TLI, CFI, and RMSEA) to choose the LTA model that fit the data the best.[54] When the indices yielded conflicting results, the BIC was ultimately used to determine the best model.

It is possible for two LPAs to yield different numbers of profiles at each time point.[205] This would indicate that the number of profiles varies over time.[55] Initially in LTA we assume the structure of HRQOL is constant over time, but this is not always the case as certain exposures (i.e., cancer treatments) may impact HRQOL trajectories.[55] In addition, the LTA may also yield different number of latent profiles at each time point than the two cross sectional LPAs.[205] The reason for this is that sometimes considering data from two different time points allows the number of latent profiles to be different at time 1 and time 2 because there is more variance explained in the models.[205] We formally tested the assumption that the number of latent profiles was the same at the two time points using a Chi-Square test comparing one model that allowed the item-response probabilities at the two time points to be different (i.e., vary over time) to another model that constrains the two probabilities to be the same.[55] Changes in the number of profiles over time suggests that exposure to the cancer care continuum impacts the HRQOL distribution. That is, if a particular number of HRQOL profiles existed at the first time point and new profiles emerged or previously existing profiles were no longer applicable at the second time point, it would suggest that the distribution changed over time. As HRQOL at time 1 is measured when a woman is undergoing active treatment and HRQOL at time 2 is measured when she is receiving adjuvant treatments or in survivorship, it is likely that the HRQOL distributions at these two points would differ. Having different number of profiles at the two time points has no bearing on whether we could perform the LTA.

Using LTA, we estimated two different parameters: latent status prevalence and transition probabilities.[205] [55] As described above, latent status prevalence is the proportion of women with BC who we expected to be in a profile at each time point.[55, 205] Using this prevalence parameter, we can determine which latent profiles are most common among our sample.[205] If latent status

prevalence was too small, we considered combining profiles in order to facilitate interpretation of our models.

A transition probability is the probability that a woman who is in one profile at time 1 transitions to a different profile or remains in the same profile at time 2.[55] This is arguably the most interesting parameter in a LTA.[205] Transition probabilities are organized in a matrix with the rows representing latent profiles at time 1 and columns representing latent profiles at time 2.[205] As such, given a woman's latent profile at time 1, we calculated the probability that she transitioned to the column latent status at time 2.[205] The diagonal of the transition matrix represents women that remained in the same latent profile at the two time points.[205] Given that we anticipated HRQOL to generally improve between the two time points as women move from active treatment to survivorship phases, remaining in a low HRQOL between time 1 and time 2 would be of concern although it would not technically be a "decrement." That is, we expected there would be improvements in HRQOL across domains over time as woman moved further away from active treatments.

We tested differences in transition probabilities between age at diagnosis, race and socioeconomic status (e.g., income, education, martial status, insurance status) using Chi-Square tests, adjusting for multiple comparisons (e.g., Bonferroni adjustments).[54] Transition probabilities differing by patient-level demographic characteristics implies that a woman's non-modifiable characteristics may impact the probability that she transitions from one profile to another between the two time points. This would offer an opportunity for us to identify women who may be at risk of transitioning to a worse HRQOL profile or staying in a low HRQOL profile over time. The variation of transition probabilities by individual characteristics is an

important finding, as we can use an individual's baseline demographic characteristics to predict their HRQOL trajectory during cancer care.

Multinomial Logistic Regression

Multinomial logit models (MLM) are maximum likelihood estimator models that build upon binary logit models when the outcome of interest has more than two categories and are not ordered.[211] Specifically, the outcome must not have an inherent order (e.g., underweight, normal weight, overweight), and must be discrete and nominal for a MLM to be most appropriate.[211] In Chapter 4 (Aim 1), MLMs were used to determine patient-level characteristics (adjusting for treatment and tumor characteristics) associated with the latent profiles identified via LPA.[54] Using the latent profiles, we created a categorical variable for each time point with the number of categories corresponding to the number of latent profiles at that time point. A separate MLM was performed for each time point with latent profiles at that time point serving as the model outcome. The highest HRQOL latent profile was the reference group for all MLMs and the other latent categories were interpreted with respect to the highest profile. We also used MLMs to determine patient factors associated with transitioning from one latent profile to another. To do this, we used the categorical variable from the second time point LPA as the outcome measure, adjusting for the latent profiles time one, demographics, socioeconomics, tumor and treatment characteristics. We also considered ordered logit models due to the general ordinal nature of the latent profiles. However, given that not all indicators followed the ordinal pattern, we decided that MLM models were more appropriate.

In order to use MLMs, the independence of irrelevant alternatives (IIA) assumption must be met.[211] This assumption states that, "the ratio of choice probabilities of any two alternatives (in response categories) are not influenced systematically by any other alternatives."[211, 212] That is, if one adds or drops an additional outcome category, the relative probabilities of the other

outcomes should remain the same.[212] If the IIA assumption is violated, this would suggest the errors are not independent across the outcome levels.[211, 213] To test the IIA assumption in Chapter 4, we performed a Hausman Test and found that the IIA assumption was not violated.[213] The Hausman Test compared estimated MLM coefficients of an unconstrained model to estimates from constrained models (i.e., ones that drop categories from the outcome).[211, 213] A significance level of 5% was used for estimate comparisons. Comparisons with p-values above 0.05 were considered to satisfy the IIA assumption.

Once we finalized our three MLM models (one for the first HRQOL assessment, one for the second HRQOL assessment and one for both time points), we calculated predicted probabilities of membership in each of the latent profiles using sample means from our cohort. That is, we estimated the probability of a woman in our sample being in a particular latent profile given a set of characteristics.[212] Predicted probabilities allowed us to identify which patient-level characteristics are most predictive of membership in a particular latent profile.[212] These predicted probabilities also allow us to identify characteristics of women who are vulnerable to certain HRQOL decrements (or lack of improvement over time). Chapter 4 focuses on assessing the relationship between non-modifiable patient characteristics and membership in the latent profiles; as these characteristics are routinely collected in clinic and can easily be used to identify women most susceptible to membership in a poor HRQOL latent profile. Therefore, we calculated the marginal effect of age on the probability of being in a particular latent profile (at each time point) as well as the differential effects of race, marital status, insurance status, education level and family income on the probability of being in a latent profile at a given time point.

Expected Outcomes

The two expected outcomes for Chapter 4 were that through the LPA, we would identify multiple distinct HRQOL profiles of women with BC and that through LTA, we would be able to predict which women were most likely to transition from one profile to another between 5 and 25-months post-diagnosis. Although LPA/LTA are empirically driven approaches, based on the literature, we expected four HRQOL profiles to emerge at each time point. This hypothesis was confirmed as we identified four profiles. There was: a high overall HRQOL (high scores in all domains), a low overall HRQOL group (low scores on all domains), a high physical functioning (high physical-well being HRQOL, but lower mental well-being) and a high psychosocial functioning profile (high emotional/social/spiritual well-being, but lower physical well-being). These expected outcomes allowed us to achieve a better understanding of HRQOL patterns among women with BC. Furthermore, we were also able determine associations between non-modifiable demographic factors (age at diagnosis, race, socioeconomic status) and membership in HRQOL profiles, which informs future preemptive identification of women who are most susceptible to poor HRQOL.

Aim 2

Hypotheses

Results from the literature review presented in Chapter 2 of this dissertation guided the development of the hypotheses used for this aim. We employed the third definition of racial disparities presented in Chapter 2, treating race and socioeconomic status as distinct constructs, which have both independent and interactive effects on health outcomes.[123] The seven hypotheses presented below reflect this approach to assessing racial disparities, as we anticipated the relationship between race and HRQOL to vary by socioeconomic status.

Hypothesis 1a: *Racial gaps in emotional and spiritual well-being HRQOL domains between Blacks and Whites will narrow from 5-months to 25-months post-diagnosis.*[14]

Hypothesis 1b: *Racial gaps in physical and functional well-being HRQOL domains between Blacks and Whites will remain the same or widen from 5-months to 25-months post-diagnosis.*[14]

Hypothesis 2a: *Changes in racial gaps in HRQOL domains from 5-months to 25-months post-diagnosis between Blacks and Whites will vary by income level.*[123, 124, 128, 131]

Hypothesis 2b: *Changes in racial gaps in HRQOL domains from 5-months to 25-months post-diagnosis between Blacks and Whites will vary by education.*[123, 124, 128, 131]

Hypothesis 2c: *Changes in racial gaps in HRQOL domains from 5-months to 25-months post-diagnosis between Blacks and Whites will vary by marital status.*[123, 124, 128, 131]

Hypothesis 2d: *Changes in racial gaps in HRQOL domains from 5-months to 25-months post-diagnosis between Blacks and Whites will vary by insurance status.*[123, 124, 128, 131]

Hypothesis 2e: *Changes in racial gaps in HRQOL domains from 5-months to 25-months post-diagnosis between Blacks and Whites will vary by urban/rural community.*[123, 124, 128, 131]

Dependent Variables

The 25-month from diagnosis HRQOL domain scores were used as primary outcomes in six separate analysis of covariance models (one for each HRQOL domain) and the 5-month from diagnosis HRQOL scores were included as covariates.

Key Independent Variables

The key independent variable for Aim 2 was self-reported race (Non-Hispanic Black or Non-Hispanic White). White was used as the reference category for this binary variable. Aim 2 also tested interaction terms between race and socioeconomic factors (e.g., education, insurance status, marital status). Although these socioeconomic factors were measured at the same time as

race (i.e., in adulthood, not at birth), they occur "after" race and are therefore considered mediators of the relationships between race and HRQOL.[214]

Descriptive Statistics

We compared demographic, socioeconomic, tumor and treatment characteristics between Black and White women in our sample using t-tests for continuous covariates (e.g., age, BMI) and chi-square tests for binary (e.g., marital status, chemotherapy) and categorical variables (e.g., education, insurance status). We compared unadjusted HRQOL scores for each FACT-B and FACIT-SP domain between Black and White women using t-tests. We also compared the 5- and 25-month HRQOL scores in our sample to normed U.S general female population scores available for the physical, functional, social and emotional well-being domains.[215] A significance level of 0.05 was used for all unadjusted analyses.

Analysis of Covariance Models

Analysis of covariance (ANCOVA) models have continuous dependent variables and either continuous and/or categorical explanatory variables.[216] These models are most appropriate in observational studies, where subjects are not assigned to particular groups at random and confounding may be of concern.[216] The primary assumption of this statistical approach is that the slopes of the two comparison groups (e.g., Black and White women) are equal and only the intercepts differ.[216]

In Chapter 5 (Aim 2), we used ANCOVA models to examine changes in HRQOL over time, adjusting for HRQOL scores (within 9-months of diagnosis), demographic, socioeconomic, treatment and tumor characteristics. We ran one model for each HRQOL domain in order to tease out domain-specific predictors that may be masked when looking at an overall HRQOL score. Our outcome for each model was the 25-month HRQOL score. To calculate change, we subtracted the 5-month score from the 25-month score. As such, positive change scores reflected

improvements in HRQOL between 5- and 25-months and negative change scores denoted decrements in HRQOL between 5- and 25-months. We controlled for HRQOL at 5-months in each ANCOVA model.

To assess racial disparities we took a step-by-step approach. First, we ran models controlling for race only (no socioeconomic factors) and tested difference in adjusted Least Square Means (LSMs) between Black and White women for each HRQOL domain. Then, we ran 6 additional models that controlled for race and socioeconomic factors and again tested the difference in adjusted LSMs between Black and White women. To implement the racial disparities approach described in Chapter 2, which considers both the independent and interactive effects of race and socioeconomic factors, we added interaction terms between race and socioeconomic factors and tested differences in adjusted LSMs for each HRQOL domain between Black and White women. From these models, we calculated the "direct effects" of the racial gap for each HRQOL domain by looking at the marginal effect of race.[214] We also calculated "mediated effects" (through socioeconomic factors) of the racial gap. To do this, differences (for each HRQOL domain separately) were computed between the coefficient from Models 1 that did not adjust for socioeconomic factors and the coefficients from Models 2 and 3a-3e that did adjust for socioeconomic factors. In these calculations, we assumed all potential confounders of the relationship between race and HRQOL were controlled for, which is a strong assumption.[214] As the interaction terms were not statistically significant, we did not have sufficient evidence that the fundamental relationship between race and HRQOL was different for Black and White women with BC. Therefore, we did not stratify Aim 2 analyses by race, although we did run Models 4a and 4b (below) as sensitivity analyses and found that the associations between HRQOL and race did not vary significantly by socioeconomic factors.

Our approach in Aim 2 differentiated between demographic (predisposing characteristics and evaluated need) and socioeconomic (enabling resources) factors. Demographic variables included age at diagnosis, smoking status, body mass index, and comorbid conditions. Evaluated need included a woman's comorbid conditions as well as the tumor characteristics of her BC. Socioeconomic factors included marital status, level of education, and insurance status. The equations for our each of our models are listed below. In total, we ran 54 different models (9 models for 6 HRQOL domains).

1. <u>No socioeconomic status:</u> 25-month HRQOL Domains = $\beta0 + \beta1$BaselineHRQOL+ $\beta2$Race + $\beta3$Demographics +$\beta4$Treatment + $\beta5$Tumor + μ

2. <u>No interaction terms:</u> 25-month HRQOL Domains = $\beta0 + \beta1$BaselineHRQOL+ $\beta2$Race + $\beta3$Demographics + $\beta4$Socioeconomics +$\beta5$Treatment + $\beta6$Tumor + μ

3a. <u>Race and Income:</u> 25-month HRQOL Domains = $\beta0 + \beta1$BaselineHRQOL+ $\beta2$Race + $\beta3$Demographics + $\beta4$Socioeconomics+ **$\beta5$Race*Income** +$\beta6$Treatment + $\beta7$Tumor + μ

3b. <u>Race and Education:</u> 25-month HRQOL Domains = $\beta0 + \beta1$BaselineHRQOL+ $\beta2$Race + $\beta3$Demographics + $\beta4$Socioeconomics+ **$\beta5$Race*Education** +$\beta6$Treatment + $\beta7$Tumor + μ

3c. <u>Race and Social Support</u>: 25-month HRQOL Domains = $\beta0 + \beta1$BaselineHRQOL+ $\beta2$Race + $\beta3$Demographics + $\beta4$Socioeconomics+ **$\beta5$Race*MaritalStatus** +$\beta6$Treatment + $\beta7$Tumor + μ

3d. <u>Race and Insurance Status:</u> 25-month HRQOL Domains = $\beta0 + \beta1$BaselineHRQOL+ $\beta2$Race + $\beta3$Demographics + $\beta4$Socioeconomics+ **$\beta5$Race*InsuranceStatus** +$\beta6$Treatment + $\beta7$Tumor + μ

3e. <u>Race and Urban/Rural:</u> 25-month HRQOL Domains = $\beta0 + \beta1$BaselineHRQOL+ $\beta2$Race + $\beta3$Demographics + $\beta4$Socioeconomics+ **$\beta5$Race*Urban/Rural** +$\beta6$Treatment + $\beta7$Tumor + μ

4a. <u>Only White women:</u> 25-month HRQOL Domains = $\beta0 + \beta1$BaselineHRQOL+

β2Demographics + β3Socioeconomics +β4Treatment + β5Tumor + μ

4b. <u>Only Black women:</u> 25-month HRQOL Domains = β0 + β1BaselineHRQOL+

β2Demographics + β3Socioeconomics +β4Treatment + β5Tumor + μ

Expected Outcomes

The expected outcome of Chapter 5 (Aim 2) was to determine whether or not racial disparities existed in changes in six HRQOL domains between 5- and 25-months post-diagnosis among women with BC. Determining whether racial disparities existed enabled us to attain Aim 2's objective of better understanding cancer's impact on two racial groups (Blacks and Whites) through the cancer care continuum. Information gleaned from this study will be used to inform more equitable HRQOL management for racial groups most vulnerable to particular HRQOL decrements.

Aim 3

Hypotheses

Our review of previous work guided hypotheses for Aim 3. Below we present our anticipated associations between HRQOL profiles at 5-months and ET non-initiation and ET non-adherence, separately. We anticipated the relationship between HRQOL at 5-months and ET utilization to vary by race and receipt of chemotherapy. Additional *a priori* hypotheses are presented below.

Hypothesis 3a: *Worse HRQOL profiles at 5-months will be significantly associated with a greater likelihood of not initiating ET among women with HR+ BC.*[30, 31, 33, 120]

Hypothesis 3b: *Worse HRQOL profiles at 5-months will be significantly associated with a greater likelihood of not adhering to ET among women with HR+ BC.*[30, 31, 33, 120]

Hypothesis 3c: *The association between HRQOL profiles at 5-months and likelihood of ET non-initiation will vary by race among women with HR+ BC.*[39, 47]

Hypothesis 3d: *The association between HRQOL profiles at 5-months and likelihood of ET non-adherence will vary by race among women with HR+ BC.*[39, 47]

Hypothesis 3e: *The association between HRQOL profiles at 5-months and likelihood of ET non-initiation will vary by receipt of chemotherapy among women with HR+ BC.*[47]

Hypothesis 3f: *The association between HRQOL profiles at 5-months and likelihood of ET non-adherence will vary by receipt of chemotherapy among women with HR+ BC.*[47]

Dependent Variables

The dependent variables for Aim 3 were whether or not a woman initiated ET and whether or not she adhered to ET. As non-initiating and non-adhering are less common occurrences in our sample, we modeled the likelihood that a woman did <u>not</u> initiate ET and the likelihood that she did <u>not</u> adhere to ET in our logit models. ET initiation came from the medical abstraction dataset and adherence came from the CBCS 25-month mail-in follow-up survey. Given that the ET initiation measure came from the medical record, it is likely a reliable estimate of whether or not a woman initiated ET. In Aim 3 analyses, ET non-initiation was treated as binary (yes-1, no-0).

ET adherence data is self-report and comes with inherent limitations, which are described at the end of the chapter. In the CBCS-III 25- month follow-up survey, ET non-adherence was asked in several different ways, but ultimately this variable was dichotomized as yes/no. We used two variables from the CBCS-III 25-month survey to construct the ET non-adherence variable: "At this time, are you taking hormonal therapy pills?" and "Over the past two weeks, how many days did you miss your hormonal pills?" Response options for the first question were "Yes, I am taking them exactly as prescribed by my doctor," "Yes, I'm taking them, but not every day," and "No, I stopped taking those pills." If a woman responded that she was taking the pills exactly as prescribed we considered her as "adherent" and if she responded that she stopped

taking the pills then we considered her "non-adherent." For women who responded that they were not taking the pills every day, we assessed their responses to the second ET adherence question. Response options included 0 days, 1 day, 2 days, 3 days, 4 days, and 5 or more days. Among who reported not taking ET as prescribed, if they missed 0, 1 or 2 days in the last two weeks we classified them as "adherent" (took their pills more than 80% of the time) and if they reported missing 3 or more days in the last 2 weeks we grouped them in the "non-adherent group" (they missed more than 20% of the time in the last two weeks). As such, both non-adheres and discontinuers are classified as "non-adherent" for the purposes of our analyses in Aim 3.

Key Independent Variables

The key explanatory variables for Aim 3 were the HRQOL profiles at 5-months, which were identified through the Aim 1 LPA. The HRQOL explanatory variable came from HRQOL data in the CBCS-III 5-month survey. The variable was categorical with the number of categories determined by the number of latent profiles resulting from the analysis in Aim 1. As in Aim 1, the highest HRQOL profile served as the reference group for Aim 3 analyses. Aim 3 also included interaction terms between the HRQOL profiles and race as well as interactions between HRQOL and receipt of chemotherapy. White was used as the reference category for the race variable.

Covariates

We adjusted for age at diagnosis, smoking status, marital status, education, insurance type, comorbid conditions (i.e., obesity, hypertension, heart disease, diabetes and COPD), tumor stage, tumor grade, and receipt of surgery, chemotherapy, radiation and Herceptin. We did not adjust for urban/rural residence and family income due to high degrees of collinearity with education and insurance. Family income and urban/rural residence both had missing values,

whereas the insurance and education data were complete.

