SYMPTOM OCCURRENCE AND SEVERITY AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH BREAST OR GYNECOLOGIC CANCER RECEIVING MATCHED CANCER THERAPY

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By

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Abstract

Background: Scientific advancements in oncology allow routine patient cancer genomic profiling, which may guide the choice of novel therapies to match genomic alterations for the treatment of cancer. Potential differences in cancer therapy-related symptom severity and occurrence as well as health-related quality of life (HRQOL) between patients who receive matched therapy and those who do not have not been previously explored.

Purposes: The purpose of this study was to describe the characteristics of patients with breast or gynecologic cancer who were receiving matched therapy or not matched therapy, as well as to describe their cancer therapy-related symptom occurrence and severity, and overall HRQOL.

Methods: Existing data from the records of 129 patients receiving care at a cancer center in the upper Midwest were used for this descriptive correlational research study. Descriptive statistics and multiple linear regression analyses were performed to address the study purpose and aims.

Results: This study found that patients receiving matched therapy had lower mean therapy-related symptom checklist (TRSC) scores (M = 14.7) than patients receiving not matched therapy (M = 16.1). Compared to prior studies, a higher percentage of patients (29%) added symptoms to the TRSC. TRSC scores for individual symptoms were similar across groups, except pain, which was higher in patients receiving matched therapy, and hair loss, which was higher in patients receiving not matched therapy. Patients receiving matched therapy had higher mean Health-Related Quality of Life – Linear Analogue Self Assessment (HRQOL-LASA) scores (M = 48.1), than patients receiving not matched therapy (M = 45.4). Patients who had prior therapy less than three months prior to the onset of the current therapy had significantly higher TRSC total scores than patients with no prior therapy (B = 6.2, p = 0.045). Patients who had a higher number of prior lines of therapy had significantly higher HRQOL-LASA scores (B = 0.56, p =

0.05). Patients with higher TRSC scores had significantly lower HRQOL-LASA (B = -0.36, $p <$ 0.001).

Conclusions: Patients receiving matched therapy did not have worse therapy-related symptoms or HRQOL. Findings provide initial information about the symptom experience and HRQOL for patients receiving matched therapy.

Acknowledgments

"Commit to the Lord whatever you do, and He will establish your plans" (Proverbs 16:3)

As I'm nearing the point of becoming a doctorally-prepared nurse, I know that this accomplishment is not my own, but is a tribute to the support I have received along the way of this journey. I could not have done this without the love and support of my husband. I have been in graduate school for most of our married life, yet he has always supported my goals, even if it has meant taking on extra "household" tasks (turns out he is a great cook so he will hopefully keep that job!). Throughout all the challenging and difficult times, he has been right there to encourage me, to give me a pep talk, to take the kids out of the house so I could focus, and most importantly, to just be there for me. Thank you, Casey. Thank you to my beautiful children, Anna and Benjamin, who have never known a time in their lives when I was not in school. They inspire me to be a better person, and I am fueled by their unconditional love. I know they are looking forward to their mom being finished with school! I also thank my parents, who have been amazing role models to me in every aspect of life. I especially thank my father, who epitomizes integrity and a strong work ethic. Thank you, Mom and Dad, for always being there for me, no matter my age. I thank my brothers, my extended family, my friends, and my co-workers who have been there to cheer me on!

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Table of Contents

List of Tables

List of Figures

Chapter One

Introduction

Approximately 14.5 million Americans are either living with cancer or have a history of cancer (American Cancer Society [ACS], 2015a). Breast and gynecologic cancers comprise approximately 323,000 of new cancer cases annually, and nearly 71,000 women died from these diseases in 2015. Advancements in cancer screening and treatment have increased the five-year survival rate for breast cancer to 89%, and the five-year survival rate for the combined gynecologic cancers to 65% (ACS, 2015a). A significant proportion of women will live more than five years after diagnosis without being cured of their disease. These women will need to receive treatment for their cancer for years; consequently their cancer is now considered a chronic disease. Physical and emotional symptoms are experienced throughout the cancer continuum, which can negatively interfere with quality of life (QOL) (de Moor et al., 2013; Heinze, 2012). In addition to the personal burden, the treatment of cancer is costly. Direct medical costs for treating breast and gynecologic cancers were an estimated $27.5 billion in 2010 (Yabroff, Lund, Kepka, & Mariotto, 2011). Thus, cancer is a major women's health concern that requires further examination and research.

The treatment of breast and gynecologic cancers involves different modalities including surgery, chemotherapy, and radiation therapy. Each treatment modality can cause specific side effects yet significant overlap exists. Common side effects arising from these treatment modalities include bone marrow suppression, mucositis, diarrhea, nausea/vomiting, and neuropathies, thereby contributing to the development of symptoms like fatigue, pain, depression, and weakness (DeVita, Lawrence, & Rosenberg, 2011; Reeve et al., 2014; Williams, Williams, Ducey, Sears & Tobin, 1997; Williams et al., 2001). The symptoms experienced (symptom experience) differs among individuals, although prior studies suggest the occurrence

and severity of the most commonly manifested symptoms varies little across primary cancer types (Kirkova et al., 2011; Reeve et al., 2014). Symptoms arising from the treatment of cancer can cause suffering (Cleeland, 2000; Komurcu et al., 2000) and distress (Kirkova, et al., 2010), and are determinants of decreased QOL (Janz et al., 2007; Miaskowski et al., 2006; Williams et al., 1997; Williams et al., 2001). Appropriate symptom management is essential for cancer patients, which not only can lead to enhanced QOL, but may also lead to greater adherence to their cancer treatment and thus improved efficacy.