Descriptive Statistics

First, we compared demographic, socioeconomic, tumor and treatment characteristics between women in each latent profile using t-tests for continuous covariates (e.g., age) and chi-square tests for binary (e.g., race, marital status) and categorical variables (e.g., education, insurance status). Then, we tested differences in the patient-level characteristics mentioned above within each latent profile by receipt of chemotherapy and between Black and White women. We also compared patient-level characteristics between women who initiated ET by 5-months and those who initiated after 5-months using chi-square tests. Finally, we also examined the distribution of patient-level characteristics between women who reported adhering to ET versus those who did not report adhering to ET using chi-square tests.

Latent Profile Analysis

The methodology for LPA models used to construct the key independent indicator for this aim are described in detail above under the Aim 1 approach section. In order to determine whether using the latent profiles from Aim 1 were appropriate for Aim 3, we explored unadjusted and adjusted differences in HRQOL between women with HR+ and HR- BC as well as between women who initiated ET before the 5-month survey and those who initiated after the 5-month survey. Results from these analyses are presented in Chapter 6 (Aim 3). Given the results from these exploratory analyses, we decided the latent profiles constructed in Aim 1 were the most appropriate to use in Aim 3 analyses.

Binary Logit Models

Binary outcome models are appropriate to use when the outcome of interest is binary.[212, 216] The three main types of binary models are linear probability, logit and probit models.[212] Linear probability models are the least sophisticated and involves estimating an Ordinary Least

Squares model for a binary outcome. This approach often leads to out of ranges predictions (i.e., predictions that are less than 0 or greater 1) and introduces heteroskedasticity into the model. Although the latter can be accounted for using robust standard errors, out of range predictions are an inherent limitation to linear probability models. As such, logit and probit models are most commonly used to model binary outcomes. Both of these models allow for continuous and categorical explanatory variables to be examined.[212] Choosing between logit and probit models varies by discipline and is typically left up to the investigator.

In Chapter 6 (Aim 3), we used logit models to predict a woman's likelihood of not initiating ET. In the initiation model, the outcome was whether the woman initiated ET according to the CBCS-III medical record abstraction data. The outcome was coded as 0/1 with 1 denoting ET non-initiation and 0 meaning ET initiation (the more common outcome and therefore the reference category). In this model, the key independent variable was the four-level categorical HRQOL latent profile variable with the highest HRQOL serving as the reference category. Demographic, socioeconomic, treatment and tumor characteristics were also controlled for in this model, as they may potentially confound the association between HRQOL and ET non-initiation. We also considered that the relationship between HRQOL and non-initiation could vary by race as well as by receipt of chemotherapy (potential effect modifiers). As such, we ran an additional model adding an interaction term between the profiles and race and another model that added an interaction term between the profiles and chemotherapy. We used the statistical significance of the interaction terms to determine if the interactions improved the overall fit of our models. We also assessed model fit using the Hosmer and Lemeshow's goodness of fit test, which is based on a chi-square distribution.[216] With a p-value above the 0.05

threshold, we assumed our models fit the data well. Given the statistical significance of the interaction terms, we ran chemotherapy and race stratified models.

We also used logit models to determine a woman's likelihood of not adhering to her ET. In this model, the outcome was whether or not the woman self-reported adhering to ET on the 25-month follow-up mail in survey. We defined adherence as self-reporting that you took your ET pills more than 80% of the time. As described in the dependent variable section above, we had access to self-report adherence data in the last 2 weeks. We considered taking pills 12 of the 14 days (86% adherence) as "adherent" and missing 3 or pills (78% adherence or less) as "non-adherent". As such, non-adhering included women who reported less than 80% adherence as well as those who discontinued all together. This outcome was coded was 0/1 with 1 meaning ET non-adherence or discontinuation and 0 meaning ET adherence. As with the initiation model, the key independent variable was the HRQOL latent profile. As described above, the reference group was the highest HRQOL latent profile and demographic, socioeconomic, treatment and tumor characteristics were adjusted for in all models. As with the ET initiation analyses, we ran additional models adding interaction terms between race and HRQOL profiles as well as chemotherapy and HRQOL profiles (one at a time), as two variables may be effect modifiers. Given the statistical significance of the interaction terms, we also ran chemotherapy and race stratified models.

Using sample means, we calculated predicted probabilities of not initiating and not adhering to ET, separately. We selected sample mean values for demographic, socioeconomic, treatment and tumor characteristics in our sample and predicted the probability that a woman would not initiate or not adhere to ET. Also using sample means of patient characteristics, we calculated the differential effect on the probability that a woman did not initiate or did not adhere

to ET by distinct HRQOL profiles. Essentially, this approaches used dummy variables (for the latent profile categories) to calculate the difference in predicted probabilities of a woman not initiating or not adhering to ET.[212] In addition, as previous studies have documented racial differences in ET non-initiation and non-adherence, we tested whether or not the differential effects of HRQOL profiles membership on the probability of not initiating and not adhering differed by race. We also tested whether differential effects were significantly different between women who received chemotherapy and those that did not. Finally, we calculated adjusted odds ratios (AORs) and 95% confidence intervals for all estimates. Models estimated for Chapter 6 analyses are listed below.

1. <u>ET initiation</u> = $\beta 0 + \beta 1$ 5-month HRQOL Profile + $\beta 2$Demographics + $\beta 3$Socioeconomics + $\beta 4$Treatment+ $\beta 5$Tumor + μ

2. <u>ET initiation</u> = $\beta 0 + \beta 1$ 5-month HRQOL Profile + $\beta 2$Race + $\beta 3$Demographics + $\beta 4$Socioeconomics + $\beta 5$Treatment+ $\beta 6$Tumor + **$\beta 7$ 5-month HRQOL Profile*Race** +μ

3. <u>ET initiation</u> = $\beta 0 + \beta 1$ 5-month HRQOL Profile + $\beta 2$Race + $\beta 3$Demographics + $\beta 4$Socioeconomics + $\beta 5$Treatment+ $\beta 6$Tumor **+ $\beta 7$ 5-month HRQOL Profile*Chemotherapy** +μ

4. <u>ET adherence</u> = $\beta 0 + \beta 1$ 5-month HRQOL Profile + $\beta 2$Demographics + $\beta 3$Socioeconomics + $\beta 4$Treatment+ $\beta 5$Tumor + μ

5. <u>ET adherence</u> = $\beta 0 + \beta 1$ 5-month HRQOL Profile + $\beta 2$Race + $\beta 3$Demographics + $\beta 4$Socioeconomics + $\beta 5$Treatment+ $\beta 6$Tumor + **$\beta 7$ 5-month HRQOL Profile*Race** +μ

6. <u>ET adherence</u> = $\beta 0 + \beta 1$ 5-month HRQOL Profile + $\beta 2$Race + $\beta 3$Demographics + $\beta 4$Socioeconomics + $\beta 5$Treatment+ $\beta 6$Tumor + **$\beta 7$ 5-month HRQOL Profile*Chemotherapy** +μ

Note: Demographics and treatment covariates in equations 1-6 include main effects for race and chemotherapy for the models that include interaction terms.

Expected Outcomes

The expected outcomes for Chapter 6 (Aim 3) were to determine if there were significant associations between a composite measure of HRQOL following BC diagnosis and under-utilization of ET at 25-months after BC diagnosis among women with HR+ disease. These expected outcomes allow us to achieve Aim 3's objective of determining whether pre-ET HRQOL can serve as a screener for women with BC who are less likely to initiate and adhere to ET. HRQOL following diagnosis can be used to identify women at risk of under-utilization early in the BC treatment process. This important finding offers an opportunity for future intervention's to target women at risk for poor HRQOL with support to increase the likelihood of ET initiation and adherence.

Limitations

There are some limitations to note in this dissertation. First, the CBCS-III dataset only includes women in North Carolina, thus limiting our generalizability to women outside of the state. We also excluded women who were not Non-Hispanic Black or Non-Hispanic White so we also cannot generalize to women beyond the two racial groups included in this dissertation. In addition, our first HRQOL assessment point occurred an average of 5.2 months (ranges from 1.8 to 8.9 months) after BC diagnosis. By this point, many women will have initiated primary BC treatments so we were unable to reliably measure pre-treatment HRQOL. However, we do have access to treatment data from the medical record, which is considered complete and reliable, so we are able to control for primary and adjuvant treatments that women received. A limitation specific to Aim 3 ET initiation analyses is that women who initiated ET prior to their first survey were not included in ET initiation analyses. This led us to exclude 646 (30%) of the 1,599

women with HR+ BC who would have been ideally included in Aim 3 ET initiation analyses. However, we compared HRQOL between women who initiated before and after the 5-month survey and did not find statistically significant differences in multivariate models across any of the HRQOL domains. Because receipt of ET may impact HRQOL, we were interested in pre-ET HRQOL assessments and could not include women who had initiated ET prior to their first HRQOL assessment. We feel confident that this decision has led us to obtain an assessment of HRQOL that is not confounded by exposure to ET, but we recognize that this limits our generalizability to all women with HR+ BC. Finally, another limitation to Aim 3 analyses is that the ET adherence data comes from self-report. As such, we were unable to confirm the reliability of the adherence data. We also combined women who were non-adherent (continued to take medication at less than the prescribed dose and schedule) and those who were discontinuers in these analyses. However, we collaborated with investigators at UNC who are also working with the ET adherence data in the CBCS-III dataset and are confident that our ET adherence classification works well and represents women who were under-utilizing this therapy.

Figure 1. Modified Version of Andersen's Behavioral Model for Health Care Utilization[171]
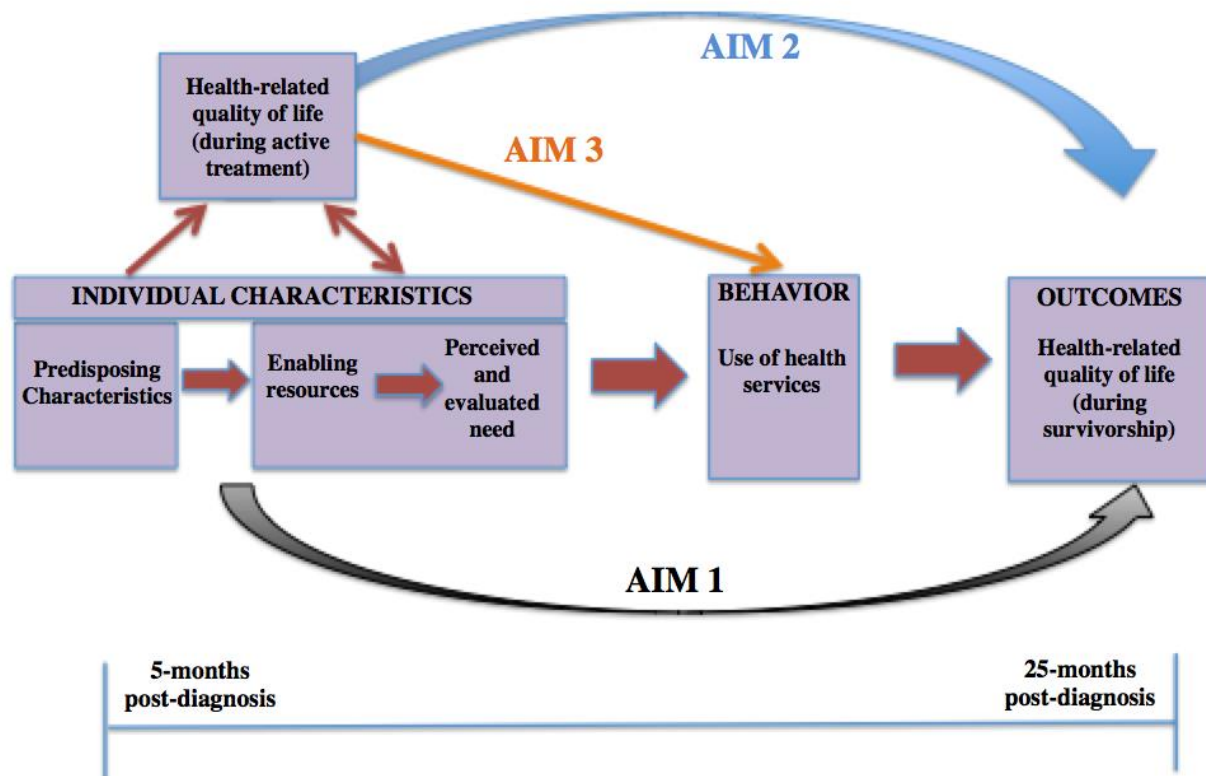
Figure 2. Modified Version of the Consolidated Standards of Reporting Trials Flow Diagram to Depict Study Sample and Eligibility[217]
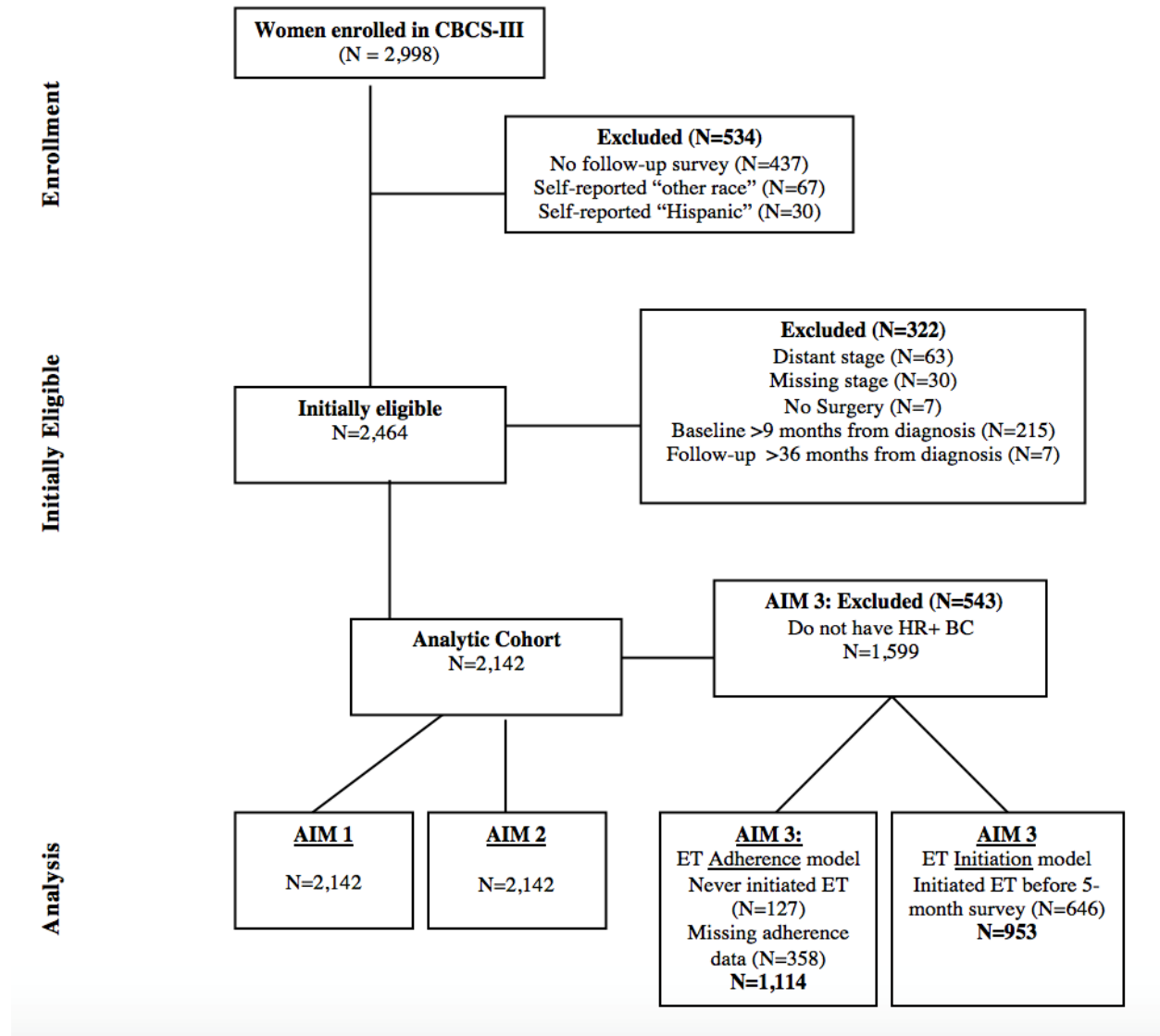
Note: NHW (Non-Hispanic Whites), NHB (Non-Hispanic Black), ET (Endocrine Therapy), HR+ (hormone receptor positive), BC (breast cancer), CBCS (Carolina Breast Cancer Study)

Table 1. Key Variables and Measures

Variable	Aims	Type of Variable	Values/Categories	Data Source
Key Explanatory Variables				
Race	1, 2, 3	Binary	White/Black	5-Month Survey
Socioeconomic characteristics	1, 2	Categorical	See below	5-Month Survey
Age at diagnosis	1	Continuous	20-74 years	5-Month Survey
Receipt of chemotherapy	3	Binary	Yes/No	Medical Record Abstraction
5-Month HRQOL profiles	3	Categorical	TBD	5-Month Survey
Covariates - Demographic Characteristics				
5-Month HRQOL domains (physical, social, emotional functional, spiritual well-being, BC-specific concerns)	2	Continuous	0-28 for first 4 domains, 0-48 for spiritual domain, 0-44 for BC-specific concerns	5-Month Survey
Age at diagnosis	1, 2, 3	Continuous	20-74 years	5-Month Survey
Race	1, 2, 3	Binary	Non-Hispanic White/Non-Hispanic Black	5-Month Survey
Smoking status	1, 2, 3	Categorical	Never/Former/Current	5-Month Survey
Body Mass Index (BMI)	1,2,3	Continuous	14.2-73.96	5-Month Survey
Comorbid conditions	1, 2, 3	Binary	Heart disease, diabetes, hypertension, etc.	5-Month Survey
Covariates - Socioeconomic Characteristics				
Marital status	1, 2, 3	Categorical	Married or partnered/Single, separated, divorced, widowed	5-Month Survey
Family Income	1, 2, 3	Categorical	1: 15-30K, 2: 30-50K, 3: >50K, 4: <15K	5-Month Survey
Level of education	1, 2, 3	Categorical	HS & Post HS, College+, < HS	5-Month Survey
Urban/Rural Environment	1, 2, 3	Binary	Urban-1, Rural-0	5-Month Survey
Insurance status	1, 2, 3	Categorical	Privately insured (self or employer), Medicaid, Medicare, Dual eligible, Uninsured	5-Month Survey
Covariates - Treatment Characteristics				
Surgery type	1, 2, 3	Categorical	Mastectomy, Mastectomy & Reconstruction, Lumpectomy, None	Medical Record Abstraction

Variable	Aims	Type of Variable	Values/Categories	Data Source
Receipt of radiation	1, 2, 3	Binary	Yes/No	Medical Record Abstraction
Receipt of chemotherapy	1, 2, 3	Binary	Yes/No	Medical Record Abstraction
Herceptin	1, 2, 3	Binary	Yes/No	Medical Record Abstraction
Covariates - Tumor Characteristics				
AJCC Tumor stage	1, 2, 3	Categorical	0/I/II/III/IV	Medical Record Abstraction
Tumor size	1, 2, 3	Categorical	T0/T1/T2/T3/T4	Medical Record Abstraction
Tumor grade	1, 2, 3	Categorical	G1/G2/G3/G4	Medical Record Abstraction
Nodal status	1, 2, 3	Binary	Yes/No	Pathology Report
Estrogen receptor positive	1, 2	Categorical	Yes/No/Borderline	Pathology Report
Progesterone receptor positive	1, 2	Categorical	Yes/No/Borderline	Pathology Report
HER-2 positive	1, 2	Categorical	Yes/No/Borderline	Pathology Report
Dependent Variables				
HRQOL profiles (at 5- and 25-month surveys)	1	Categorical	TBD	5-Month & 25-Month Survey
Change in HRQOL domains between 5- and 25-months	2	Continuous	0-28 for first 4 domains, 0-48 for spiritual domain, 0-44 for BC-specific concerns	25-Month Survey
Non-initiation of endocrine therapy	3	Binary	Yes/No	Medical Record Abstraction
Non-adherence to endocrine therapy	3	Binary	Yes/No	25-Month Survey

Table 2. Parameterizations of the Covariance Matrix Σ_k for Multidimensional Data[210]

identifier	Model	HC	EM	Distribution	Volume	Shape	Orientation
E		●	●	(univariate)	equal		
V		●	●	(univariate)	variable		
EII	λI	●	●	Spherical	equal	equal	NA
VII	$\lambda_k\,I$	●	●	Spherical	variable	equal	NA
EEI	λA		●	Diagonal	equal	equal	coordinate axes
VEI	$\lambda_k A$		●	Diagonal	variable	equal	coordinate axes
EVI	λA_k		●	Diagonal	equal	variable	coordinate axes
VVI	$\lambda_k A_k$		●	Diagonal	variable	variable	coordinate axes
EEE	λDAD^T	●	●	Ellipsoidal	equal	equal	equal
EEV	$\lambda D_k A D_k^T$		●	Ellipsoidal	equal	equal	variable
VEV	$\lambda_k D_k A D_k^T$		●	Ellipsoidal	variable	equal	variable
VVV	$\lambda_k D_k A_k D_k^T$	●	●	Ellipsoidal	variable	variable	variable

Note: This table is from Technical Report No. 597 Version 4 for R: Normal Mixture Modeling for Model-Based Clustering, Classification and Density Estimation

CHAPTER 4: EXAMINING HEALTH-RELATED QUALITY OF LIFE PATTERNS IN WOMEN WITH BREAST CANCER

Introduction

Women with breast cancer (BC) in the United States experience health-related quality of life (HRQOL) decrements following diagnosis, during active treatment, and through survivorship [1-3]. HRQOL concerns include fear of BC recurrence or death, lymphedema, fatigue, early menopause, and difficulty returning to work [1, 4, 5, 7]. Poorly managed HRQOL is associated with increased mortality risk [8]. Incorporating HRQOL assessments into treatment decisions may help ensure more patient-centered care and improve BC outcomes.