State-of-the-art cancer care now includes personalizing strategies to treat an individual's cancer based on their unique genomic signature, which is found by cancer genomic profile testing (commonly abbreviated "genomic profiling"). Cancer treatment (therapy) that is chosen based on the alterations found in genomic profiling is called "matched therapy". Matched therapy is a shift to a more personalized approach to treating cancer based on the crucial insights into the genomic alterations and molecular pathways influencing the development and progression of cancer (McDermot, Downing, & Stratton, 2011). Drugs have been developed that block the growth and spread of cancer by interfering with the spread of molecular, or molecular targets, involved in the growth and spread of cancer (NCI, 2014). The use of these drugs is called targeted therapy. Targeted therapies are often combined with other treatment modalities such as chemotherapy. Increasingly, genomic profiling is being incorporated into routine clinical practice to identify specific genomic alterations of an individual's cancer so that the therapies selected are more precise.

An important issue that must be considered with matched therapy is the tolerability or risk/benefit ratio of the matched therapies especially since it involves combining drugs, based on an individual's unique genomic signature, each of which have a narrow margin between efficacy and excess toxicity. Prior studies examining symptoms related to the treatment of cancer and

their impact on QOL have focused on not matched therapies (e.g. chemotherapy, radiation, surgery). Matched therapy brings the promise of increased efficacy, but little is known about the symptom experience or QOL for patients undergoing this new treatment modality.

A study to examine patient reported symptom occurrence and severity and health-related quality of life (HRQOL) while receiving matched therapy is considered to be a timely and valuable endeavor given the current gaps in knowledge about this increasingly utilized approach for treating cancer. Knowledge gained from this study will better prepare health care professionals to provide safe, effective, and efficient care to oncology patients. Such inquiries are important to advancing nursing science, because the data from these studies will assist in the promotion of health, optimize patient outcomes, and keep nursing at the forefront of science (National Institute of Nursing Research [NINR], 2016).

Background

Breast cancer is the most common cancer diagnosis in American women, and remains the second leading cause of cancer-related death among American women despite impressive advances in screening, detection, and treatment (ACS, 2015a). Breast cancer is a complex and heterogeneous disease with individual biological features and corresponding behaviors (Weigelt & Reis-Fiho, 2009; Winer et al., 2009). Breast cancer is typically classified both by its histologic type (tissue in which the cancer originates and its structural pattern) and its molecular type (underlying genetic changes). The majority of breast cancers by histologic type are invasive ductal carcinoma (50-80%) followed by invasive lobular carcinoma (5-15%) (Weigelt & Reis-Fiho, 2009). Molecular types of breast cancer include luminal (either A or B), human epidermal growth factor receptor 2 (HER2), and basal subtypes (Schnitt, 2015). Luminal subtypes have a higher expression of estrogen/progesterone receptors (ER/PR) (luminal A > luminal B) and comprise approximately 70% of all invasive breast cancers. Tumors that exhibit ER and/or PR

positivity use estrogen and/or progesterone to promote cancerous cell growth (Kos & Dabbs, 2016).

Representing 15% to 20% of all invasive breast cancer types is the HER2 subtype (Biooncology, 2015; Kos & Dabbs, 2016). This subtype has a higher expression of HER2 and has been linked with poorer outcomes (Kos & Dabbs, 2016). HER2 is a gene that makes HER2 proteins, which are expressed on a number of body cells (Carpenter & Lo, 2013). HER2 is a member of the human epidermal growth factor receptors (HER) family, (HER1, HER2, HER3, HER4) all of which help regulate cell growth, survival, differentiation, and migration through several cell signaling pathways (Kos & Dabbs, 2016). Amplification or overexpression of the HER2 gene leads to aggressive and unrestrained neoplastic cell growth and survival (Bose et al., 2006; Wieduwilt & Moasser, 2008).

Basal subtypes have a high expression of basal epithelial genes, and tend to be triple negative, meaning the tumor lacks estrogen and progesterone receptors, and is HER2 negative. About 15% of invasive breast cancers are classified as basal subtypes and, like the HER2 subtype, are associated with aggressive tumors and correspondingly poorer prognoses (Schnitt, 2015).