HRQOL is a multidimensional concept representing an individual's perception of well-being, including spiritual, functional, physical, emotional, and social well-being [7, 94]. This abstract concept is often presented as a single global score, which limits understanding of nuances in HRQOL and the utility of such scores as screening tools for poor health outcomes. For example, a woman may experience optimal physical well-being throughout BC treatment, but suffer significant decrements in psychosocial well-being. Thus, by focusing on a single, overall score; a clinician may inadvertently overlook decrements in their patients HRQOL [3].

Although many studies continue to use a global indicator of HRQOL, domain-specific measures are also often used to represent the multidimensional nature of HRQOL. However, traditional methods to analyzing differences or changes in domain-specific HRQOL, which compare means and standard deviations, are criticized for not representing heterogeneity in HRQOL experiences [75]. Examining mean differences in HRQOL scores alone may lead us to erroneous conclusions regarding outliers or subgroups [75]. That is, small differences or patterns

may be masked and subgroups of women who experience improvements or decrements may be missed [75]. While mean differences in HRQOL scores reflect group-level HRQOL effects of diagnosis or treatment, these overall scores may conceal subgroups of patients experiencing unusually large decrements in a particular domain, or decrements across multiple domains. Such patients may benefit from more targeted intervention.

To address such limitations, the objectives of this study were to 1) employ latent profile analysis (LPA) to identify subgroups of women with BC who experienced different HRQOL patterns at 5- and 25-months after diagnosis, 2) determine patient-level characteristics associated with membership in the HRQOL subgroups, 3) assess the probability of transitioning from one subgroup to another between the two distinct phases of the BC care continuum, and, finally, 4) identify patient-level characteristics associated with transitioning from one LP to another LP between 5- and 25-months. To our knowledge, no studies have used LPA and LTA in a large, population-based BC cohort to examine HRQOL pattern. The clinical meaningfulness of HRQOL subgroups will help inform and may improve targeted HRQOL management for women with BC in the U.S.

Methods

Data

We used data from the third phase of the Carolina Breast Cancer Study (CBCS-III). Through rapid case ascertainment, CBCS-III enrolled 2,998 women diagnosed with incident, invasive, pathologically confirmed BC between 2008 and 2013 across 44 counties in North Carolina [46, 188]. By oversampling young and Black women, the population-based CBCS-III cohort is 50% Black and 50% under the age of 50. CBCS-III intended to be representative of women across the state and, therefore, enrolled those in rural and urban regions, women with private, public or no insurance, and of varying income levels [46]. Demographics, lifestyle factors,

and HRQOL data were first collected in-person by nurses within 9-months of BC diagnosis and at a median of 5.2 months post-diagnosis (range 1.8-8.9 months) [46, 189]. At the initial interview, participants consented for researchers to abstract their medical records [46, 188, 189]. Women also completed a follow-up survey, which included additional HRQOL questionnaires at a median of 25 months post-diagnosis (range 20-36 months), which is referred to as the "25-month survey". Medical record abstraction data included comorbidities and BC treatments. Pathology report data provided information regarding tumor stage and grade. This study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Participants

We limited our sample to women who completed both 5-and 25-month surveys. Additional exclusions included: women identifying as Hispanic or "other race" due to their small representation (3%), distant stage BC (3%), women who completed their initial survey more than 9 months after diagnosis (7%), and those who completed their follow-up survey more than 36 months after diagnosis (<1%). Therefore, 2,142 Non-Hispanic Black and White women with Stage I-III BC were included.

HRQOL Measures

The Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) and Functional Assessment of Chronic Illness Therapy for Spiritual Well-Being (FACIT-SP) were used to measure HRQOL at both 5- and 25-months. The FACT-B is a BC-specific instrument with domains for: physical, social, emotional, and function well-being, and BC-specific concerns [191]. The FACT-B has been psychometrically validated and shown to be sensitive to changes over time in women with BC [56]. The FACIT-SP is a validated chronic disease instrument commonly used to measured spiritual well-being [56, 192, 196]. FACT-B and FACIT-SP domains are treated as continuous measures with higher scores indicating better HRQOL [56, 192, 193]. Minimally important

differences (MID) or smallest differences in HRQOL that are considered meaningful to the patient or provider are 2-4 points per HRQOL domain [195].

Independent Variables

Primary predictors of HRQOL subgroup membership at 5- and 25-months reflect self-reported individual characteristics captured on the 5-month survey, including age at diagnosis, race, marital status, education, and insurance status.

Covariates

Self-reported smoking status, medical-record confirmed comorbid conditions (e.g., diabetes, chronic obstructive pulmonary disease, obesity, hypertension, heart disease), tumor stage and grade, surgery type, and receipt of radiation, chemotherapy, and Herceptin were included in analyses.

Statistical Analysis

Analyses were performed in R (Version 3.2.3) and SAS 9.3 with two-sided statistical tests and significance level of 5%.

LPA

Using the continuous FACT-B and FACIT-SP domains, we used the "mclust" model-based clustering package in R to implement a latent profile analysis (LPA) to identify clusters of women who experienced distinct HRQOL patterns [218]. Probabilistic clusters of women were grouped together as HRQOL latent profiles (LP) at 5 and 25-months post-diagnosis, separately [54, 190, 205, 207]. To perform the LPA, we assumed homogeneity within and across LPs, conditional independence, and LP separation (i.e., item-response probabilities allow for clear differentiation between LPs) [190, 205, 209]. A combination of underlying theory, interpretability of findings, and model fit indices guided model selection and, thus, the ideal number of LPs at each time point [205]. We used the Bayesian Information Criteria (BIC) to compare fits of models with different

covariance structures and number of LPs and selected the model with the lowest BICS [190, 205].

We then calculated prevalence rates or the proportion of women with BC expected in each LP at 5- and 25-months [55, 205]. We also determined mean FACT-B and FACIT-SP scores in each LP and compared scores across LPs and to U.S. norm scores (considering both MIDs and statistical significance).

Predicting LP Membership

We employed two approaches to determine if patient-level characteristics were significantly associated with LP membership, adjusting for smoking status, comorbid conditions, treatment, and tumor characteristics, which could influence HRQOL at a single time point and HRQOL changes over time. Variables presented in Table 1 were potential covariates for adjusted models. Before selecting which variables to include in the models, we conducted univariable analyses to determine covariates that were significantly associated with LP membership. We used a significance level of 0.05 to select relevant covariates to include in multivariable analyses. Next, we employed a one-step approach, which simultaneously estimates a LP model and a multinomial logit structural model to determine covariates associated with LP membership [219, 220]. Given our large sample, we also used multinomial logit models (MLMs) to examine associations between the relevant patient characteristics and LP membership. We estimated a separate MLM predicting LPs at each time point. Specifically, one MLM was estimated for the HRQOL LPs identified at 5-months and another MLM was estimated for the LPs identified at 25-months. The highest HRQOL LP served as the reference category in each MLM. We performed Hausman Tests for each MLM to assess the independence of irrelevant alternatives assumption (IIA). The Hausman Test compared estimated MLMs coefficients of unconstrained models to estimates from constrained models (i.e., ones that dropped categories from the outcome) [211, 213]. Comparisons with p-values above 0.05 were considered to satisfy the IIA

assumption. Given that the one-step approach is most commonly reported in the LPA literature, we present estimates obtained from this approach.

LTA

We used a longitudinal extension of LPA, latent transition analysis (LTA), to assess the transition probability (i.e., the probability of a woman remaining in the same HRQOL LP or transitioning to another LP from 5- to 25-months) [54, 55, 221]. To determine patient-level characteristics associated with transitioning, we estimated four separate MLMs (one for each 5-month LP) to predict LP transitions, adjusting for covariates presented in Table 1. In these models, 25-month HRQOL LPs (four categories) were used as the outcomes. The highest HRQOL LP at 25-months was the reference category in all MLMs. We also used MLM to examine patient-level predictors of improving to a better LP from 5- to 25-months, deteriorating to a worse LP, and remaining in the same LP from 5- to 25-months.

Results

Unadjusted

5-month LPs: We identified four HRQOL LPs at 5-months (Figure 3). LP1 had the poorest HRQOL scores across all domains (well below U.S. norms) and LP4 had the highest HRQOL scores across domains (well above U.S norms). The second poorest HRQOL LP (LP2) had physical and functional well-being scores below U.S. norms, but not as low as LP1 (Table 4). Differences between LPs 1 and 2 exceeded MID thresholds of 2-points for every domain except physical well-being. LP3 had physical and functional well-being scores above U.S norms, but below LP4. Mean differences between LP 3 and 4 were above MID thresholds for social, functional, and spiritual well-being and BC-specific concerns. LP3 had mean BC-specific concerns scores 4-points higher than LP2 and 7-points higher than LP1, which both well exceed the MID threshold. Patient prevalence rates at 5-months for LPs 1-4 are as follows: 32%, 29%

28% and 11%, respectively. Over 60% of women with BC were in the two poorest HRQOL LPs during active treatment.

25-month LPs: We also identified four HRQOL LPs at 25-months (Figure 4). Similar to 5-month LPs, the poorest HRQOL LP was LP1 and the highest HRQOL LP was LP4. Scores across all domains were low for LP 1, but especially in physical and functional domains, which are more than one standard deviation below U.S. norm scores. LP2 had physical and spiritual well-being scores higher than LP3, but lower functional, social and emotional well-being and BC-specific concerns (Table 4). LP2 scores in social and emotional HRQOL were below U.S. norms. LP3 scores were generally high across all domains, but lower than LP4 scores. The proportion of patients within each LP at 25-months for LPs 1-4 are as follows: 26%, 12%, 37% and 25%, respectively. More than 60% of the women with BC were in the highest HRQOL LPs at 25-months post-diagnosis.

5- to 25-month Transitions: Overall, mean HRQOL scores in LP1 were lower at 25-months than at 5-months, but scores at 25-months were higher than 5-months in LP 4. Compared to mean scores at 5-months, scores 25-months in LP2 were higher for physical and functional well-being, lower for social, emotional and spiritual domains, and remained the same for BC-specific concerns. Mean scores at 5- and 25-months for LP3 were generally the same. There were 951 (44%) women who improved to a better HRQOL LP from 5- to 25-months, 864 (40%) who remained in the same LP over time, and 327 (15%) who deteriorated to a worse HRQOL LP. Among women in the poorest HRQOL LP at 5-months, 52% remained in LP1 at 25-months, and 48% transitioned to a better HRQOL LP at 25-months (Table 5). Of the women in LP2 at 5-months, 11% remained in LP 2, 22% declined in HRQOL to LP1 and 67% transitioned to LP3 or LP4 at 25-months. We observed the largest change in mean domain-

specific scores from 5- to 25-months in LP2 as well as the largest proportion of women transitioning to other LPs at 25-months. Among women in LP3 at 5-months, 18% declined in HRQOL to LPs 1 or 2 and 35% improved in HRQOL to LP4 at 25-months. Finally, among those in LP4 at 5-months most remained in the highest HRQOL LP (65%), 24% declined to LP3, and 11% to LPs 1 or 2 at 25-months.

Adjusted

Relevant covariates for adjusted models, which met the 0.05 threshold included: race, age at diagnosis, smoking status, marital status, education, insurance status, diabetes, COPD, heart disease, hypertension, obesity, surgery, chemotherapy, Herceptin, and stage of disease (Table 3). The IIA was satisfied for all MLMs with Hausman Test p-values greater than the 0.05 threshold. Estimates from MLM and one-step approaches were nearly identical.

5-month LPs: Compared to the highest HRQOL LP (LP4), White race, younger age at diagnosis, being unmarried, having public or no insurance (versus private), prevalence of COPD, and receiving chemotherapy were significantly associated with membership in the poorest HRQOL LP (LP1) (Table 6). Compared to LP4, membership in LP2 was significantly associated with younger age, COPD, obesity and receipt of chemotherapy. Membership in LP3 was significantly associated with White race, higher level of education, COPD, and not receiving chemotherapy compared to membership in LP4.

25-month LPs: Compared to LP4, membership in LP1 at 25-months was significantly associated with Black race, being a current or former smoker, COPD, heart disease, obesity, receiving chemotherapy and having more advanced stage BC (Table 7). Membership in LP2 was significantly associated with younger age, smoking, being unmarried, COPD, heart disease, obesity, chemotherapy, Stage 2 or 3 BC, and having public or no insurance (compared to

membership in LP4). Finally, relative to LP4, membership in LP3 was significantly associated with White race, younger age at diagnosis, higher education and prevalence of COPD.

Transitions: There were no patient-level characteristics significantly associated with transitioning from a particular HRQOL LP to another LP from 5- to 25-months. Compared to women who improve from one HRQOL LP to a better LP or remain in the same LP, Black race aOR1.32, 95% CI 1.02-1.72 and being a current smoker aOR 1.54, 95% CI 1.13-2.12 were significant predictors of HRQOL LP deterioration from 5-to 25-months. Compared to women who improve to a better HRQOL, the only predictor of remaining in the same HRQOL over time was having public (versus private) or no insurance aOR 1.52, 95% CI 1.18-1.96 and aOR 2.10, 95% CI 1.34-3.29, respectively.

Discussion

The objective of this study was to employ a novel, patient-centered approach to characterizing HRQOL patterns in women from a large population-based BC cohort and to determine patient-level characteristics associated with patterns. We identified four distinct HRQOL LPs at 5- and 25-months. Membership in poorer HRQOL LPs at 5-months was significantly associated with younger age, White race, lack of social support, public insurance or being uninsured, comorbid conditions (e.g., obesity, COPD), being a smoker, and more intensive BC treatment. At 25-months, membership in poorer HRQOL LPs was associated with modifiable patient-level factors such as smoking and obesity, as well as non-modifiable factors such as younger age, Black race, and prevalence of comorbid conditions. More advanced stage of BC and receipt of chemotherapy was also associated with poorer HRQOL LPs at 25-months. To our knowledge, no previous study has used LPA and LTA in a BC cohort to describe and characterize HRQOL patterns [55].

Cluster analysis has been used to identify subgroups of patients at increased risk of poor health outcomes with the expectation of tailoring treatment choices to patient-specific needs [40, 41, 199-201] Previous studies found that meaningful subgroups of cancer patients could be identified and clinical interventions may have seen better outcomes if an individual's HRQOL had been considered in care decisions [40, 41]. For example, women who were identified to be in emotionally unhealthy clusters could have been supported with psychotherapy sessions following diagnosis to ameliorate the emotional impacts of BC and to help them cope with diagnosis and treatment [40, 41, 222]. However, the work that has focused on identifying clusters of women with BC using HRQOL measures has been somewhat limited. Several studies combined multiple cancer types, many were conducted abroad, most were cross sectional, and all had sample sizes of fewer than 500 women [202-204, 223]. Using a large, population-based study of over 2,000 women with BC offers an opportunity to expand upon previous HRQOL cluster analysis work and draw conclusions more generalizable to women with BC in the U.S.

LPA and LTA are viewed as patient-centered approaches to identifying women susceptible to poor HRQOL [55, 205]. LPA is considered optimal for identifying patterns within large, heterogeneous groups of individuals because it takes individual HRQOL patterns into account rather than aggregating scores across individuals [55, 190, 205]. This is a probabilistic model-based approach, which groups patients together based on probabilities rather than grouping symptoms or HRQOL scores together based on pre-determined distances [222]. Furthermore, LPA is considered to have stronger model fit statistics than traditional cluster analysis approaches, which supports the stability of the LPs identified through LPA [221, 224]. Identifying subgroups of women with BC can offer clinically meaningful guidance on distinct HRQOL patterns experienced by this population [223]. For example, a previous study in pediatric oncology

suggested that LPA could be used to develop prediction models that preemptively identify individuals who might be vulnerable to membership in poor HRQOL LPs so action can be taken early on in their care trajectories [222]. Furthermore, LTA might be able to help predict patients who are likely to transition to poorer HRQOL LPs as they move through the cancer continuum. This type of prediction tool could be especially relevant for women with BC who are in the BC care continuum for several years and could benefit from targeted HRQOL management.

We also identified patient-level characteristics associated with membership in the 5- and 25-month LPs, which offers insights for interventions wishing to target specific groups of patients who are risk for poor HRQOL. As these are non-modifiable characteristics routinely collected in clinic, these factors could be used to easily identify women who are most susceptible to membership in a poor HRQOL LP. Characteristics associated with lower HRQOL LP membership were generally similar at 5- and 25-months including younger age at diagnosis, race, comorbid conditions, and receipt of chemotherapy. However, some distinct differences that may help inform better HRQOL support exist. For example, membership in the poorest HRQOL LP at 5-months was associated with White race as well as socioeconomic factors such as lack of partner support, and insurance coverage and type. At 25-months, Black race was actually associated with membership in the poorest HRQOL LP, but no other socioeconomic factors were associated with poorest HRQOL LP membership. Understanding which patient-level characteristics might be most associated with poor HRQOL LP membership at different phases of the BC care continuum helps inform HRQOL management strategies, which can vary over time [225]. For example, if clinicians are aware that particular characteristics are associated with worse HRQOL patterns at specific BC continuum phases, they might be better equipped to provide the necessary support for patients. Conversely, if supportive resources such as

counseling or nursing support are limited, they could be targeted to the patients most in need. Furthermore, some modifiable patient factors such as obesity and smoking status were also strongly associated with membership in poorer HRQOL LPs as well as deteriorating to a worse LP over time, and could potentially be intervened upon in order to help support HRQOL management in women with BC.

Limitations

Our study was limited to Non-Hispanic White and Black women with Stage 1-3 disease residing in North Carolina from 2008-2013. As such, results may not be generalizable to women of other races/ethnicities, those with advanced stage BC, and women in other states. Although we restricted analyses to women who had completed their first survey within 9-months of BC diagnosis and their follow-up survey within 36-months of BC, the timing of the HRQOL assessments ranged and we were unable to determine how assessment timing may impact LP membership. Finally, although we had a large sample size, when we estimated individual MLMs for each 5-month HRQOL LP in order to predict transitions, our sample sizes for each model became small, which may partially explain why we did not find statistically significant predictors of LP transitions. Future studies with larger samples of women with BC should further explore predictors of LP transitions.

Conclusions

LPA is a probabilistic model-based approach used to identify subgroups of individuals who share similar characteristics that might be associated with their HRQOL patterns.[222] By identifying women with BC who are likely to belong to poor HRQOL LPs, this approach offers a unique opportunity for women with BC to be offered targeted HRQOL support early in the BC care continuum [222]. This could potentially lead to downstream effects such as improved long-term HRQOL, greater adjuvant treatment adherence, and ultimately, better BC outcomes (i.e.,

BC recurrence and survival). Results from this work suggest that we can potentially use routinely collected patient characteristics to help identify women at increased risk for experiencing poor HRQOL during active treatment and survivorship phases of their BC care. These findings are clinically relevant, as there is a national emphasis on patient-centered care that encourages clinicians to routinely collect and monitor HRQOL through electronic health records [11, 13, 89, 92, 187, 226]. Furthermore, patient-level characteristics such as age at diagnosis and race are regularly collected in clinic and could easily be used to identify women at risk for poor HRQOL. If these women were identified following BC diagnosis, they could be connected to mental health specialists, support groups from the onset of active treatment, nutritionists to control weight gain or loss, and physical therapists to help manage physical and functional well-being ailments following treatments. Leveraging LP membership to preemptively anticipate HRQOL needs of women with BC is in line with providing cancer care that reflects patient needs, preferences, and values.

Table 3. Cohort Characteristics Collected at 5-months Post-diagnosis

	Total Cohort N=2,142	%
Age at diagnosis *		
<35 years	79	4%
35-50 years	922	43%
50-64 years	745	35%
65+ years	396	18%
Race *		
White	1105	52%
Black	1037	48%
Smoking status *		
Never	1200	56%
Former	577	27%
Current	365	17%
Marital status *		
Not married	899	42%
Married	1243	58%
Education level *		
<HS	166	8%
HS & Post HS	1108	52%
College+	868	41%
Insurance status *		
None	108	5%
Private	1535	72%
Public	499	23%
Diabetes *	322	15%
COPD *	53	2%
Heart Disease *	106	5%
Obesity *	1023	48%
Hypertension *	969	45%
Surgery *		
Not specified	17	1%
Lumpectomy	1405	66%
Mastectomy	720	34%
Chemo *	1336	62%
Radiation	1570	73%
Herceptin *	308	14%
Stage *		
I	936	44%
II	837	39%
III	256	12%
HR positive	1599	75%
HER 2 positive	336	16%

Note: HS (High School), HR (Hormone receptor), COPD (Chronic Obstructive Pulmonary Disease) * indicates variables that were included in multivariable models.

Table 4. Domain-specific HRQOL by 5- and 25-month Latent Profiles

	Normed U.S Mean (SD)	5-Month Scores				25-Month Scores			
		LP 1 N=682	LP 2 N=617	LP 3 N=606	LP 4 N=227	LP 1 N=554	LP 2 N=252	LP 3 N=799	LP 4 N=537
Physical	22.1 (5.4)	15.8 (6.5)	16.6 (5.7)	24.8 (2.2)	25.5 (2.3)	15.1 (6.5)	23.9 (2.8)	23.4 (3.3)	26.6 (1.3)
Social	19.8 (6.8)	18.6 (5.5)	25.2 (2.3)	24.6 (2.7)	27.3 (0.9)	17.3 (6.5)	17.8 (5.9)	24.2 (3.1)	26.4 (1.9)
Emotional	19.4 (5.1)	15.8 (4.6)	20.5 (2.6)	20.9 (2.2)	22.8 (1.6)	15.4 (4.7)	17.9 (4.3)	20.9 (2.2)	22.4 (1.8)
Functional	18.3(6.9)	14.4 (5.6)	17.9 (5.4)	22.9 (3.5)	26.5 (1.4)	12.7 (5.4)	21.1 (4.3)	21.9 (3.4)	26.9 (1.2)
BC-Specific	N/A	19.9 (6.4)	22.9 (5.9)	26.9 (4.5)	30.3 (3.6)	18.4 (6.9)	22.6 (6.5)	25.4 (5.1)	30.1 (3.6)
Spiritual	N/A	33.5 (8.4)	43.9 (3.6)	41.3 (4.7)	47.8 (0.5)	31.5 (9.9)	41.1 (4.8)	40.2 (6.2)	45.8 (2.7)

Note: Mean scores and standard deviations are presented above. Normed US scores are only available for Physical, Social, Functional and Emotional FACT-B domains and come from Brucker et al.[215]

Table 5. Unadjusted Latent Profile Transitions from 5- to 25-months

5-months	25-months			
	LP 1 (N=554)	LP 2 (252)	LP 3 (N=799)	LP 4 (N=537)
LP 1 (N=682)	356 (52%)	114 (17%)	166 (24%)	46 (7%)
LP 2 (N=617)	137 (22%)	65 (11%)	289 (47%)	126 (20%)
LP3 (N=606)	49 (8%)	59 (10%)	288 (47%)	210 (35%)
LP 4 (N=237)	12 (5%)	14 (6%)	56 (24%)	155 (65%)

Note: LP (Latent profiles). The table above displays row percentages. Row 1 shows the number and percent of women who were in LP 1 at 5-months and who remained in LP 1 at 25-months, who transitioned to LP 2, LP 3 and LP 4.

Table 6. Factors Associated with 5-Month HRQOL Latent Profile Membership

	LP 1		LP 2		LP 3	
	aOR	95% CI	aOR	95% CI	aOR	95% CI
Race (ref=White)						
Black	0.52	(0.35-0.75)***	1.09	(0.74-1.62)	0.28	(0.18-0.43)***
Age at diagnosis (years)	0.95	(0.93-0.96)***	0.98	(0.96-0.99)*	0.98	(0.96-1.0)
Smoking status (ref=never)						
Former/Current	1.41	(1.10-1.81)**	1.25	(0.97-1.62)	1.09	(0.82-1.45)
Marital status (ref=not married)						
Married	0.50	(0.35-0.72)***	0.71	(0.48-1.03)	1.01	(0.56-1.78)
Education level (ref=<HS)						
>HS, College	0.50	(0.78-1.43)	1.00	(0.73-1.36)	2.15	(1.49-3.09)***
Insurance status (ref=private)						
Public	3.09	(1.96-4.83)***	1.32	(0.81-2.12)	1.35	(0.78-2.34)
Uninsured	6.51	(2.12-20.1)***	2.17	(0.66-7.15)	2.59	(0.64-10.43)
COPD (ref=no)	267.68	(147.61-485.44)***	330.4	(170.71-639.46)	64.91	(23.95-175.91)***
Obesity (ref=no)	1.43	(0.99-2.05)	1.80	(1.24-2.60)***	0.84	(0.56-1.28)
Chemotherapy (ref=no)	1.85	(1.22-2.81)***	4.92	(3.13-7.74)***	0.54	(0.34-0.88)**

Note: Latent Profile (LP) 4 was used as the reference category. Models also included prevalence of diabetes, heart disease, obesity, hypertension, receipt of surgery, radiation, and Herceptin, tumor stage and grade. aOR (adjusted odds ratio), 95% CI (95% confidence interval). Statistical significance is denoted as: * <0.05, ** <0.01, *** <0.001

Table 7. Factors Associated with 25-Month HRQOL Latent Profile Membership

	LP 1		LP 2		LP 3	
	aOR	95% CI	aOR	95% CI	aOR	95% CI
Race (ref=White)						
Black	1.75	(1.18-2.60)**	1.03	(0.71-1.47)	0.47	(0.32-0.69)***
Age at diagnosis (years)	0.98	(0.96-1.00)	0.95	(0.93-0.97)***	0.98	(0.96-0.99)*
Smoking status (ref=never)						
Former/Current	1.39	(1.06-1.82)*	1.89	(1.49-2.42)***	1.23	(0.96-1.60)
Marital status (ref=not married)						
Married	1.02	(0.69-1.50)	0.65	(0.46-0.92)*	0.88	(0.61-1.28)
Education level (ref=<HS)						
>HS	1.17	(0.85-1.60)	0.88	(0.65-1.17)	1.78	(1.30-2.44)***
Insurance status (ref=private)						
Public	1.29	(0.80-2.11)	2.79	(1.81-4.33)***	1.06	(0.64-1.78)
Uninsured	3.11	(0.94-10.27)	4.77	(1.53-14.82)**	2.04	(0.55-7.51)
COPD (ref=no)	142.52	(78.84-257.65)***	189.62	(118.23-304.10)***	95.24	(48.62-185.55)***
Heart disease (ref=no)	3.45	(1.24-9.61)*	3.42	(1.27-9.19)*	1.85	(0.59-5.86)
Obesity (ref=no)	2.16	(1.49-3.15)***	1.94	(1.37-2.74)***	0.96	(0.66-1.38)
Chemo (ref=no)	1.92	(1.21-3.05)**	1.76	(1.15-2.69)**	0.93	(0.60-1.45)
Stage 2/3 (ref=Stage 1)	1.45	(1.07-1.97)*	1.34	(1.01-1.78)*	1.12	(0.83-1.53)

Note: Latent Profile (LP) 4 was used as the reference category. Models also included prevalence of diabetes, hypertension, receipt of surgery, radiation and Herceptin, and tumor grade. aOR (adjusted odds ratio), 95% CI (95% confidence interval). Statistical significance is denoted as: * <0.05, ** <0.01, *** <0.001

Figure 3. Mean HRQOL Scores by 5-month Latent Profiles
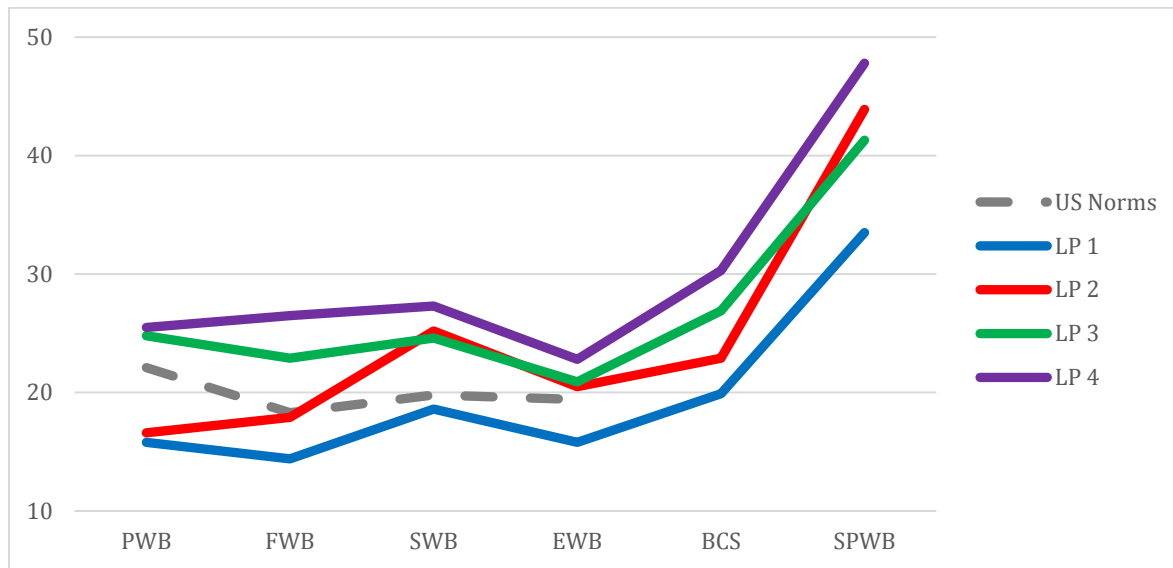
Note: Mean HRQOL domains by latent profile (LP) are presented above. PWB (Physical Well-Being), SWB (Social Well-Being), EWB (Emotional Well-Being), FWB (Functional Well-Being), BCC (Breast Cancer Specific Concerns), SPWB (Spiritual Well-Being). Normed US scores are only available for Physical, Social, Functional and Emotional FACT-B domains and come from Brucker et al. [215]

Figure 4. Mean HRQOL Scores by 25-month Latent Profiles
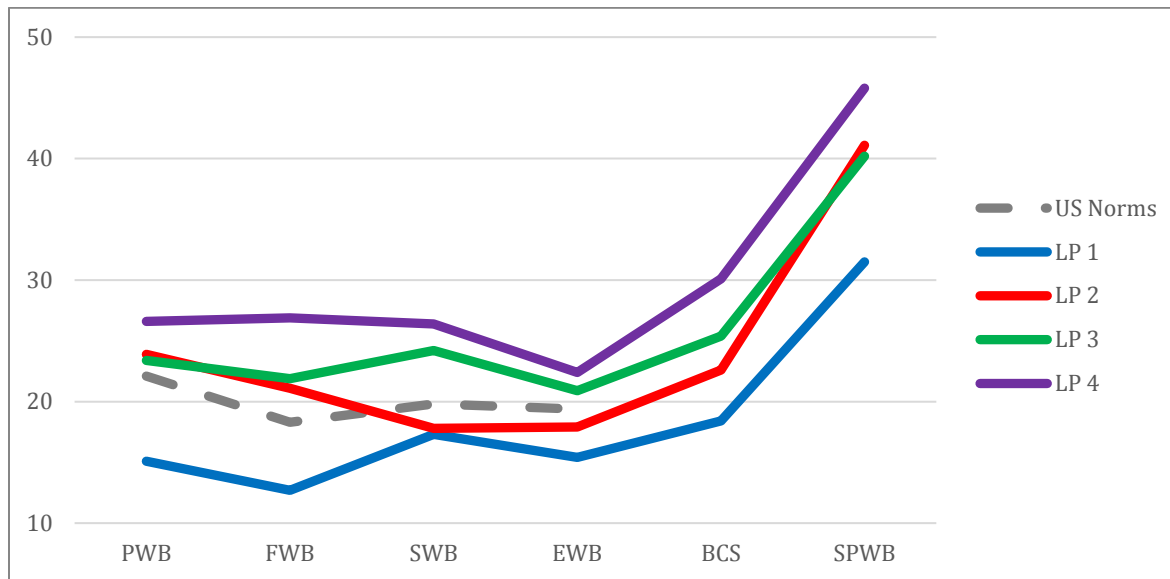

Note: Mean HRQOL domains by latent profile (LP) are presented above. PWB (Physical Well-Being), SWB (Social Well-Being), EWB (Emotional Well-Being), FWB (Functional Well-Being), BCC (Breast Cancer Specific Concerns), SPWB (Spiritual Well-Being). Normed US scores are only available for Physical, Social, Functional and Emotional FACT-B domains and come from Brucker et al. [215]

CHAPTER 5: UNDERSTANDING RACIAL DIFFERENCES IN HEALTH-RELATED QUALITY OF LIFE IN A POPULATION-BASED COHORT OF BREAST CANCER SURVIVORS

Introduction

Over 3 million women in the United States (U.S) are currently living with breast cancer (BC) or have a history of BC [60]. Given that 5- and 10-year BC survival rates are 90% and 80%, respectively, most women diagnosed with BC become long-term survivors [59]. As the number of women surviving BC grows, monitoring and characterizing changes in health-related quality of life (HRQOL), as well as identifying women at high-risk for long-term HRQOL deterioration during survivorship, is critical to ensuring patient-centered care across the BC care continuum.

Thirty percent of women experience poor psychosocial and physical HRQOL before, during, and after treatments [3, 96]. Women with BC report greater levels of treatment-related symptoms compared to similarly aged healthy women [5, 100, 101]. Studies have shown BC is a risk factor for poor mental health, and rates of depression are twice as high among adults with cancer than those without cancer [4, 5].

BC risk and burden varies systemically between Black and White women [135]. Although BC incidence rates do not differ significantly between Black and Whites, Blacks are more likely to die from BC [59]. Black women are more likely to be diagnosed at younger ages with more aggressive tumors [48]. As Blacks are over-represented in lower socioeconomic groups, they may be more likely to experience diagnosis and treatment delays associated with worse survival [142] [46].

Racial gaps in HRQOL are well-documented in BC, but differences are not uniform across ages or HRQOL domains [3, 14, 16-18, 42]. Specifically, compared with their White

counterparts, Black women with BC report worse physical and functional HRQOL [42, 156].

However, this may not be the case at different phases of BC care. A retrospective Medicare study

found that while racial disparities in HRQOL were prevalent before cancer diagnosis, gaps in

certain domains narrowed following exposure to the cancer care system [14]. Once Black women

are diagnosed with BC and engage with the health care system, Black-White differences may

narrow because previously unaddressed needs are met, which positively impacts HRQOL [14].

To our knowledge, no study has assessed racial disparities in changes in individual

HRQOL domains over time in a large, multi-payer, population-based cohort. Our objective was

to determine whether or not HRQOL varied between White and Black women during active

treatment, survivorship, and in changes between these two time points. To do this, racial

differences in six HRQOL domains (i.e., physical, social, emotional, functional, and spiritual

well-being, and BC-specific concerns) were examined between 5- and 25-months after diagnosis

among Black and White women with BC in North Carolina.

Methods

Data

Data for this study came from the third phase of the Carolina Breast Cancer Study

(CBCS-III). CBCS-III enrolled 3,000 women diagnosed with incident, invasive, pathologically

confirmed BC between 2008 and 2013. Participants spanned 44 counties in North Carolina and

were identified using rapid case ascertainment [46]. To ensure representation of young and Black

women, eligible participants were sampled from four strata (sampling fractions in parentheses):

Blacks under 50 years (100%), Blacks 50 years and older (60%), Whites under 50 years (40%),

and Whites 50 years and older (15%) [46]. As such, 50% of CBCS-III consists of Black women, of

whom approximately half are under 50. CBCS-III includes women residing in rural and urban

settings, with private and/or public insurance (and uninsured), and those of varying income

levels [46]. In-person surveys were administered to women within 9-months of diagnosis, and at a median of 5.2 months post-diagnosis (referred to as the "5-month survey" and ranging from 1.8-8.9 months) [46]. Surveys collected data on demographics, socioeconomics and HRQOL [46, 188]. Twenty-five months post-diagnosis women completed a follow-up mail-in survey, which included HRQOL questionnaires. Participants completed informed consent, including permission for researchers to abstract medical records [46, 188]. This study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Participants

As the study was interested in changes in HRQOL between active treatment and survivorship (in terms of diagnosis and primary treatment), the cohort was restricted to women who completed both 5-and 25-month surveys. Furthermore, as the focus of this study was in Black-White differences in HRQOL, only Non-Hispanic Black and White women were included. Of the 2,998 women who completed a 5-month survey, 2,561 (85%) completed a 25-month survey. Additionally, 97 (4%) women were excluded because they identified as "other race" or Hispanic. Women with distant stage BC represented less than 3% of the cohort and were excluded to ensure tumor and treatment homogeneity. The final cohort included 2,142 women.

Outcome

HRQOL instruments included the Functional Assessment of Cancer Therapy for BC (FACT-B) and the Functional Assessment of Chronic Illness Therapy for Spiritual Well-Being (FACIT-SP). The FACT-B includes 5 domains: Physical Well-Being, Social Well-Being, Emotional Well-Being, Functional Well-Being, and BC-specific Concerns [56]. The FACT-B has been validated and shown to be responsive among women with BC [56]. Minimally important differences (MID) or smallest differences in HRQOL perceived as clinically meaningful are 2-points per domain [195].