The risk for developing any of the subtypes of invasive ductal carcinoma of the breast is dramatically increased by inherited genetic alterations, called germline alterations. A germline alteration refers to the presence of an altered gene within the germ cell, so that the altered gene can be passed on to future generations (Genetics Home Reference, 2016). The most well studied germline alterations are the breast cancer susceptibility gene 1 and 2 (BRCA1 and BRCA2) (ACS, 2015a). BRCA1 and BRCA2 produce tumor suppressor proteins, which are involved in repairing double strand breaks by homologous recombination (Chandramouly, Willis, & Scully, 2011; NCI, 2015a). BRCA1 is the first gene to function in homologous repair, and recruits

BRCA2 to the break site. Loss of function of either gene initiates genomic instability, thereby triggering tumor formation (Chandramouly et al., 2011). By the time a woman reaches 70 years of age, 55%-65% of women who inherit a BRCA1 alteration will develop breast cancer while around 45% of women who inherit a BRCA2 alteration will develop breast cancer (NCI, 2015a). BRCA1 alterations are associated with the basal subtype of breast cancer, while BRCA2 alterations are generally associated with the luminal B subtype, although this is not universal (Larsen et al., 2013). Five to 10% of all breast cancer cases occur due to germline alterations (ACS, 2015a); therefore somatic alterations represent the vast majority of breast cancer causes. Somatic alterations are alterations in DNA that are acquired after conception and can occur in any cell in the body except germ cells (sperm and egg), meaning they are not passed on to future generations (Genetics Home Reference, 2015).

Gynecologic cancers, which affect a woman's reproductive organs, include ovarian, fallopian, peritoneal, endometrial, vaginal, vulvar, and cervical cancer. Endometrial cancer is the most common gynecologic cancer, with an estimated 54,870 new cases estimated in 2015, and 10,170 deaths attributed to this disease (ACS, 2015a). Ovarian cancer is the seventh most common cancer in women with 21,290 new cases estimated in 2015 (ACS, 2015a). It should be noted that cancers of the ovary, fallopian tube, and peritoneal are often combined due to the similar clinical and molecular characteristics (Fadare & Khabele, 2015). Typically fatal, these cancers are estimated to be responsible for 14,180 deaths in 2015 (ACS, 2015a). Approximately 10-20% of ovarian cancers are linked to a germline alteration such as BRCA1 or BRCA2 (Fadare & Khabele, 2015). Roughly 39% of women who inherit the BRCA1 alteration and 17% of women who inherit the BRCA2 alteration will develop ovarian cancer by the time they reach 70 years of age (NCI, 2015a). The estimated number of deaths for cervical, vulvar, and vaginal cancers in 2015 was 4,100 (ACS, 2015a), 1,080 (National Cancer Institute [NCI], 2015c), and

910 (Siegel, Miller, & Jemal, 2015) respectively. Gynecologic cancers may be further classified into histological subtypes (McCluggage, 2011). For example, four common subtypes in ovarian cancer are serous, endometrioid, clear cell, and mucinous carcinomas (McCluggage, 2011), and endometrial cancer subtypes include endometrioid and nonendometrioid (Binder & Mutch, 2014) carcinomas. Serous, clear cell, and undifferentiated classifications are included within the nonendometrioid subtype (Binder & Mutch, 2014).

In summary, breast and gynecologic cancers are major health concerns for women. Scientific advancements such as genomic profiling have shown that breast and gynecologic cancers are a heterogeneous group of diseases necessitating a personalized approach for selecting the most appropriate treatment modalities. The implementation of genomic profiling and its potential to identify specific genomic alteration(s) that can be matched to specific therapies that target the alteration(s) is rapidly changing the field of oncology. Given the novelty of matched therapy, nurses and other clinicians are unfamiliar with the symptoms patients experience and the impact of these symptoms on HRQOL. This is a new and emerging field of study in contemporary oncology care.

Purpose, Aims and Research Questions

Purpose and Aims

The purpose of this study is to describe the characteristics of patients with breast or gynecologic cancer undergoing matched therapy or not matched therapy, as well as to describe cancer therapy-related symptom occurrence and severity, and overall HRQOL for patients undergoing matched therapy and not matched therapy. Study aims are to: (a) describe the characteristics of the patients by type of therapy (matched, not matched); (b) describe symptom occurrence and severity of cancer therapy-related symptoms as well as HRQOL among patients receiving matched therapy and those not receiving matched therapy; (c) examine the association

between type of therapy (matched therapy, not matched therapy) and overall symptom occurrence and severity as reported on the Therapy-Related Symptom Checklist (TRSC) after controlling for person and health/illness factors; and (d) examine the relationship between type of therapy (matched therapy, not matched therapy) and HRQOL as reported on the Health-Related Quality of Life – Linear Analogue Self Assessment (HRQOL-LASA) after controlling for person and health/illness factors.

Research Questions

Research Question #1. What are the characteristics (demographic data, socioeconomic data, length of therapy, concurrent therapy, prior lines of therapy [number and type], cancer type and stage, and number of comorbidities) of patients by type of therapy (matched therapy, not matched therapy)?

Research Question #2. What is the occurrence and severity of cancer therapy-related symptoms as reported on the Therapy-Related Symptom Checklist (TRSC) and overall HRQOL as reported on the Health-Related Quality of Life – Linear Analogue Self Assessment (HRQOL-LASA) for patients receiving matched therapy and those receiving not matched therapy?

Research Question #3. What is the association between type of therapy (matched therapy versus not matched therapy) and overall occurrence and severity of cancer therapy-related symptoms as reported on the TRSC after controlling for person (age) and health/illness factors (cancer type, cancer stage, length of therapy, number of prior lines of therapy, and number of comorbidities)?

Research Question #4. What is the association between type of therapy (matched therapy versus not matched therapy) and overall HRQOL as reported on the HRQOL-LASA after controlling for person (age) and health/illness factors (cancer type, cancer stage, length of

therapy, number of prior lines of therapy, number of comorbidities, and overall symptom occurrence and severity)?