The FACIT-SP is a validated chronic disease specific and includes the Spiritual Well-Being domain [56]. The FACIT-SP is the most commonly used instrument to measure spiritual well-being in cancer [192]. As with the FACT-B, higher scores indicate better HRQOL [56] [192].

Independent Variable

Self-reported race (Non-Hispanic Black or White).

Covariates

Demographic and lifestyle characteristics included age at diagnosis, smoking status, body mass index, and comorbid conditions (e.g., diabetes, chronic obstructive pulmonary disease, obesity, hypertension, and heart disease). Socioeconomics included marital status, education, family income, urban/rural residence, and insurance status at 5-months. Given a high degree of collinearity between socioeconomic factors (r>0.80), only education and insurance status were included in our models. Treatment covariates included surgery, radiation, chemotherapy, and Herceptin. Although we examined racial differences by tumor stage, size, grade, nodal status, and hormone receptor (HR) status, due to collinearity (r>0.80), we only controlled for tumor stage and HR status.

Statistical Analysis

We compared characteristics between Black and White women using t-tests for continuous covariates and chi-square tests for categorical variables. We tested differences in unadjusted mean HRQOL scores for FACT-B and FACIT-SP domains between Black and White women. We also compared physical, functional, social and emotional well-being domains [215]. Changes in HRQOL domains between 5- and 25-months were calculated as 5-month scores subtracted from 25-month scores. Positive changes show improvements and negative changes denote decrements.

Analysis of covariance (ANCOVA) models were used to examine predictors of HRQOL at 25-months, adjusting for 5-month scores, demographics, comorbidities, socioeconomics, treatment, and tumor characteristics. Each model's outcome was the 25-month HRQOL score. We ran one model per domain to isolate domain-specific predictors that may be masked by overall HRQOL score. Given a sample size of 2,142 women and significance level of 5%, we were powered at nearly 100% to detect minimally important differences (MIDs) for each domain. Analyses were performed in SAS 9.3 with two-sided statistical tests and a significance level of 5% for all analyses.

Assessing Racial Disparities

We explored three approaches to assessing racial disparities to better understand if racial gaps in HRQOL existed and to identify potential mediators of HRQOL disparities. ANCOVA models controlling for race, treatment and tumor characteristics, but not socioeconomic factors were estimated. Differences in adjusted Least Square Means (LSMs) between Black and White women were tested for each domain. This was the study's primary approach and is consistent with the Institute of Medicine's (IOM) operationalization of racial disparities in health care, which conceptualizes race as a social construct linked to a range of mediating factors, including socioeconomic status [123]. The IOM considers a disparity as the difference in quality of care between two racial groups that cannot be explained by clinical differences, health status or patient preferences [128]. The motivation behind this approach is that minority groups are overrepresented in low socioeconomic groups; thus, including both race and socioeconomics in a model may underestimate racial differences [123]. The following two approaches were implemented as sensitivity analyses to explore the extent to which racial differences were mediated by measurable socioeconomic factors.

ANCOVA models controlling for race and socioeconomic factors (and tumor and

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treatment characteristics) were estimated. Differences in adjusted LSMs between Blacks and Whites were tested. This approach is the residual direct effect (RDE) of race on health care, because it controls for all measurable mediators of the relationship between race and the outcome, thereby resulting in a "race" parameter estimate reflecting the unmediated effect of race on HRQOL [128] [130].

Models testing interaction terms between race and socioeconomic factors were estimated. This final approach treated race and socioeconomic status as distinct constructs which have independent and interactive effects on HRQOL [123]. That is, socioeconomic status is on the causal pathway between race and HRQOL and may moderate associations [124].

As additional sensitivity analyses, we ran race-stratified models to determine if race modified relationships between individual characteristics and HRQOL. An age-stratified model was also run to evaluate if disparities existed among women below or above age 40, which is the age at which women begin mammography screening. Finally, models stratifying women by menopausal status were estimated to determine if relationships between race and HRQOL varied.

Results

Participant Characteristics

Table 8 presents race-stratified characteristics of the cohort. Age at diagnosis, surgery type, receipt of Herceptin, and prevalence of COPD and heart disease did not differ significantly between groups. Compared to Whites, Blacks were less likely to be married, have public insurance, and less education. Diabetes, obesity and hypertension were twice as common among Blacks. Blacks were more likely than Whites to be diagnosed with later stage BC and receive aggressive treatments such as chemotherapy and radiation.

Unadjusted HRQOL

During active treatment (5-month survey), mean physical well-being scores were 1.2-3.7 points below U.S norm scores (Table 9) [215]. White women reported physical and functional well-being scores 2.5 and 1.9 points higher, respectively, than Blacks (p<0.0001). Blacks reported spiritual well-being scores 2.1 points higher than Whites at 5-months (p<0.0001).

During survivorship (25-month survey), Whites reported HRQOL scores above U.S norms across physical, social, emotional and functional well-being domains (Table 9, Figures 5-8) [215]. Blacks, however, reported physical well-being scores 1.2 points below U.S norms and 2.3 points below their White BC counterparts (p<0.0001). Whites reported functional well-being scores 2.4 points higher on average than Blacks (p<0.0001), exceeding MID thresholds. Black women reported spiritual well-being scores 2-points higher than Whites (p<0.0001).

As women entered survivorship, MIDs of 2.3-2.5 points (improvements over time) were seen in physical well-being for Whites and Blacks. We did not observe meaningful changes for other domains (Table 9). On average, social well-being declined 1-point from 5- to 25-months for both groups, but was 1.7-3.0 points above U.S norms (Figure 6). From active treatment to survivorship, spiritual well-being declined 1-point for both groups while emotional well-being remained unchanged. On average, Black-White differences in HRQOL changes from 5- to 25-months ranged from 0.1-0.8 points. Differences between Blacks and White in functional well-being and BC-specific concerns changes from 5- to 25- months were statistically significant, but did not exceed MID thresholds.

Adjusted HRQOL

In models adjusting for characteristics in Table 8, older age was significantly associated with better HRQOL at 25-months across all domains (Table 10). Being a smoker was associated with 1.2-1.9-point decreases in HRQOL across domains except for social well-being. Higher

education was associated with the largest increase in physical and functional HRQOL. Obesity was significantly associated with decreases in BC-specific concerns.

IOM

We observed statistically significant racial differences in physical, emotional, functional and spiritual well-being (Figure 11) during survivorship. Specifically, Whites had physical and functional well-being scores 0.5 ($p<0.05$) and 1.0 ($p<0.0001$) points higher, respectively, than Blacks. However, Blacks had emotional and spiritual well-being scores 0.5 ($p<0.05$) and 0.8 ($p<0.01$) points, respectively, higher than Whites. Differences were statistically significant, but none exceeded 2-point MID thresholds.

RDE

Once socioeconomics were added to adjusted models, emotional, functional, and spiritual well-being domains remained significantly different between Black and White women (Figure 5) during survivorship. Black race was significantly associated with a 0.5-point ($p<0.01$) increase in emotional well-being and a 1.2-point ($p<0.01$) increase in spiritual well-being, while White race was associated with a 0.5-point ($p<0.05$) increase in functional HRQOL. Although differences were statistically significant, none exceeded 2-point MID thresholds.

Race and Socioeconomic Interactions

Interaction terms between race and socioeconomic factors were not statistically significant at the 0.05 level.

Sensitivity Analyses

In race-stratified models, patient and treatment characteristics had similar associations with HRQOL in terms of estimates' direction, magnitude and significance for Blacks and Whites (results not shown). One notable difference was that among Black women, receipt of Herceptin was significantly associated with 0.8-1.2 point lower physical, emotional, functional and BC-

specific concerns scores (p<0.01), but this association was not seen among Whites. White-Black Differences in HRQOL by age or menopausal status were not observed.

<u>Discussion</u>

Domain-specific HRQOL patterns were examined to assess if Black and White women with BC are equally susceptible to poor HRQOL during active treatment and survivorship. Using the RDE approach, we found statistically significant, but not clinically meaningful Black-White differences in emotional and spiritual well-being at 25-months. Implementing the IOM approach, we again found small, but significant differences in physical, functional, emotional and spiritual well-being domains during survivorship. These findings are similar to other BC survivor studies that found racial differences in HRQOL following treatment were small and not clinically meaningful [227]. Previous work attributed racial differences in HRQOL to BC stage, treatments, comorbidities, and socioeconomics related to health care access [228].

Racial differences in physical and functional HRQOL appear to be mediated by socioeconomics. Race coefficients for physical and functional well-being domains attenuated by 50% once socioeconomics were controlled for, whereas emotional and social well-being coefficients remained unchanged. Gaps in spiritual well-being actually widened once socioeconomics were added to the model. Worse physical and functional HRQOL may be related to racial differences in access (e.g., financial barriers) to cancer care, which often emphasize management of physical and functional effects of cancer and its treatment [229]. Thus, racial differences in access to care are more likely to impact physical and functional well-being. Furthermore, physical and functional HRQOL may be impacted by comorbid conditions such as obesity, diabetes and hypertension, all of which were more prevalent in Black women in our study. A systematic review of BC survivors concluded that, in general, Black women report worse physical and functional well-being than their White counterparts, however, once

demographic, socioeconomic and medical characteristics were adjusted for, physical and functional well-being differences between Black and White women attenuated, suggesting differences may be largely mediated by demographic and socioeconomic factors [44]. Socioeconomic-related barriers to physical and functional well-being must be addressed to help narrow gaps in these domains. Potential ways to improve physical and functional HRQOL could be to help manage other comorbidities and promote greater physical activity. Black women with BC tend to report lower levels of physical activity, which has been associated with poorer physical well-being and overall HRQOL [3, 158]. Studies have also confirmed that although BC survivors report less physical activity compared to the general population, Whites with BC have higher levels of physical activity compared to Blacks, which may facilitated by physical well-being and vitality [42, 156, 158].

Our findings are consistent with previous work concluding that women with BC report greater levels of social support compared to healthy women their age [22]. Increased social support among women with BC has been associated with better adjustment following primary BC treatments [229, 230]. As such, it is not surprising that women in our study reported social well-being scores well above U.S norms during active treatment. Black women were less likely to be married, suggesting that their social support may have come from sources other than partners (i.e., community, religious organizations) [229]. Previous studies also suggest Blacks experience positive growth following BC diagnosis and treatment, which may support social and emotional well-being [22, 159].

Black women consistently report the importance of spirituality in coping with BC [156, 160, 162]. Spirituality has been described as a source of hope and comfort for Black women struggling with the psychosocial burden of BC diagnosis and treatment [159]. In fact, clinicians have been

recommended to promote spirituality as a coping mechanism among Black women with BC, as it may mitigate effects of BC on psychosocial health [44] [159]. This is consistent with our findings that Blacks reported significantly higher levels of emotional and spiritual well-being than Whites, even after adjusting for patient characteristics.

Emotional and spiritual well-being were the only HRQOL domains not attenuated by socioeconomic factors. Racial differences in spiritual well-being actually widened after adjusting for socioeconomics. At first, it seems this suggests emotional and spiritual well-being domains may not be impacted by socioecological burden Black women more often endure [156]. Financial stressors, urban residence, job insecurity, and balancing multiple responsibilities (e.g., house, parental, job) make dealing with BC more difficult for Blacks [42, 44, 156]. Following diagnosis, Black women struggle with these challenges, exacerbating physical and functional well-being, which often decline following BC treatment [42, 156]. This is in line with our observations that physical and functional HRQOL were lower among Blacks during active treatment. Emotional and spiritual well-being domains, however, appear more resistant to life stressors affecting other domains due to increased spirituality and community support. Another possibility is that BC and socioeconomic factors actually impact emotional and spiritual well-being, but in a way that reinforces these domains. The Superwoman role, a theory stating Black women feel they must exude strength, suppress emotions, and demonstrate perseverance when faced with adversity, may partially explain this [231]. If Black women do not allow themselves to acknowledge weakness or stress related to BC, self-reported emotional and spiritual well-being may not appear to suffer [231].

Limitations

First, we only included Non-Hispanic Black and White women in North Carolina, limiting generalizability to women outside of the state and of other racial groups. As most women have initiated primary BC treatments by 5-months, there is no pre-treatment HRQOL measure. However, BC treatments (from medical records) were adjusted for in analyses. We were unable to control for unmeasured confounders such as patient preferences, culture, economic, political, and legal factors that may impact HRQOL.[124] As such, even in conservative models, race coefficients encompassed unmeasurable factors such as institutional racism, different care seeking behavior and access to health care networks that are not determined by insurance status, education and income, introducing potential bias.

Conclusion

The richness of CBCS-III made it an ideal platform to understand racial disparities in HRQOL among women with BC in North Carolina. Statistically significant racial differences in HRQOL changes (from active treatment to survivorship) were identified, but differences were not considered clinically meaningful. Results suggest socioeconomic factors may considerably mediate racial gaps in physical and functional HRQOL between White and Black women with BC. Supportive services should consider domain-specific findings to provide targeted HRQOL management across socio-demographic groups of women with BC.

Table 8. Cohort Characteristics by Race

	Whites N=1,105		Blacks N=1,037		P-value
Demographics					
Age at diagnosis					0.1327
<35	39	4%	40	4%	
35-50	482	44%	440	42%	
50-64	363	33%	382	37%	
65+	221	20%	175	17%	
Smoking status					<0.0001***
Never	593	54%	607	59%	
Former	346	31%	231	22%	
Current	166	15%	199	19%	
Socioeconomics					
Married	802	73%	441	43%	<0.0001***
Education					<0.0001***
<High School	47	4%	119	11%	
Completed High School	514	47%	594	57%	
College+	544	49%	324	31%	
Insurance status					<0.0001***
None	30	3%	78	8%	
Private	917	83%	618	60%	
Public	158	14%	341	33%	
Comorbidities					
Diabetes	91	8%	231	22%	<0.0001***
COPD	29	3%	24	2%	0.6443
Heart Disease	51	5%	55	5%	0.4629
Obesity	100	9%	190	18%	<0.0001***
Hypertension	350	32%	619	60%	<0.0001***
Treatments					
Surgery					0.2337
Not specified	11	1%	6	<1%	
Lumpectomy	709	63%	696	66%	
Mastectomy	385	34%	335	32%	
Chemotherapy	627	57%	709	68%	<0.0001***
Radiation	785	71%	785	76%	0.0149*
Herceptin	143	13%	165	16%	0.0502
Tumor characteristics					
Stage					<0.0001***
I	570	52%	416	40%	
II	416	38%	466	45%	
III	119	11%	155	15%	
Hormone Receptor Status					<0.0001***
Positive/Borderline	909	81%	690	65%	
Negative	196	18%	347	33%	

p<0.05 *, p<0.01 **, p<0.0001***

Table 9. Unadjusted HRQOL Scores by Race and U.S Norms[215]

| | U.S Norms | 5-Month Scores | | 25-Month Scores | | 5 to 25-month Changes | |
		White	Black	White	Black	White	Black
Physical	22.1 (5.4)	20.9 (6.0)	18.4 (6.8)	23.2 (5.3)	20.9 (6.3)	2.3	2.5
Social	19.8 (6.8)	23.7 (4.5)	22.6 (5.1)	22.8 (5.3)	21.5 (6.2)	-0.9	-1.1
Emotional	19.4 (5.1)	19.4 (3.7)	19.3 (4.5)	19.5 (3.9)	19.5 (4.6)	0.1	0.2
Functional	18.3(6.9)	20.1 (5.8)	18.2 (6.7)	21.8 (5.6)	19.4 (7.0)	1.7	1.2
BC-Specific	N/A	23.9 (6.1)	23.6 (6.9)	25.0 (6.3)	23.9 (7.5)	1.1	0.3
Spiritual	N/A	39.3 (7.9)	41.4 (7.1)	38.5 (8.7)	40.5 (8.1)	-0.8	-0.9

Means (standard deviations). Change was calculated as 5-month scores subtracted from 25-month scores.

Table 10. Analysis of Covariance Models by HRQOL Domain

	25-Month HRQOL					
	Physical	**Social**	**Emotional**	**Functional**	**BC-Specific**	**Spiritual**
5-Month HRQOL	0.46***	0.68***	0.54****	0.52***	0.58***	0.68***
Demographics						
Black race (ref=white)	-0.17	-0.18	0.54**	-0.52*	0.04	1.12**
Age at diagnosis	0.04**	0.03*	0.04***	0.03*	0.06***	0.04**
Smoking status (ref=never)						
Former	0.08	-0.27	-0.02	-0.21	-0.31	0.31
Current	-1.34**	-0.77*	-1.32***	-1.84***	-2.03***	-2.25***
Socioeconomics						
Marital status (ref=not married)	-0.08	-0.31	0.12	0.24	0.02	0.51
Education level (ref=<HS)						
HS & Post HS	0.76	0.85*	0.56	1.75***	0.39	0.36
College+	1.53**	0.77	0.63	1.95***	0.57	0.16
Insurance status (ref=private)						
Public	-1.55***	0.01	-0.43*	-1.65***	-1.35***	-0.69
Uninsured	-1.72**	-0.25	-0.01	-2.02***	-2.14***	-0.25
Comorbid Conditions						
Diabetes (ref=no)	-0.34	-0.48	-0.23	-0.33	0.52	0.34
COPD (ref=no)	-0.93	-0.59	-0.34	-1.45*	-0.91	-0.01
Heart Disease (ref=no)	-1.04*	-0.29	-0.88*	-1.22*	-0.51	-1.44*
Obesity (ref=no)	-0.90***	-0.05	-0.33*	-0.66**	-1.03***	-0.33
Hypertension (ref=no)	-0.11	-0.24	-0.25	-0.21	-0.25	-0.34
Treatments						
Surgery (ref=lumpectomy)						
Mastectomy	-0.29	-0.11	-0.07	-0.01	-0.56	-0.15
Not specified	0.36	0.15	1.41	0.65	-0.57	1.89
Chemotherapy (ref=none)	0.24	-0.13	0.03	0.65*	0.52	-0.08
Radiation (ref=none)	0.03	-0.03	-0.02	0.18	0.04	-0.12
Herceptin (ref=none)	-0.43	-0.11	-0.35	-0.51	-0.51	-0.35
Tumor characteristics						
Stage (ref=Stage I)						
II	-0.36	-0.23	-0.28	-0.31	-0.94**	-0.13
III	-0.15	0.04	-0.18	-0.15	-1.09*	-0.11
HR negative (ref=positive)	0.29	-0.31	0.21	0.27	-0.27	0.18

p<0.05 *, p<0.01 **, p<0.0001* 25-month HRQOL scores are adjusted for HRQOL at 5-months.

Figures 5-8: HRQOL at 5- and 25-months by race with dotted line representing U.S norms

Figure 5. Physical Well-Being at 5- and 25-months by Race

Physical Well-Being

White — Black — US Norm Score
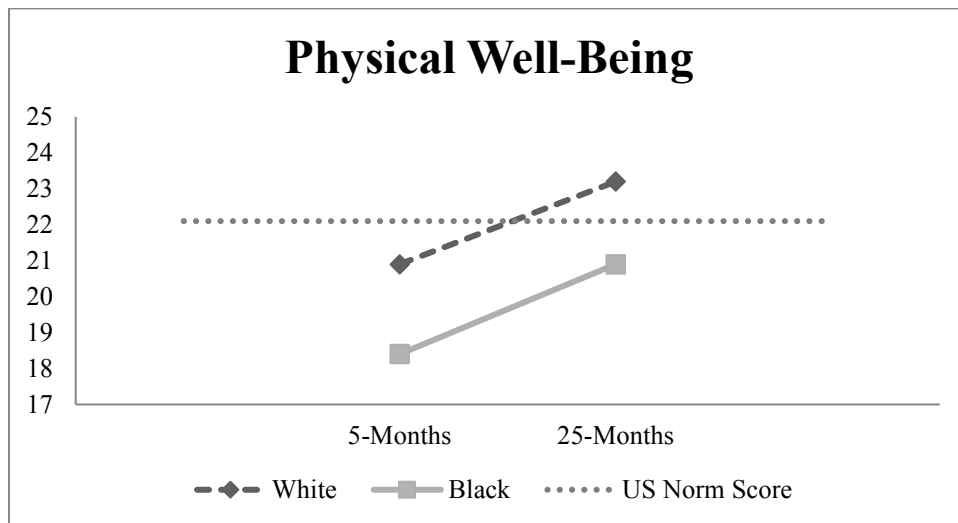
Figure 6. Social Well-Being at 5- and 25-months by Race

Social Well-Being

White — Black — US Norm Score
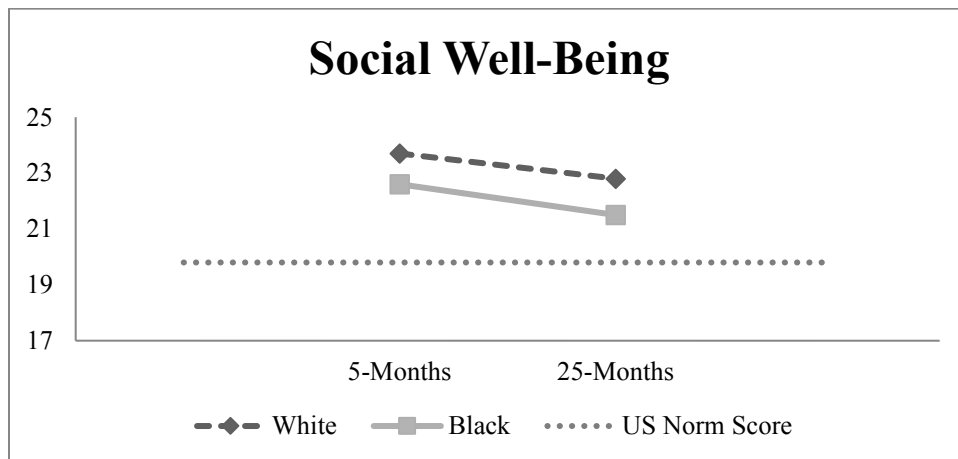
Figure 7. Emotional Well-Being at 5- and 25-months by Race

Emotional Well-Being
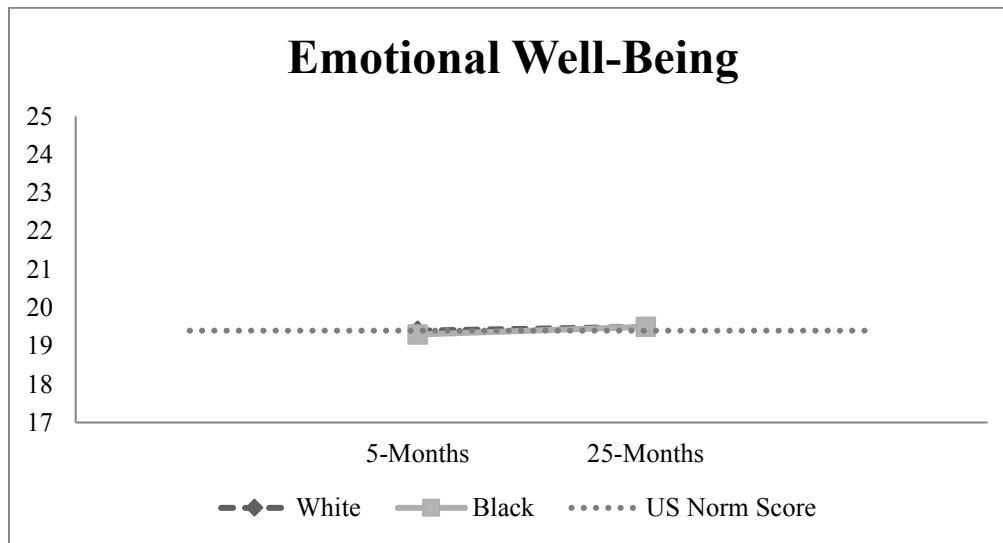
Figure 8. Functional Well-Being at 5- and 25-months by Race

Functional Well-Being
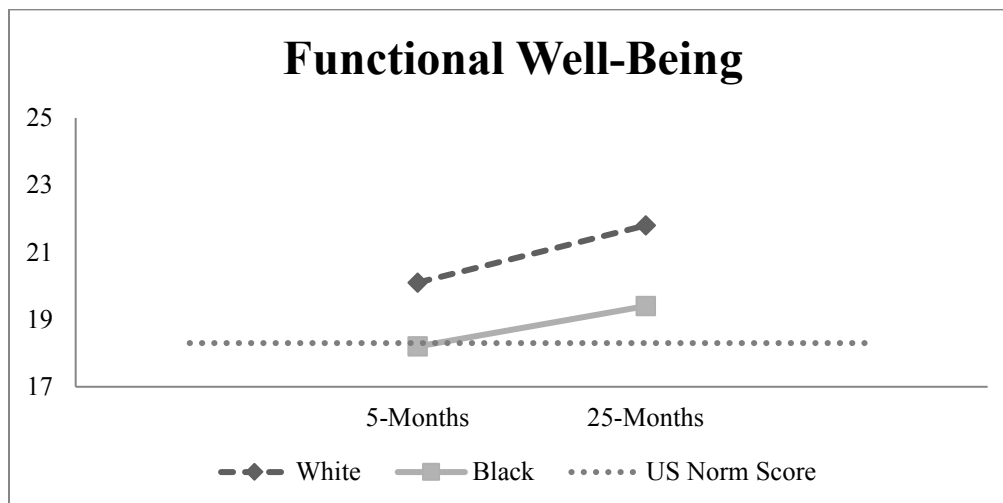
Figure 9. Breast Cancer-Specific Concerns at 5- and 25-months by Race

Breast Cancer Specific Concerns

White ----◆----
Black ——■——
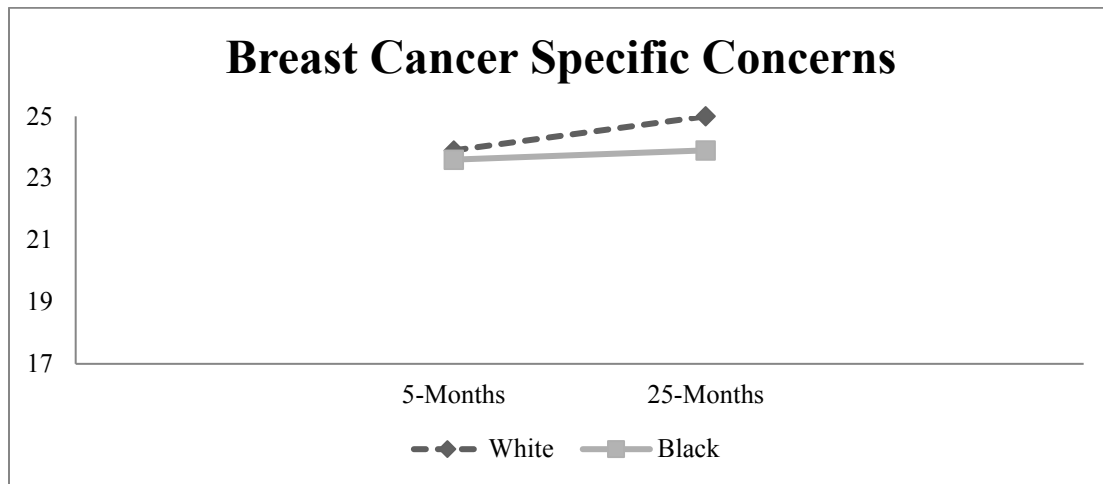
Figure 10. Spiritual Well-Being at 5- and 25-months by Race

Spiritual Well-Being
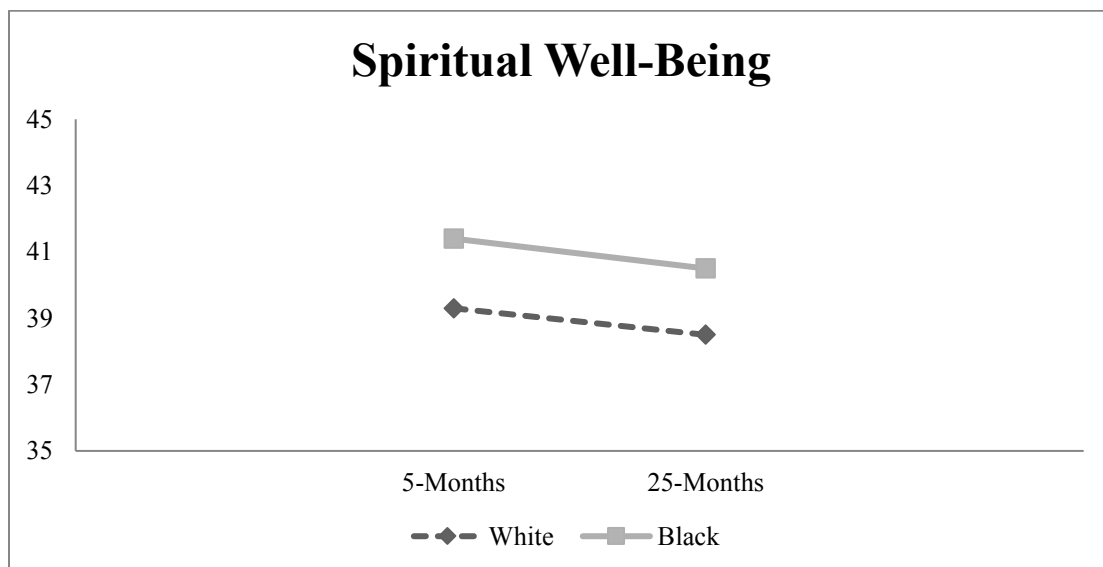
White ----◆----
Black ——■——

Figure 11. Adjusted Least Square Mean Differences in 25-Month Scores by HRQOL Domain
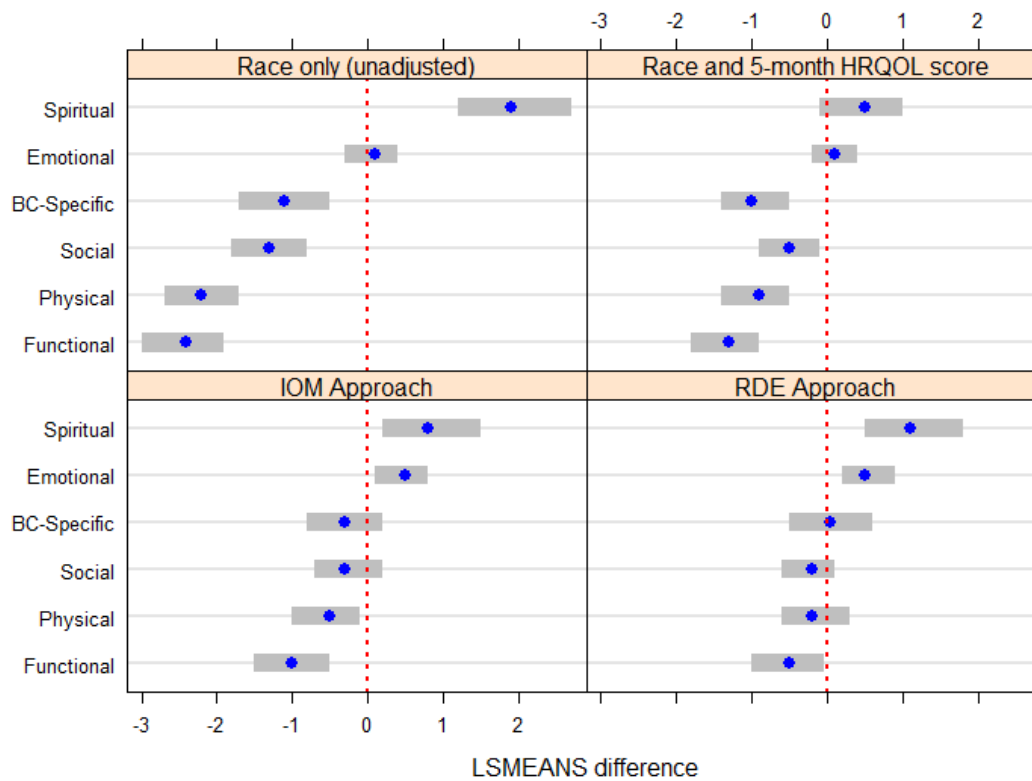
Note: Blue dots represent adjusted LSM differences. Grey bars represent 95% confidence intervals. Differences calculated as White scores subtracted from Black scores. Negative differences indicate White women have higher HRQOL than Black women.

CHAPTER 6: INVESTIGATING ASSOCIATIONS BETWEEN HEALTH-RELATED QUALITY OF LIFE AND ENDOCRINE THERAPY UNDER-UTILIZATION IN WOMEN WITH EARLY STAGE BREAST CANCER

Introduction

Breast cancer (BC) is a heterogeneous disease with several tumor subtypes, each of which respond differently to treatments.[57] Hormone receptor positive (HR+) subtypes account for 80% of BCs and include tumors expressing receptors for estrogen or progesterone hormones.[25, 57, 61] Following primary local treatment, sustained targeted therapy against hormone receptors using endocrine therapy (ET) improves the prognosis of these tumors significantly.[57, 61] [3,4] ET, indicated for nearly all HR+ BCs, is recommended as a daily pill for 5 years following primary BC treatments.[76 36, 77]

ET is a highly effective adjuvant treatment associated with a 40% reduction in BC recurrence and 30% reduction in BC-related mortality.[27-31, 78] Despite its clinical benefits, 10-30% of HR+ women never initiate therapy and, among those who initiate, 50% are non-adherent by 5 years.[27-31] Under-utilization is concerning, as women who are inconsistent in medication use or who discontinue ET before 5 years do not realize full benefits.[31, 34, 78] Specifically, women who under-utilize ET have worse BC outcomes (i.e., BC recurrence and survival) compared to women who take ET for 5 years.[34, 85]

ET is associated with side effects and poor health-related quality of life (HRQOL).[75 74 36] As poor HRQOL following diagnosis may persist after primary treatments, HRQOL may interfere with adjuvant treatment decisions.[108 19] Poorly managed HRQOL during active treatment may contribute to under-utilization, as poor HRQOL can hinder a woman's ability to

cope with ET side effects as she struggles to acclimate to life after primary BC treatments.[32-37] In this study, we operationalized under-utilization as not initiating or not adhering to ET.[39]

Although studies have collected data on poor HRQOL while women take ET, to our knowledge, no studies have examined associations between ET initiation and HRQOL prior to initiating. Some work has evaluated relationships between HRQOL and non-adherence and non-persistence, but results have been mixed, with some reporting no associations and others reporting that poor HRQOL is associated with non-adherence. [35, 50, 121] Findings from one recent study indicated that worse psychosocial HRQOL and greater patient distress were predictive of ET non-persistence.[121]

Evidence from previous work should be interpreted with caution, as many studies employed post-ET initiation HRQOL assessments, which may be confounded by ET side effects and few employed BC-specific HRQOL instruments. [19, 21] Additionally, all studies were carried out in small cohorts of predominantly Non-Hispanic White women.[50 35, 75 121] The objectives of our study were to examine associations between pre-ET HRQOL and non-initiation as well as HRQOL during active treatment and non-adherence in a large, racially and socio-economically diverse, population-based cohort of women with BC. Identifying associations between HRQOL, a modifiable factor, and inappropriate ET use offers opportunities for future interventions to reduce under-utilization, thus improving BC outcomes among HR+ women.

Methods

Data

Three thousand women diagnosed with invasive BC between 2008-2013 in North Carolina were enrolled in the third phase of the Carolina Breast Cancer Study (CBCS-III) through rapid case ascertainment.[46 188] Fifty percent of CBCS-III consists of Black women and 50% of women are under age 50. CBCS-III includes women in rural and urban settings across 44

counties, those with private, public and no insurance, and women of varying income levels.[46]

Four data sources were combined for this study: CBCS-III baseline ("5-month survey") medical

record abstraction, pathology reports, and follow-up ("25-month survey").[225] Demographics,

lifestyle, and HRQOL were collected in-person at a median post-diagnosis time of 5.2 months

(1.8-8.9 months).[46, 189] Participants consented for researchers to obtain and abstract medical

records.[46, 188, 189] Women completed a follow-up survey at a median of 25.1 months post-

diagnosis (20-36 months), which included adherence questions. Medical record abstraction data

included comorbidities and treatments. Pathology reports included tumor stage, grade, and HR+

status. The Institutional Review Board at the University of North Carolina at Chapel Hill

approved this study.

Participants

Of the 2,998 women enrolled in CBCS, we excluded women who: did not complete

adherence questions (6%), identified as "other race" or Hispanic (3%), had distant stage BC or

no surgery (3%), or their first survey occurred more than 9 months post-diagnosis (5%). Limited

representations of other races and Hispanics precluded us from making inferences about these

groups. The cohort was further restricted to women with HR+ BC to ensure ET eligibility

(n=1,599). Two separate cohorts were used for initiation and adherence analyses. ET initiation

analyses were limited to 953 women who did not initiate ET before their 5-month survey. Of the

1,599 women, adherence analyses were limited to 1,114 women who initiated ET and completed

adherence questions.

Outcomes

Primary study outcomes were 1) whether or not a woman initiated ET and 2) whether or

not she adhered to ET. Non-initiation was a binary variable obtained from medical records. Non-

adherence was categorized as a binary variable from 2 self-reported questions on the 25-month

survey: 1) "At this time, are you taking hormonal therapy pills?" and 2) "Over the past 2 weeks, how many days did you miss your hormonal pills?" Response options for the first question were "Yes, I am taking them exactly as prescribed by my doctor," "Yes, I'm taking them, but not every day," and "No, I stopped taking those pills." If a woman responded she was taking pills as prescribed she was considered "adherent" and if she responded that she stopped taking pills she was considered "non-adherent." Among women who reported not taking ET every day, self-reported pill consumption in the past 2 weeks from a modified Morisky questionnaire was used to determine adherence. Those who missed 2 or fewer days in the last 2 weeks were considered "adherent" (>80%) and those who reported missing 3 or more days in the last 2 weeks were considered "non-adherent"(< 80%).[78] Women who were non-adherent or who discontinued were grouped as "non-adherent" for analyses.

HRQOL Instruments

HRQOL was measured using the Functional Assessment of Cancer Therapy for BC (FACT-B) and Functional Assessment of Chronic Illness Therapy for Spiritual Well-Being (FACIT-SP). The FACT-B is BC-specific and includes physical, social, emotional and functional well-being, and BC-specific concerns.[191][191] The FACIT-SP measured spiritual well-being.[56] FACT-B and FACIT-SP domains were assumed to be continuous with higher scores representing better HRQOL.

Key Independent Variable

The primary explanatory HRQOL variable had 4 levels and was derived using a cluster-based modeling approach, latent profile analysis (LPA).[218] LPA used FACT-B and FACIT-SP domains from the 5-month survey to identify 4 latent profiles (LPs) of women who experienced distinct HRQOL patterns.

Covariates

Self-reported demographic and lifestyle covariates: age at diagnosis, race (non-Hispanic Black and White), smoking, marital status, education, and insurance at 5-months. Comorbid conditions (e.g., diabetes, chronic obstructive pulmonary disease, obesity, hypertension, and heart disease) from the medical record were included. Tumor stage and grade; surgery type; and receipt of radiation, chemotherapy, and Herceptin were included in models.