Significance of the Study for Nursing

Concerted efforts have been made to increase the survival benefits of the therapies used to treat cancer, yet the impact of these therapies on the individual has traditionally been given less consideration. More recently, there has been increased national attention to symptoms and other patient reported outcomes including QOL. The NINR has included advancing QOL through symptom research as one of its five focuses for advancing the science of health (Grady & Gough, 2015; NINR n.d., 2016). A major tenet of this focus is to support research that improves the understanding of symptoms in order to improve QOL, especially in the context of chronic health conditions and precision medicine, which is an approach for disease treatment and prevention that takes individual variability in genes, environment, and lifestyle for each person into account (Grady & Gough, 2015; National Institutes of Health [NIH], n.d.a.; NINR, 2016). Improving the QOL of cancer survivors is now listed in Healthy People 2020 objectives (Healthy People, 2015), and the NCI has advocated for expanding research on patient reported outcomes such as symptoms and QOL (Reeve et al., 2014).

To meet these national research objectives, nursing research must be aligned with the most up to date practices, which in oncology includes genetic and genomic science. Professional nursing organizations have proclaimed the need for nursing to incorporate genomic knowledge and skills into nursing practice (Hamilton, 2009), and competency and curricula guidelines now exist for nursing education (American Nurses Association [ANA], 2006; 2009). The Oncology Nursing Society (ONS) has called for the "need for oncology nurses to integrate genetic and genomic information into every aspect of oncology nursing care" (ONS, 2013, p.10).

Conceptual Framework

The Symptom Management Theory (SMT), (see Figure 1) with its core concept of symptoms, is well matched to the quantitative research proposed in this paper and was used to identify and classify variables relevant to the study. The SMT was initially developed by a group of nursing scientists at the University of California at San Francisco School of Nursing in 1994 through a deductive process based on their combined scope of practice and research programs in chronically ill populations (Linder, 2010). Revisions to the original were published in 2001 (Dodd et al., 2001), and again in 2008 (Humphreys et al., 2008).

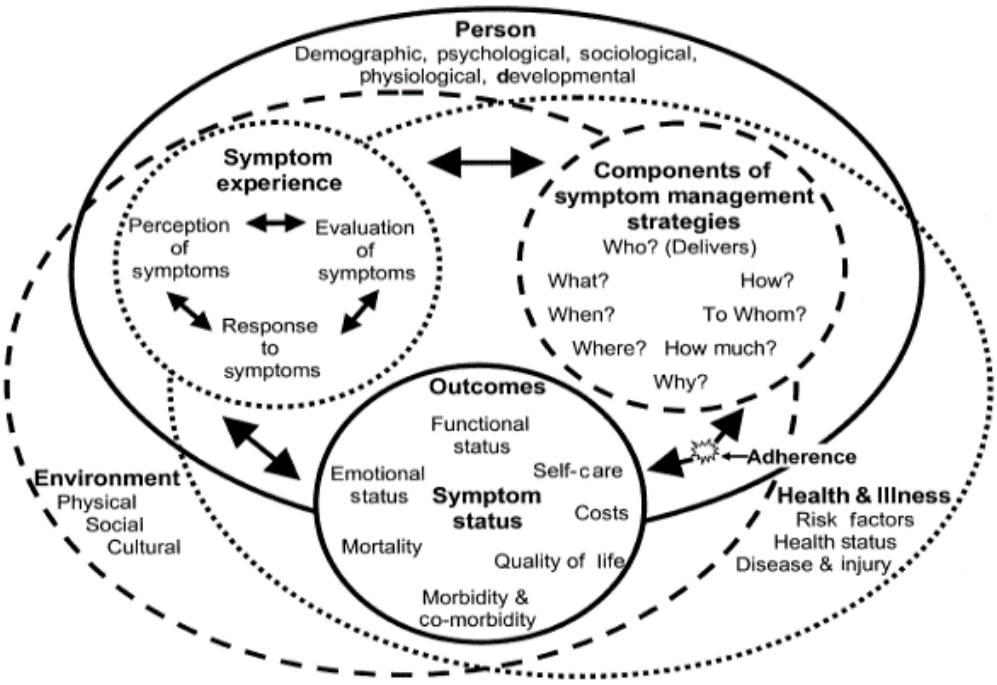

Figure 1. Symptom Management Theory conceptual framework (from Dodd et al., 2001).

The SMT describes three key concepts of symptom management: (a) Symptom experience, (b) Symptom management strategies, and (c) Symptom status outcomes (Linder, 2010). Each concept is nested within the person, health/illness, and environment domains of nursing science (Humphreys et al., 2008) due to the potential influences from these domains. Relationships among the concepts are depicted as a dynamic process with the use of the

bidirectional arrows. Effective symptom management requires attention to all three components (Linder, 2010).

The symptom experience served as one focus of the study. Symptoms are conceptually defined in the SMT as "a subjective experience reflecting changes in the biopsychosocial functioning, sensations, or cognition of an individual" (Dodd et al., 2001 p. 669). According to SMT assumptions, the gold standard for the study of symptoms is based on the perception of the individual experiencing the symptom and his/her self-report (Dodd et al., 2001, p. 669-670). This assumption guided the choice of and provides support for the instrument that was used in the study, the TRSC, which measured symptom occurrence and severity per patient self-report.