Statistical Analyses

Unadjusted comparisons of demographics, comorbidities, tumor, and treatment characteristics across women in the 4 HRQOL LPs were performed using chi-square tests. As women who initiated ET by 5-months might differ from women who initiate after 5-monthis (i.e., earlier stage of disease, better access to care), characteristics of those who initiated before and after 5-months were compared. As sensitivity analyses, unadjusted and adjusted HRQOL scores (1) between women with HR+ and HR- BC; and (2) between women who initiated ET before or after 5-months were examined.

Multivariable logistic regression was used to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CI) between HRQOL LPs and the likelihood of not initiating or adhering to ET, separately. The best HRQOL LP (LP 4) was set as the reference group. As race and chemotherapy may be effect measure modifiers of associations between HRQOL and ET use, race- and chemotherapy-stratified models were estimated for non-initiation and non-adherence outcomes, separately. In sensitivity analyses, associations were examined between continuous, rather than categorical, HRQOL measures and (1) non-initiation and (2) non-adherence. As a final sensitivity analysis, non-adherence models were stratified by whether or not women initiated ET by their 5-month survey to determine if associations between HRQOL

and non-adherence varied by initiation timing. Analyses were performed in SAS 9.3 with two-sided statistical tests and significance of 5%.

Results

5-month HRQOL LPs

LP1 had the poorest HRQOL across all domains and LP4 reported the best HRQOL scores across domains (Figure 12). LP2 had physical and functional scores similar to LP 1, but LP 2 had higher social and spiritual well-being. LP3 was similar to LP4, but spiritual and social well-being were lower than LP2.

Participant Characteristics

Characteristics for the 1,599 HR+ women stratified by the 4 HRQOL LPs are presented in Table 11. Fifty-seven percent of women were in the 2 lowest LPs. Overall, women in poorer LPs (i.e., LPs 1 and 2) were more likely to be young, Black, unmarried, obese, had no insurance, Stage 2-3 BC, and received chemotherapy or Herceptin. There were patient-level differences between the 2 lowest LPs, but few differences between the 2 highest LPs. Compared to LP2, women in LP1 were more likely to be educated, unmarried, without insurance, earlier stage BC, and less likely to receive chemotherapy. Overall, women in LP1 received less aggressive BC treatments than LP2. Women in the 2 highest LPs (LPs 3 and 4) had similar demographic, tumor, and treatment characteristics. LP3 and 4 varied by race, with LP3 having a larger proportion of Whites.

ET Use

Among the 953 women who had not yet initiated ET at their 5-month survey, 16% never initiated ET. Among the 1,114 women who initiated ET according to their medical records, 19% were considered non-adherent. Factors associated with non-initiating and non-adherence

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included younger age, Black race, higher education, public (versus private) insurance, breast-conserving surgery (versus mastectomy), and not receiving chemotherapy or radiation.

HRQOL and ET Initiation

In adjusted and unadjusted analyses, among women who had not initiated ET at their 5-month survey, there were no significant associations between HRQOL LPs and non-initiation (Table 12). Among non-chemotherapy users, LP1 membership was significantly associated with increased adjusted odds of non-initiation aOR 5.5 (95% CI 1.7-17.4) (Table 3). We found no significant adjusted associations among chemotherapy users or for Blacks and Whites (Table 3).

HRQOL and ET adherence

Among women who initiated ET, membership in poorer HRQOL LPs (LPs 1 and 2) was significantly associated with increased likelihood of non-adherence with unadjusted OR 2.4 (95% CI 1.3-4.2) and OR 2.0 (95% CI 1.1-3.6), respectively (Table 12). After adjustment, ORs attenuated (LP1 aOR 2.2; 95% CI 1.2-4.0; LP2 aOR=1.9; 95% CI 1.1-3.6). Although not statistically significant, LP3 was associated with an elevated likelihood of non-adherence aOR 1.5 (95% CI 0.8-2.8).

Associations between LPs and non-adherence were not statistically significant among chemotherapy users, but among non-users, membership in the poorest LP was associated with increased adjusted odds of non-adherence aOR 2.1 (95% CI 1.2-5.1) (Table 13). Among Blacks, membership in the second lowest LP was associated with non-adherence aOR 2.5 (95% CI 1.1-6.1), but for Whites, membership in LP1 was associated with non-adherence aOR 2.4 (95% CI 1.1-5.6).

Sensitivity Analyses

In unadjusted analyses using continuous, rather than categorical, HRQOL scores as predictors, we observed associations between better HRQOL and increased likelihood of non-initiation, but in multivariable models, associations became small and non-statistically significant. In unadjusted models, better continuous HRQOL was associated with lower likelihood of non-adherence, but in multivariable analyses, continuous HRQOL was not associated with non-adherence.

There were 646 women who initiated ET before ("early initiators") and 804 who initiated ET after their 5-month survey ("late initiators"). Compared to late initiators, early initiators had better HRQOL scores across domains with differences ranging from 1-4 points per domain. In multivariable models, differences dropped to below 1-point and became non-statistically significant.

Results from multivariable non-adherence analyses were similar when stratified by early and late initiators. The magnitude of associations between poor LPs and non-adherence was greater for early initiators (LP1 aOR 4.1, 95% CI 1.1-8.8 and LP2 aOR 3.1, 95% CI 1.4-11.9) compared to late initiators (LP1 aOR 1.8, 95% CI 1.2-3.9 and LP2 aOR 1.3, 95% CI 1.1-3.0). Regardless initiation timing, compared to the best HRQOL LP, membership in the 2 poorest LPs was associated with non-adherence.

Discussion

To our knowledge, this is the first study to examine associations between HRQOL and ET under-utilization in a large, population-based, multi-payer HR+ BC cohort. Although we did not observe statistically significant associations between pre-ET HRQOL and non-initiation, aORs for LPs 1-3 were 1.9, 1.4, and 2.1, suggesting a trend toward associations between poor

HRQOL and non-initiation. We observed significant associations between worse HRQOL during active treatment and non-adherence with aORs ranging from 1.7-2.2.

Studies have demonstrated associations between social and provider support and ET use in BC.[232] Greater support is associated with increased adherence.[232, 233] Associations with social support are consistent with our results, as the 2 lowest LPs (most associated with under-utilization) had higher percentages of unmarried women. Provider support is important because when patients feel supported and empowered to make treatment decisions in line with personal preferences, they are more likely to adhere to therapies.[233, 234] Provider support might help manage HRQOL during active treatment. One study reported that while older age at diagnosis and side effects were unadjusted predictors of non-adherence, once demographics, treatments, and tumor characteristics were included, only social support and patient-centered care measures (i.e., patient role in decision-making) remained associated with non-adherence.[234]

Chemotherapy moderated associations between HRQOL and under-utilization. Women undergoing chemotherapy have worse HRQOL than women who do not undergo chemotherapy.[98] [118] [101] Chemotherapy is associated with body image concerns, fear of recurrence and worse sexual functioning among women with BC.[118] [101] [119] In this study, among non-chemotherapy users, poor HRQOL was significantly associated with non-initiation and non-adherence. Women undergoing chemotherapy may attribute poor HRQOL to the aggressive treatment, whereas women not receiving chemotherapy may associate poor HRQOL with ET, making them more likely to not adhere. Additionally, chemotherapy side effects may dissipate over time; enabling women to deal better with ET-related difficulties than those whose initial HRQOL was poor for other reasons. Alternatively, women who experienced severe chemotherapy side effects may view problems encountered on ET as relatively tolerable.

HRQOL may be a useful screener for under-utilization among women who do not undergo chemotherapy. More research is needed to disentangle possible explanations for our findings.

Associations between HRQOL and non-adherence were modified by race. Among Whites, membership in the poorest LP was significantly associated with non-adherence, but membership in the second poorest LP was associated with non-adherence for Blacks. Women in LP1 and LP2 reported poor physical and functional scores, but social and spiritual well-being were better in LP2. Low physical and functional scores in both groups suggest these domains should be prioritized in clinical care, as they are potentially associated with increased likelihood of non-adherence. Moreover, previous studies indicate Black women with BC consistently report the importance of spirituality, including religious community support, in coping with their disease. [22, 156, 159, 160, 162] Some studies have documented associations between greater spirituality and lower likelihood of receiving recommended care (e.g., medication adherence, end-of-life care), which may partially explain our observed association between membership in LP2 (higher spiritual HRQOL) and non-adherence among Blacks.[235, 236] A possible explanation for this association that has been described in the literature is that spirituality and religious community affiliation may be linked to a belief in "miraculous healing," which may influence treatment decisions that are not necessarily in line with clinical recommendations.[236] When Black women in LP2 experience poor physical and functional HRQOL, they may rely even more on religious communities for support. As such, identifying better ways to manage HRQOL (especially physical and functional), including culturally sensitive approaches that integrate spiritual support in the clinical setting (e.g., having religious leaders serve as lay health advisors), may help increase the likelihood for ET adherence in both White and Black women with BC.

Limitations

Non-Hispanic White and Black women residing in North Carolina were included in this study, limiting generalizability to women in other states and of other races/ethnicities. However, CBCS-III is a large cohort, which provides broader inference with a population-based sample as opposed to a hospital or clinic-based sample. Additionally, women who initiated ET by 5-months were excluded from initiation analyses. We conducted sensitivity analyses to determine if these women differed in HRQOL and found that once patient characteristics were accounted for, no significant HRQOL differences between women who initiated ET before or after 5-months existed. Women who initiated ET by their 5-month survey were included in adherence analyses. As ET may negatively impact HRQOL, including these women could potentially confounded associations between HRQOL and non-adherence. Therefore, sensitivity analyses were conducted including stratifying models by whether or not a woman initiated before or after her 5-month survey. As results were similar, all HR+ women were included in adherence analyses to increase generalizability of results to women with HR+ BC. Finally, because ET adherence was self-reported, reliability of adherence data was not confirmed.

Conclusion

Our findings suggest HRQOL measured soon after diagnosis can be used to identify women who may not initiate or adhere to ET during survivorship. HRQOL is modifiable and can be intervened on early in the BC continuum to help reduce under-utilization. Women with poor HRQOL during active treatment should receive targeted HRQOL support to reduce the risk of inappropriate adjuvant treatment decisions.[40, 41] Those experiencing poor physical and functional well-being may be at greater risk for under-utilization, as lower scores in these domains were most associated with under-use. Furthermore, BC subgroups such as non-chemotherapy users and Blacks may especially benefit from additional physical and functional HRQOL management.

As Blacks present with more aggressive BC subtypes at younger ages and report worse physical and functional HRQOL, they might be more susceptible to under-utilization.[42, 44, 57, 158, 237 48, 137, 138] Reducing ET under-utilization among Black women may offer an opportunity to help reduce racial disparities in BC outcomes. Using self-reported HRQOL as a potential indicator for inappropriate ET use is inexpensive and easy to do with validated HRQOL instruments, making these findings particularly appealing. Women most vulnerable to under-utilization should be identified early in the BC continuum and provided ongoing HRQOL management to support ET use and improve BC outcomes.[31, 168]

Table 11. Cohort Characteristics by 5-Month HRQOL Latent Profiles

	LP 1 N=503	%	LP 2 N=412	%	LP 3 N=483	%	LP 4 N=201	%	P value
Age at diagnosis									<0.0001***
<35 years	22	4%	11	3%	15	3%	4	2%	
35-50 years	238	47%	190	46%	171	35%	63	31%	
50-64 years	167	33%	137	33%	181	37%	75	37%	
65+ years	76	15%	74	18%	116	24%	59	29%	
Race									<0.0001***
Non-Hispanic White	263	52%	207	50%	330	68%	109	54%	
Non-Hispanic Black	240	48%	205	50%	153	32%	92	46%	
Smoking status									<0.0001***
Never	237	47%	227	55%	265	55%	122	61%	
Former	143	28%	112	27%	149	31%	60	30%	
Current	123	24%	73	18%	69	14%	19	9%	
Marital status									<0.0001***
Not married	262	52%	165	40%	158	33%	64	32%	
Married/partnered	241	48%	247	60%	325	67%	137	68%	
Education level									<0.0001***
<HS	61	12%	23	6%	27	6%	13	6%	
HS & Post HS	241	48%	235	57%	201	42%	115	57%	
College+	291	58%	154	37%	255	53%	73	36%	
Insurance status									<0.0001***
None	48	10%	12	3%	16	3%	3	1%	
Private	304	60%	301	73%	387	80%	160	80%	
Public	151	30%	99	24%	80	17%	38	19%	
Diabetes	78	16%	68	17%	55	11%	31	15%	0.1295
COPD	18	4%	12	3%	9	2%	0	0%	0.0316*
Heart Disease	28	6%	29	7%	21	4%	7	3%	0.1923
Obesity	251	50%	219	53%	187	39%	89	44%	<0.0001***
Hypertension	237	47%	190	46%	186	39%	99	49%	0.0135*
Surgery									0.0058**

	LP 1 N=503	%	LP 2 N=412	%	LP 3 N=483	%	LP 4 N=201	%	P value
Not specified	5	1%	3	1%	0	0%	1	0%	
Lumpectomy	327	65%	247	60%	334	69%	148	74%	
Mastectomy	171	34%	162	39%	149	31%	52	26%	
Chemotherapy	303	60%	293	71%	173	36%	75	37%	<0.0001***
Radiation	363	72%	290	70%	340	70%	150	75%	0.6563
Herceptin	75	15%	72	17%	37	8%	12	6%	<0.0001***
Tumor stage									
I	228	45%	154	37%	294	61%	125	62%	<0.0001***
II	208	41%	188	46%	157	33%	62	31%	
III	67	13%	70	17%	32	7%	14	7%	
Tumor grade									<0.0001***
Well differentiated	127	25%	75	18%	162	34%	55	27%	
Moderately differentiated	221	44%	184	45%	233	48%	96	48%	
Poorly differentiated/unknown	155	31%	153	37%	88	18%	50	25%	

Note: LP (latent profile). LP1 represented the worst HRQOL profile, relatively, and LP4 represented the best HRQOL profile, relatively. Statistical significance is denoted as follows: $p<0.05$ *, $p<0.01$ **, $p<0.0001$*

Table 12. Unadjusted and Adjusted Associations between 5-Month HRQOL Latent Profiles and Endocrine Therapy Non-Initiation and Non-Adherence

	ET Non-Initiation				ET Non-Adherence			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	95% CI	aOR	95% CI	OR	95% CI	aOR	95% CI
5-Month LP (ref=LP4)								
LP 1	1.1	(0.6-1.9)	1.9	(0.9-4.2)	2.4	(1.3-4.2)*	2.2	(1.2-4.0)*
LP 2	0.8	(0.4-1.5)	1.4	(0.7-3.1)	2.0	(1.1-3.6)*	1.9	(1.1-3.6)*
LP 3	1.5	(0.8-2.8)	2.1	(0.9-4.4)	1.6	(0.9-3.0)	1.7	(0.9-3.1)

Adjusted models include all covariates listed in Table 1. * denotes statistical significance at the 0.05 level. OR (odds ratio), aOR (adjusted odds ratio), CI (confidence interval), ET (endocrine therapy), LP (latent profile). LP 4 was the reference category for analyses.

Table 13. Adjusted Associations between 5-Month HRQOL Latent Profiles and Endocrine Therapy Non-Initiation and Non-Adherence Stratified by Chemotherapy and Race

	ET Non-Initiation		ET Non-Adherence	
	aOR	95% CI	aOR	95% CI
Black women only (ref=LP 4)				
LP 1	1.3	(0.5-3.8)	1.9	(0.8-4.6)
LP 2	1.2	(0.4-3.6)	2.5	(1.1-6.1)*
LP 3	1.6	(0.5-4.7)	1.8	(0.8-4.5)
White women only (ref=LP 4)				
LP 1	2.6	(0.8-8.1)	2.4	(1.1-5.6)*
LP 2	1.4	(0.4-4.7)	1.4	(0.6-3.5)
LP 3	2.1	(0.7-6.6)	1.4	(0.6-3.3)
Chemotherapy-users (ref=LP 4)				
LP 1	1.1	(0.3-3.2)	1.8	(0.7-4.4)
LP 2	1.4	(0.4-4.5)	1.5	(0.6-3.7)
LP 3	1.4	(0.4-4.9)	1.3	(0.5-3.4)
Non-chemotherapy users (ref=LP 4)				
LP 1	5.5	(1.7-17.4)**	2.1	(1.2-5.1)*
LP 2	1.0	(0.3-3.2)	2.0	(0.8-5.1)
LP 3	2.8	(0.9-7.9)	1.8	(0.8-3.9)

Adjusted models include all covariates listed in Table 1. * denotes statistical significance at the 0.05 level. aOR (adjusted odds ratio), CI (confidence interval), ET (endocrine therapy), LP (latent profile). LP 4 was the reference category for analyses.

Figure 12. Mean 5-month HRQOL Scores by Latent Profiles Compared to U.S Norms
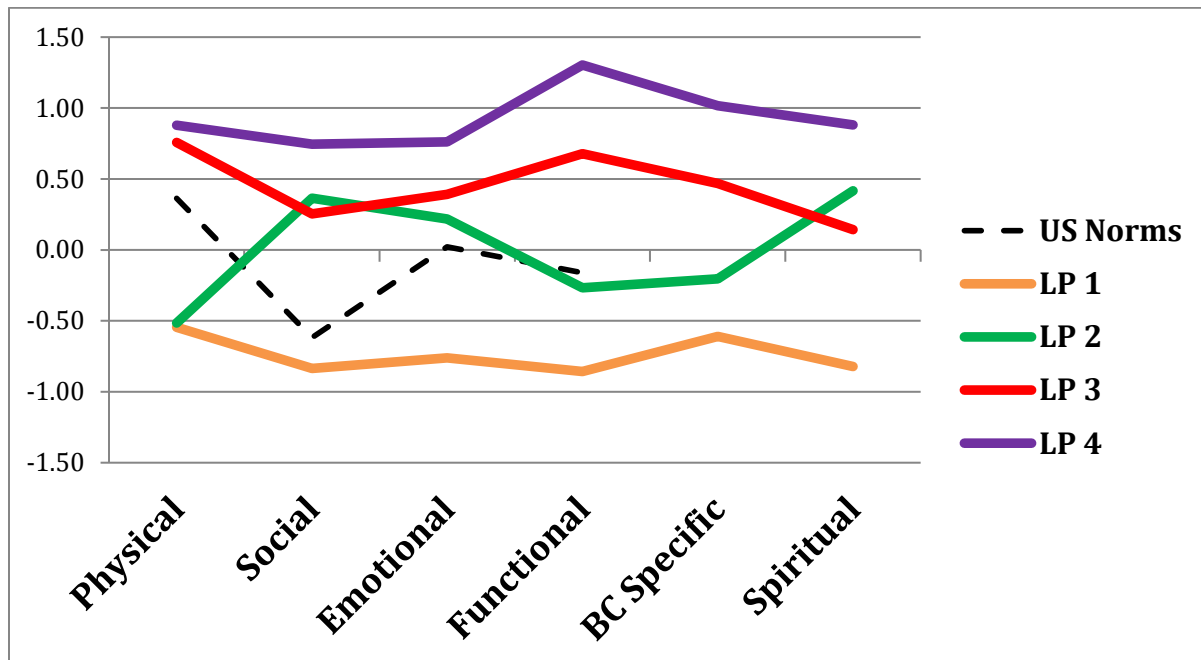
Note: Mean HRQOL scores were converted to Z-scores. LP (latent profile), Normed US scores are only available for Physical, Social, Functional and Emotional FACT-B domains and come from Brucker et al.[215]

CHAPTER 7: OVERALL FINDINGS AND IMPLICATIONS

<u>Objectives</u>

The overall goals of this dissertation were to gain a better understanding of health-related quality of life (HRQOL) patterns in women with breast cancer (BC) and to determine if HRQOL can be used to identify women at risk for under-utilization of adjuvant endocrine therapy (ET). We conducted three separate studies (Aims 1-3) in order to achieve these objectives. In Aim 1, we employed a novel cluster-based modeling approach - latent profile analysis (LPA) - to identify latent profiles (LPs) of women with BC who experienced different HRQOL patterns during two distinct time points in the BC care continuum (i.e., active treatment and survivorship). We then determined if patient characteristics were associated with membership in the identified HRQOL LPs. In Aim 2, our objective was to understand how HRQOL of two racial groups (Non-Hispanic Whites and Non-Hispanic Blacks) might be differentially impacted during active treatment and survivorship phases of the BC care continuum. To do this, we assessed whether or not racial disparities existed at each of these two time points and in changes between the two time points in six HRQOL domains (e.g., physical, functional, emotional, social, and spiritual well-being, and BC-specific concerns). Finally, in Aim 3 we assessed if HRQOL could be used preemptively to identify women who might be at increased risk for under-utilizing adjuvant ET. To do this, we evaluated associations between active treatment HRQOL LPs and not initiating or not adhering to ET during survivorship in women with hormone receptor positive (HR+) BC. A deeper understanding of predictors of HRQOL patterns and ET under-use offers valuable insights into how to provide targeted care management for

women with BC who are most susceptible to poor HRQOL and into potential solutions for improving BC outcomes.