Health and illness factors can have direct effects on the symptom experience (Dodd et al., 2001). In this quantitative study, the type of cancer therapy a patient receives falls within the health and illness domain. Other variables falling within the health and illness domain that were included are as follows: cancer type, cancer stage, comorbidities, number of prior lines of therapy, and length of therapy. Person factors can also have direct effects on the symptom experience by influencing the way an individual responds to the symptom experience (Dodd et al., 2001). Age, ethnicity, insurance type, and drug coverage type fall within the person domain and were included as variables for this study. All research questions focused on these variables of the symptom experience of breast and gynecologic cancer patients, which are further described in Chapter 2. The third research question examined associations among these variables.

The fourth research question relates to the outcome component of the SMT. Outcomes emerge from the symptom experience and include QOL (Dodd et al., 2001). In the proposed study, HRQOL was used in place of QOL since it provides a narrower focus and refers to aspects that are related to health, illness, and treatment (Ferrans, Zerwic, Wilbur, & Larson, 2005).

Definition of Terms

Key terms have been conceptually and operationally defined. Other terms relevant to this study are defined in Chapter Three.

Matched Therapy is conceptually defined as the matching of a specific cancer therapy or therapies that is/are known to target a genomic alteration(s) to the patient's genomic alteration(s), which is/are found on genomic profiling. The operational definition is the use of at least one drug that is known to target the genomic alteration of at least one of the patient's genomic alterations found on genomic profiling.

Not Matched Therapy is conceptually defined as therapy or therapies used to treat cancer that is/are not matched to specific genomic alteration(s). The operational definition is the use of drugs that are not specifically matched to genomic alterations. Patients receiving not matched therapy may or may not have had genomic profiling testing.

Symptoms are conceptually defined as "A subjective experience in the biopsychosocial functioning, sensations, or cognition of an individual" (Dodd et al., 2001, p. 669). The operational definition is cancer therapy-related symptom occurrence and severity as measured by the Therapy-Related Symptom Checklist (TRSC).

Health-Related Quality of Life (HRQOL) is conceptually defined as an individual's perception of health-related well-being based on principle health components including the physical, emotional, mental, social, spiritual, and overall QOL (Bretscher et al., 1999; Ferrans, Zerwic, Wilbur, & Larson, 2005). The operational definition is HRQOL (physical, emotional, mental, social, spiritual, and overall QOL) as measured by the Health-Related Quality of Life-Linear Analogue Self Assessment (HRQOL-LASA).

Surgery is conceptually defined as using operations in the treatment of disease or injury (MedicineNet.com, 2016). The operational definition is using surgery to treat patients with breast or gynecologic cancers as identified in the patient health care record.

Chemotherapy is conceptually defined as the use of cytotoxic, systemic, and non-specific chemical agents to kill rapidly dividing cells (ACS, 2017b). The operational definition is using non-specific chemotherapeutic agents to treat patients with breast or gynecologic cancers as identified in the patient health care record.

Radiation Therapy is conceptually defined as the use of high-energy radiation to shrink tumors and kill cancer cells (NCI, 2010). The operational definition is using radiation therapy to treat patients with breast or gynecologic cancers as identified in the patient health care record.

Targeted Therapy conceptually refers to drugs or other substances that block the growth and spread of cancer by interfering with specific molecules, or molecular targets, that are involved in the growth and spread of cancer (NCI, 2014). The operational definition is using targeted therapy to treat patients with breast or gynecologic cancers as identified in the patient health care record.

Cancer Genomic Profiling is conceptually defined as the examination and characterization of DNA or RNA sequences of cancer cells which is accomplished through laboratory testing. The information generated from this testing includes: a) identification of nucleotide bases/their order, b) copy number and sequence variants, c) mutation status, and d) structural changes such as chromosomal translocations and gene fusions (Wikipedia, 2017).

The operational definition of cancer genomic profiling for this study is the genomic profiling of breast or gynecologic tumors using the FoundationOne Assay. Results are used in practice and in the setting for this study to match patient specific therapy/therapies to alteration(s) identified on genomic profiling tests.

Study Assumptions

1. Symptoms are based on the perception of the individual and their self-report.

2. Patients truthfully report their demographic characteristics, cancer therapy-related symptoms, and perceptions of HRQOL.

3. The electronic health record (EHR) documentation accurately reflects the patients' type and stage of cancer, demographic information, length of therapy, and number of comorbidities.

4. Patients received their therapies (past and current) as documented in the EHR.

Chapter Two

Literature Review

Advancements in the field of genomics (the study of genes and their function) are rapidly changing how cancer is treated (World Health Organization [WHO], 2015). Therapy choices are no longer restricted by where the primary tumor originated, but are increasingly being based on the genomic cancer alterations to increase specificity and efficacy. Matched therapy, therefore, may translate to using therapies in combinations that are not routine, or were previously uncombined. Numerous previous studies regarding cancer therapy-related symptoms and impacts on HRQOL have been conducted in populations that have not received matched therapy, including cancer treatment modalities involving surgery, chemotherapy, and/or radiation therapy. Currently there is limited information available concerning the symptom experience of cancer patients and their HRQOL while receiving therapy that is matched to their specific cancer genomic alterations.

This chapter will review the following: (a) Cancer; (b) Cancer Treatment Modalities – Surgery, Radiation Therapy, Chemotherapy; (c) Cancer Treatment Modalities – Precision Medicine, Targeted Therapy, Matched Therapy; (d) Therapy-Related Symptom Occurrence and Severity; (e) Symptom Measurement Tools; (f) Other Variables Influencing the Effects of Cancer Treatment; (g) Health-Related Quality of Life (HRQOL); and (h) Health-Related Quality of Life (HRQOL) Measures.

Cancer

Cancer is a generic name applied to a group of disorders that involves uncontrolled division of body cells (ACS, 2015b; NCI, 2015f). Cancer is characterized by one or more of the following alterations: sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, replicative immortality, inducement of angiogenesis, and activation of invasion and

metastasis (Hanahan & Weinberg, 2011). These alterations result in uncontrolled division of body cells that are due to DNA aberrations, which can be inherited (germline) or acquired (somatic). Somatic mutations can occur spontaneously during an individual's lifetime or can be induced by environmental (e.g. sun exposure), lifestyle (e.g. cigarette smoking), or other factors. The majority of cancers are due to somatic mutations versus inherited/germline mutations (ACS, 2015b).

Cancer has been generally classified by the type of tissue in which the cancer originates, its structural pattern (histological type), and by the location where the cancer first developed (primary site) (NCI, 2015b). Most cancers are also assigned a grade of 1, 2, 3, or 4, which refers to how abnormal the tumor cells and tumor tissue look under a microscope (NCI, 2013). If the tumor cells and the structure of the tumor tissues closely resemble the normal cells and tissues, then the cancer is referred to as well-differentiated. Tumors that are well-differentiated tend to grow and spread at a slower rate, thus are assigned a lower grade. Conversely, cancers that have tumor cells and tumor tissues that do not resemble the normal cells and tissues are described as poorly differentiated. Poorly differentiated tumors typically grow more rapidly, thus are assigned higher grades. Tumors with higher grades are associated with a more aggressive cancer (ACS, 2015b). Table 1 shows an example of a general grading system.

Table 1

General Cancer Grading System

Amount of Abnormality	**Associated grade**
GX: Grade unable to be assessed	Undetermined grade
G1: Well-differentiated	Low grade
G2: Moderately differentiated	Intermediate grade
G3: Poorly differentiated	High grade

Table 1 Continued

Amount of Abnormality	Associated grade
G4: Undifferentiated or Dedifferentiated	High grade

Note. Adapted from example of cancer grading system, NCI 2013

A modification of the general cancer grading system, called the Nottingham grading system, is used for breast cancers. The Nottingham grading system is based on the evaluation of three features: (a) Tubule formation, which refers to how much of the tumor tissue has normal breast duct structures; (b) Nuclear grade, which is an evaluation of the size and shape of the tumor nuclei; and (c) Mitotic rate, which measures how many dividing cells are present to determine how fast the tumor cells are dividing (NCI, 2013). Each feature is scored from one to three, one meaning the tumor cells look the most like normal cells, and three meaning the tumor cells look the most abnormal. The scores are summed to determine the grade. Table 2 shows the grades associated with the Nottingham scores.

Table 2

Nottingham Score and Corresponding Grades for Breast Cancer

Total Nottingham Score	Grade
3-5	Grade 1, Low Grade
6-7	Grade 2, Intermediate Grade
8-9	Grade 3, High Grade

Note. Adapted from Nottingham score in breast cancer, NCI 2013

Cancers are further classified according to stage. In most cancers, the stage is based on four factors: (a) location of the primary tumor, (b) tumor size and extent of tumors, (c) lymph node involvement, and (d) presence or absence of metastasis (AJCC, 2015). Decisions regarding the best way to treat each cancer diagnosis are dependent on this entire classification process.

Cancer Treatment Modalities – Surgery, Radiation Therapy, Chemotherapy

National Comprehensive Cancer Network (NCCN) Guidelines have been in existence since 1996 to standardize the treatment of all cancer types (NCCN, 2015). Historically, surgery,

radiation therapy, and chemotherapy have been the primary modalities of cancer treatment. Depending on the type of cancer and on the extent of the disease, one or more of these treatment modalities may be used.

Surgery. Using surgery to remove cancer has been documented since ancient times, although this modality is only successful for local control of the cancer. In other words, if the cancer has spread or metastasized to other areas in the body, then surgery will not be curative. However, surgery may be used even if the cancer has spread in order to palliate symptoms, for example if one or more of the tumor(s) is causing significant pain or pressure (NCI, 2015d). Surgery may also be performed before or after other treatment modalities such as chemotherapy and radiation.

Radiation therapy. At the beginning of the 20th century, radiation therapy was being used to diagnose cancer and to treat cancer. High energy radiation such as X-rays, gamma rays, and charged particles are used to treat cancer due to their ability to damage DNA directly or create free radicals within the cells that in turn damage DNA. Like surgery, it is typically used for local control of the cancer. Systemic radiation therapy is less common and uses radioactive substances that travel in the bloodstream, such as radioactive iodine for the treatment of thyroid cancer. Radiation may occur before surgery to shrink the size of the cancer, during the surgery so that the radiation goes straight to the cancer without passing through the skin, or after surgery to kill any potential cancer cells that may remain (NCI, 2010).