Important Findings

Each aim described above had notable study findings, which are described in detail by aim.

Aim 1

Through LPA, we identified four distinct HRQOL LPs of women with BC during active treatment and survivorship phases of the BC care continuum. Women in the poorest HRQOL LP had the lowest HRQOL scores across all six HRQOL domains, and women in the best HRQOL LP had the highest HRQOL scores across all of these domains. The second lowest HRQOL LP (LP 2) generally had poor physical, functional and BC-specific HRQOL, but fared much better in social, emotional and spiritual well-being. The second highest HRQOL LP had better physical and functional HRQOL compared to the two lowest LPs, but poorer psychosocial and spiritual HRQOL than LP 2.

After controlling for comorbid conditions, treatment and tumor characteristics, and lifestyle factors (e.g., smoking), we found that non-modifiable demographic and socioeconomic factors such as age at diagnosis, race, social support, insurance, and education were significantly associated with membership in poor HRQOL LPs at both 5- and 25-month after BC diagnosis. Specifically, younger age at diagnosis, lack of social support, and having public insurance or being uninsured was associated with an increased likelihood of being in a lower HRQOL LP. Although factors associated with LP membership were relatively similar at 5- and 25-months post-diagnosis, we observed a difference in associations between race on LP membership between these two time points. During active treatment, White race was significantly associated with membership in the poorest HRQOL LP (aOR 1.48, 95% CI 1.25-1.65), but at 25-months,

Black race (aOR 1.75, 95% CI 1.18-2.60) was significantly associated with membership in the lowest HRQOL LP. This suggests that non-modifiable demographic factors affecting a woman's HRQOL may have varying effects at different points in the BC care continuum. As such, different socio-demographic groups might be at risk for compromised HRQOL at different points in their care trajectories.

Chemotherapy, an aggressive BC treatment, was also significantly associated with poor HRQOL LP membership (aOR 1.85, 95% CI 1.22-2.81 and aOR 1.92, 95% CI 1.21-3.05) at both 5-months and 25-months, respectively, which was in line with the literature related to poor HRQOL associated with chemotherapy.[101, 118, 119] Receipt of chemotherapy has been associated with long-term body image concerns, fear of recurrence and worse sexual functioning.[101, 118] One study found that after adjusting for demographic, clinical and treatment characteristics, receipt of chemotherapy was a significant predictor of poorer long-term HRQOL.[119]

Prevalence of comorbid conditions and disease severity became stronger predictors of membership in the two poorest HRQOL LPs as women transitioned from active treatment and into survivorship. This finding is not surprising, as these factors may influence the types of adjuvant treatments women receive (i.e., chemotherapy, ET) and how difficult it is to adjust to "normal" life following primary BC treatments. Women with multiple comorbid conditions may struggle with the added burden of having to take oral ET for 5 years following completion of primary BC treatments.

Aim 2

During active treatment, mean physical well-being scores were significantly lower (1.2-3.7 points) than U.S. norms for all women in our study. However, White women reported scores 1.9-2.5 points higher than Black women, which was considered both clinically meaningful and statistical significant. Black women, however, reported spiritual well-being scores over 2-points

higher than White women in our study, which also exceed our 2-point threshold for clinical significance. These results are consistent with what we found in the racial disparities literature: Black women with and without cancer generally have worse physical and functional well-being compared to White women, but report better social and spiritual well-being through community support and increased religiosity. [22, 42, 156, 159, 160, 162]

During the BC survivorship phase of our study, White women's HRQOL scores rebounded to above U.S norms across physical, functional, social and emotional HRQOL domains. Black women continued to report mean physical well-being scores below U.S. norms and more than 2-points below their White counterparts at 25-months. However, as Black women moved from active treatment to survivorship, they sustained spiritual well-being scores 2-points higher than White women, suggesting that their spiritual or community support was sustained for the first two years of their BC care experience.

In terms of patterns of change in HRQOL between 5- and 25-months post-diagnosis, we observed small, statistically significant racial differences in HRQOL scores, but differences were not large enough to be considered clinically meaningful. This is consistent with previous studies documenting no racial disparities in HRQOL once treatment and tumor characteristics were taken into consideration.[227, 228] Racial differences attenuated considerably when socioeconomic factors were included in our models and widened a bit when we allowed the race coefficient in our model to represent the socioeconomic factors. These results suggest socioeconomic factors may considerably mediate racial gaps in physical and functional HRQOL between White and Black women with BC.

Emotional and spiritual well-being were the only HRQOL domains in which racial differences were not attenuated by socioeconomic factors. In fact, spiritual well-being gaps

between White and Black women actually widened when socioeconomic factors were included in models, suggesting that perhaps these factors may strengthen or reinforce this domain. Emotional and spiritual well-being domains appear more resistant to life stressors affecting other domains due to increased spirituality and community support. Another possibility is that BC and socioeconomic factors do impact emotional and spiritual well-being, but in a way that reinforces these domains. The Superwoman role, a theory stating that Black women may exude strength, suppress emotions, and demonstrate perseverance when faced with adversity, may partially explain this finding.[231] If Black women do not allow themselves to acknowledge weakness or stress related to BC, self-reported emotional and spiritual well-being may not appear to suffer.[231]

Aim 3

Overall, poor HRQOL during active treatment was not significantly associated with a woman's likelihood of ET initiation among HR+ women who had not initiated ET by the time their HRQOL was measured. We did find a significant association between poor HRQOL and an increased likelihood of non-initiation among women who did not receive chemotherapy (aOR 5.5, 95% CI 1.7-17.4), which offers a potential group of women to target with HRQOL management. Although we did not find statistically significant associations between HRQOL and ET non-initiation, we did observe a consistent trend toward lower likelihood of initiation among women in worse HRQOL groups. The adjusted ORs for these trends were all well above 1.0 with wide confidence intervals crossing 1.0. A larger sample size would be required to further investigate if a significant association between poor HRQOL and lower likelihood of ET initiation exists, as our confidence intervals would narrow.

We observed significant associations between poor HRQOL (i.e., membership in the two poorest HRQOL LPs as described above) and an increased likelihood of ET non-adherence with aOR 2.2 (95% CI 1.2-4.0) in LP1 and aOR 1.9 (95% CI 1.1-3.6), in LP2, respectively. As we

saw in ET initiation analyses, a strong association between poor HRQOL and non-adherence was also observed among non-chemotherapy users (aOR 2.1, 95% CI 1.2-5.1). Our results suggest that women with poor HRQOL during active treatment may be at increased risk for ET under-utilization (both non-initiation and non-adherence) and that women who do not undergo chemotherapy may especially benefit from early HRQOL screening to anticipate ET under-use.

<u>Implications for Clinical Practice</u>

These dissertation findings are particularly relevant for BC clinical practice. First, results from Aim 1 suggest that we can use non-modifiable patient characteristics such as age at diagnosis and race to preemptively identify women at increased risk for experiencing poor HRQOL during active treatment and survivorship phases of their BC care. By creating clinically meaningful HRQOL LPs with electronic health record data, clinicians could be made aware of patients that may be especially vulnerable to poor HRQOL during distinct phases of BC care. These findings have important clinical implications, as there is a national emphasis on patient-centered care that encourages clinicians to routinely collect and monitor HRQOL through their electronic health records. [9-13] If approaches such as LPA were applied to clinical practice data and subgroups of women could be identified following BC diagnosis, we may see improvements in BC outcomes for women with poor HRQOL. Through early identification, women could be connected to mental health specialists, support groups from the onset of active treatment, nutritionists to control weight gain or loss, and physical therapists to help manage physical and functional well-being ailments following primary treatments. Clinics should consider using their own patient-reported HRQOL data to create clinically meaningful LPs to inform HRQOL management. Leveraging LP membership to anticipate HRQOL needs of women with BC is in line with providing cancer care that reflects patient needs and values and is a meaningful way to use electronic health record data collected in the clinic.

Aim 2 conclusions highlight a need to address socioeconomic-related barriers to physical and functional well-being in order to help narrow gaps in these particular domains, which are consistently lower among Black women with BC than among White women with BC. Potential ways to improve physical and functional HRQOL could be to help manage other comorbidities (e.g., hypertension, diabetes) and to promote greater physical activity following BC diagnosis. Black women with BC tend to report lower levels of physical activity and higher rates of hypertension and diabetes, which have been associated with poorer physical well-being and overall HRQOL. [3, 158] Studies have also confirmed that although BC survivors report less physical activity compared to the general population, White women with BC have higher levels of physical activity than Black women with BC.[3, 20, 158] If clinicians could connect BC patients with resources to support their physical and functional HRQOL throughout the BC care continuum, we may see gaps in these domains narrow considerably or disappear. Supportive BC services should consider domain-specific findings to provide targeted HRQOL management across socio-demographic groups of women with BC and recognize that different socio-demographic groups require tailored support at distinct phases of the BC care continuum.

Arguably, our findings from Aim 3 have the greatest clinical relevance, as they suggest that HRQOL measured soon after BC diagnosis can be used to identify women who may not initiate or not adhere to ET during BC survivorship. We recommend that women with poor HRQOL during active treatment receive targeted HRQOL support to reduce the risk of inappropriate adjuvant treatment decisions.[40, 41] Women experiencing poor physical and functional well-being during active treatment may be at greater risk for under-utilization (compared to women in the best HRQOL LP with high physical and functional well-being

scores), as low scores in these two particular domains appeared to be most associated with ET under-use in our study.

In Aim 2, we saw that physical and functional well-being scores were lower among Black women than White women, which leads us to wonder if targeting these particular domains would help address racial disparities both in HRQOL and ET-use. As Black women present with more aggressive BC subtypes at younger ages, they often experience worse BC outcomes (BC recurrence and survival).[48, 57, 137, 138] Compared with their White counterparts, Black women with BC are known to report worse physical and functional HRQOL and, thus, might be more susceptible to ET under-utilization.[42, 44, 158, 237] Reducing ET under-utilization among Black women with BC may offer an opportunity to help reduce racial disparities in BC outcomes. Results from Aim 3 have particular clinical appeal, as using post-diagnosis HRQOL screening as an indicator for poor future ET under-use is potentially inexpensive and easy to do with validated HRQOL instruments. Women who may be most vulnerable to ET under-utilization should be identified early in the BC care continuum and provided ongoing HRQOL management to support ET use and potentially improve BC outcomes.[31, 168]

Implications for Research

Findings from this dissertation offer opportunities for future work in the area of HRQOL, BC outcomes, and racial disparities. Below we highlight each of these opportunities by aim.

First, Aim 1 of this dissertation addresses limitations of using traditional approaches to assessing HRQOL patterns, which compare means and standard deviations and have been criticized for not truly representing heterogeneity in HRQOL experiences.[75] That is, examining mean differences in HRQOL scores may lead us to miss outliers or subgroups, which are often masked by an overall HRQOL score.[75] Aim 1 used two patient-centered approaches (LPA and LTA) to identify and characterize HRQOL patterns in women with BC. This approach has

tremendous value in HRQOL research, as it is a cluster-based model approach that identifies clinically meaningful subgroups of individuals with similar characteristics that might be associated with their HRQOL patterns.[222] Future HRQOL work could benefit from using these methods when studying HRQOL patterns and outcomes.

Results from Aim 1 also inform potential interventions to target women who are more likely to experience poor HRQOL (i.e., members of the poorest HRQOL LPs). Aim 1 identified non-modifiable patient characteristics such as age at diagnosis, race, and marital status, which are routinely collected in clinic and could be used in interventions wishing to target women most susceptible to poor HRQOL following diagnosis or during BC survivorship. Therefore, Aim 1 contributes to a greater understanding of patient-level predictors of HRQOL patterns among women with BC and uses patient-level characteristics to identify subsets of women who are at risk for poor HRQOL.

Findings from Aim 2 also support the use of domain-specific HRQOL measures in future HRQOL work so that we can tease out domain-specific racial differences, which may be masked by an overall HRQOL score. Results from this particular aim highlight White-Black HRQOL differences that would likely have been missed had we simply used the overall FACT-B measure of HRQOL, which has been often used in other studies. In addition, Aim 2 also highlighted the importance of selecting the appropriate racial disparities approach (i.e., Institute of Medicine, Residual Direct Effect, race and socioeconomic interactions) for one's particular research question, as conclusions from the varying approaches differ. The racial diversity (i.e., 50% of our sample is Black) of the CBCS dataset used in this dissertation makes contributions from Aim 2 especially relevant for the racial disparities literature, as much of the previous work in HRQOL racial disparities has been done in samples with a much smaller minority representation. Results

from Aim 2 inform and support the development of more equitable approaches to domain-specific HRQOL management for women with BC.

Results from Aim 3 of this dissertation inform future interventions that wish to target HRQOL, a modifiable factor, in order to potentially increase the likelihood of appropriate ET use. Given the age and racial diversity of this population-based cohort, results from Aim 3 are highly generalizable to women with BC in the United States. As such, Aim 3 fills an important gap in the literature, as much of the previous work has been done in exclusively Non-Hispanic White Medicaid or Medicare populations. We recommend that Aim 3 be repeated in datasets that capture ET adherence data in claims or through prescription refills in order to strengthen the association between poor HRQOL and increased likelihood of ET non-adherence. Using self-reported adherence measures may introduce some misclassification if women are more or less likely to accurately report there ET adherence. However, conclusions from this aim contribute to the BC outcomes literature, as we identify a potential mechanism to preemptively identify women at risk for poor HRQOL, which may support women more appropriately receive life-saving adjuvant treatments such as ET.

<u>Implications for Health Policy</u>

Findings from this dissertation are also relevant for health policy, as cancer care that considers patient-reported outcomes is consistent with the national emphasis on patient-centered care.[9-11] [12, 13] The number of women diagnosed with and surviving from BC in the U.S. is anticipated to grow by more than 20% between 2010 and 2020.[238] A deeper understanding of the HRQOL patterns and needs of this specific population will allow us to provide care that is more line with patient needs and values. Previous work in this area has been limited, as studies were done in small samples of older, primarily White populations using generic HRQOL instruments, and treating HRQOL domains independently. As such, findings from other studies have not been

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generalizable to the larger U.S. population, which has become increasingly diverse in terms of race, ethnicity, socio-economics, and culture.

The age and racial diversity of the population-based CBCS dataset is unparalleled for BC disparities research, as 50% of the sample is Black, 50% White, 50% less than 50 years of age and 50% older than 50 years. Many research studies struggle to have a large representation of minority groups, thus limiting their ability to draw recommendations that are generalizable to these under-represented populations. The racial composition of the CBCS dataset makes it an ideal platform for racial disparities work. Findings from this dissertation inform more equitable approaches to HRQOL management and suggest that greater efforts be made to support physical and functional well-being, especially among Black women with BC. In doing so, we may be able to narrow some HRQOL racial gaps that currently exist, which may also have positive downstream effects on other health outcomes including medication adherence, BC recurrence, and death. These findings will be of interest to policy-makers aiming to reduce racial health disparities in the U.S.

Limitations

Only Non-Hispanic White and Non-Hispanic Black women residing in North Carolina were included in this dissertation (across all three aims), limiting generalizability to women in other states and of other races/ethnicities. We also excluded women with distant stage BC, as they are distinct from women with early stage BC in terms of prognosis, treatment burden and HRQOL outcomes. As such, as do not know if our conclusions would be similar in a metastatic BC population. In addition, across all three aims, as most women have initiated primary BC treatments by 5-months, there was no pre-treatment HRQOL measure available. However, BC treatments such as receipt of radiation, chemotherapy, surgery and Herceptin (obtained from medical records) were included all adjusted analyses.

In Aim 1, we employed relatively exploratory approaches (LPA and LTA) with numerous model assumptions in order to identify HRQOL LPs. However, we used established statistical fit indices such as the Bayesian Information Criteria to ensure optimal model fit. We also assessed the robustness of our results by performing various sensitivity analyses. Furthermore, in Aim 1 LTA, restricted sample sizes may have limited our ability to detect statistically significant associations with LP transitions in our sample. Finally, we primarily focused on non-modifiable predictors of LP membership, which limits our ability to inform interventions aiming to target modifiable factors associated with poor HRQOL.

In Aim 2, we were unable to control for unmeasured confounders such as patient preferences, culture, and economic, political, and legal factors that may impact HRQOL and contribute to White-Black differences in HRQOL. Therefore, even in fully adjusted models (i.e., residual direct effect), race coefficients encompassed unmeasurable factors such as institutional racism, different care seeking behavior and access to healthcare networks that are not determined by insurance status, marital status, education and income, introducing potential bias.

Finally, in Aim 3 of this dissertation, ET adherence was classified from self-report data, which did not allow us to confirm the reliability of ET adherence. Furthermore, given the limited sample of HR+ women, we were unable to examine associations between poor HRQOL and non-specific patterns of medication non-adherence such as quitting versus intermittent use or under-use, which is not necessarily a limitation, but could be of interest in future studies.

Despite these notable limitations, CBCS-III is a large, multi-payer, age and racially diverse population-based cohort of women with BC in North Carolina, which allows us to draw broader inferences in comparison to other, less diverse study populations such as those from a single-institution or a clinical trial.

Future Directions

This dissertation offers valuable opportunities for continued work. Specifically, it supports the use of evidence-based interventions to target HRQOL soon after diagnosis in women with HR+ BC in order to help support future ET use. It is our recommendation that such interventions specifically focus on targeting physical and functional well-being, as these domains were particularly low in the two poorest HRQOL LPs and among Black women in our sample. The importance of focusing on physical and functional HRQOL was also observed in results from Aim 2, thus further supporting interventions that better meet physical and functional HRQOL needs. In doing so, potential interventions might help narrow racial gaps in HRQOL, because Black women with BC tend to have worse physical and functional HRQOL than their White counterparts. In addition, future work should consider exploring associations between HRQOL and under-utilization of other BC treatments including radiation, chemotherapy and Herceptin. This work could be extended beyond BC into other cancer types or chronic diseases such as diabetes and hypertension, where patients take medications for years and improving adherence to medications is of interest to providers.

Conclusions

Through this dissertation, we gained a greater understanding of non-modifiable demographic predictors of HRQOL patterns among women with BC in North Carolina and determined that a woman's self-reported HRQOL soon after BC diagnosis can be used to identify women who may be at increased risk for under-utilization of ET. Results from this dissertation contribute to the HRQOL research field by 1) employing innovative approaches to identify clinically meaningful HRQOL patterns among women with BC, 2) determining individual-level characteristics that are associated with membership in HRQOL sub-groups, 3) contributing to the evidence pertaining to racial disparities in BC research by using three

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competing approaches to assessing racial disparities in HRQOL, and 4) identifying an

opportunity for future interventions to target women with BC at risk of ET under-utilization early

in their BC care process by focusing on improvements to their HRQOL.

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