Chemotherapy. Chemotherapy is used to destroy cells that grow and divide rapidly. Most chemotherapies affect the process of cell division and are classified according to whether they are cytotoxic during active division of cells, or during the proliferative and resting phases of division (Payne & Miles, 2008). Chemotherapies destroy cancerous cells and normal cells and therefore are associated with significant side effects. Similar to radiation therapy, chemotherapy

may be used to shrink a tumor before surgery – called neoadjuvant chemotherapy, or may be used after surgery to destroy potential remaining cancer cells – called adjuvant chemotherapy (NCI, n.d.a). Neoadjuvant and/or adjuvant chemotherapy are frequently used in non-metastatic breast and gynecologic cancers (Gradishar & Salerno, 2016; Wright et al., 2016). Chemotherapy can also be used to control the progression of the cancer in cases when the disease has metastasized to other parts of the body.

Chemotherapy regimens may include the use of a single chemotherapy drug or a combination of chemotherapy drugs, the latter being more common. Combining chemotherapies that have different mechanisms of action is typically more effective since the cancer cells are attacked in several different ways (ACS, 2017b). For example, alkylating chemotherapy agents are used in certain breast cancer and gynecologic cancer chemotherapy regimens to directly damage the deoxyribonucleic acid (DNA) of the cancer cells. Alkylating agents can be combined with anthracycline chemotherapy agents, which interfere with cancer cell DNA replication, and/or mitosis in the M phase of the cell cycle (ACS, 2017b). These are a few examples of the many classes of chemotherapeutic drugs used.

The length of time a chemotherapy regimen is given as well as the frequency of the regimen is highly dependent on the classes of drugs used and the intent of the outcome of the treatment of the cancer (curative, palliative). In a neoadjuvant or adjuvant setting where the intent of treatment of the cancer is curative, the regimen is usually given every two to three weeks. Many different chemotherapy regimens exist for metastatic cancer; a regimen may be given every week, every two to three weeks, or even every four weeks. The total length of time a typical chemotherapy regimen is administered for breast cancer in the neoadjuvant or adjuvant setting is 20 to 24 weeks. If the breast cancer is the HER2 subtype, a type of targeted therapy called trastuzumab which specifically targets the HER2 proteins is given for an additional nine

months after the chemotherapy is completed. The length of time a typical chemotherapy regimen is administered in the neoadjuvant or adjuvant setting in gynecologic cancers is 18 weeks. In the metastatic setting, chemotherapies are given indefinitely depending on the tolerability of the regimen and the disease response to the regimen (NCCN, 2016; 2017).

Disadvantages of treatment with surgery, radiation therapy and chemotherapy. As discussed above, surgery and radiation therapy are effective treatments of cancer only in the case of local control. If the cancer has spread, then surgery and radiation therapy become palliative rather than curative in nature. The disadvantage of treatment protocols using chemotherapy is that the protocols do not acknowledge the heterogeneity of tumors. For example, the same chemotherapy regimen is used to treat patients with ovarian cancer regardless of whether they have a serous subtype, endometrioid, clear cell subtype, or mucinous subtype of ovarian cancer. Patients with the clear cell and mucinous ovarian cancer subtypes are typically resistant to chemotherapy at baseline and both are associated with worse prognoses (Raja, Chopra & Ledermann, 2012). Approximately 75% of patients with the serous subtype of ovarian cancer will achieve remission with initial chemotherapy yet half of these patients will have recurrent disease within two years (Ozols, 2006). Many times, the exact same chemotherapies are administered when the disease recurs, with much smaller rates of remission (Ozols, 2006).

The treatment of breast cancer is advanced in terms of tailoring therapies to the different subtypes and corresponding features. Nevertheless, breast cancer is still the second leading cause of cancer-related death among American women (ACS, 2015a). Breast cancer has long been recognized as a heterogeneous disease, and data compiled from comprehensive genomic profiling results have led to the now accepted belief that no two breast cancers possess the same genomic alterations (Natrajan, 2015). As a result of this diversity, therapies will have varying effects in patients. To illustrate, luminal subtypes of breast cancer have higher expressions of

ER/PR, and thus are predicted to respond to endocrine therapy. Endocrine therapy blocks the tumor's ability to use estrogen and/or progesterone for survival and proliferation. However, approximately 50% of patients that have metastatic breast cancer are resistant to endocrine therapy at baseline, and those that are not will likely acquire resistance during ongoing use of the therapy (Osborne & Schiff, 2011).

Although cancer survival rates have improved using surgery, radiation therapy, and chemotherapy, cancer, in many cases, remains an incurable disease. Surgery and radiation therapy are still only effective in early-stage cancers or in palliative settings. Some cancer cells become resistant to chemotherapy, while other cancer cells are inherently resistant at baseline. Consequently, patients with the same primary tumor and the same type of therapy can have very different outcomes. Moreover, all of the treatment modalities, especially chemotherapy, can cause significant side effects (DeVita, Lawrence, & Rosenberg, 2011; Reeve et al., 2014). This has fueled the desire to develop a more personalized and targeted approach to treat cancer in order to maximize the risk/benefit ratio.

Cancer Treatment Modalities - Precision Medicine, Targeted Therapy, Matched Therapy

Precision Medicine. Precision medicine is a general term for the treatment of diseases that takes into account individual variability in genes, environment, and lifestyle for each person (NIH, n.d.a). Funding to support precision medicine called the "Precision Medicine Initiative" was announced by former President Obama in 2015. This new initiative, is expected to accelerate biomedical discoveries that will provide clinicians with new tools, knowledge, and therapies that can be applied to patients for the treatment of diseases on an individual basis. The use of precision medicine is most advanced in the treatment of cancer, which is largely due to the fact that cancer is a known disease of the genome (NIH, n.d.b.). Research over the past two decades has focused on cancer therapies that can directly target cancerous cells.

Targeted therapy. Targeted therapies were introduced into routine oncology practice during the late 1990's. A targeted therapy is generally considered to be chemotherapy, but their mechanisms of action are different. Whereas chemotherapy primarily acts on rapidly dividing normal and cancerous cells (cytotoxic), targeted therapies block the proliferation of cancer cells by interfering with specific molecules required for tumor growth (cytostatic) (Gerber, 2008). Targeted therapies can block cancer cell proliferation in a number of ways such as interfering with the function of receptors, ligands, or cell surface markers (Belum, Cercek, Sanz-Motilva, & Lacouture, 2013). Depending on their mechanism of action, many types of targeted therapies exist and, while not an exhaustive list, include: a) Signal transduction inhibitors, which inhibit proteins used for signaling cancer cell growth; b) Angiogenesis inhibitors, which reduce tumors from producing new blood vessels; c) Monoclonal antibodies, which attack a specific target on cancer cells; and d) Proteasome inhibitors, which stop the proteasomes in the cancer cells from breaking down proteins that inhibit apoptosis (Belum et al., 2013; Gerber, 2008; NCI, 2014).

One of the earliest examples of a targeted therapy is trastuzumab, which is an antibody directed against the HER2 receptor (Leyland-Jones, 2002; Slamon et al., 2001). When HER2 dimerization occurs, tyrosine kinase phosphorylation is activated, thereby initiating multiple signaling events that lead to cell survival and proliferation, and inhibition of apoptosis (Leyland-Jones & Smith). Although the mechanism of action is disputed, it is thought that trastuzumab binds to the HER2 receptor once it is dimerized, thus eliciting an immune response and inhibiting the signaling cascade, that ultimately results in tumor cell death (Leyland-Jones, 2002; Leyland-Jones & Smith, 2011). It is proposed that the mitogen-activated protein-kinase and phosphatidylinositol 3-kinase and Akt pathways are inhibited as a result of trastuzumab, both of which are involved in fundamental cellular processes including cell survival, proliferation, and apoptosis (Arnould et al., 2006). Since the Food and Drug Administration (FDA) approval of

trastuzumab, examining breast cancer cells for HER2 amplification has become a routine pathology test. Detection of HER2 amplification can be accomplished by a) Immunohistochemical stains (IHC), in which special stains or markers are used to identify the HER2 protein; or b) Fluorescent in situ hybridization (FISH), in which fluorescent pieces of DNA that stick to copies of the HER2 gene are counted (ACS, 2017a). The survival rate of women with HER2 amplified breast cancers has dramatically improved because of trastuzumab (Untch et al., 2008).

Trastuzumab is only used when HER2 amplification is detected, but other targeted therapies may be used without a corresponding detectable target. For instance, everolimus is a drug that inhibits the activation of the mammalian Target of Rapamycin (mTOR), which is a key regulatory kinase (NCI, n.d.b). A kinase is an enzyme that modifies other proteins through phosphorylation, and are known to regulate the majority of cellular pathways (Manning, 2016). Everolimus is approved for treatment of breast cancer, renal cell cancer, and certain soft tissue sarcomas as part of the standard NCCN guidelines due to the increased percentage of mTOR alterations found in these cancers. Thus, everolimus is being used as therapy for these cancers due to clinical experience instead of a specific genomic profiling data. However, if mTOR alterations are not the driving mutations in these cancers, which they are not universally, then everolimus is less likely to be effective. Genomic profiling is able to identify the individual's specific tumor alteration(s) enabling the precise use of agents that target the alteration(s).

Matched therapy. Matched therapy refers to matching a specific cancer therapy or therapies that is/are known to target a specific genomic alteration(s) found on cancer genomic profiling. Matched therapy represents a major paradigm shift in the treatment of cancer, which has evolved over the past several decades. Data from research suggest that each cancer has its own genomic signature, with some features specific to the tumor and other features common to

multiple types of cancers (Collins & Varmus, 2015). This heterogeneity is what is believed to be responsible for the differences in responses to the same type of therapy among patients with the same histologic type (McDermott et al., 2011). Genomic profiling has the capability of revealing specific genomic alterations and thus, tumor heterogeneity.

It is now possible and feasible to perform genomic profiling on a patient's tumor in routine clinical practice, which has the potential to find their specific genomic alterations. Genomic profiling is performed using technologies now referred to as next generation sequencing and high-throughput sequencing, in which millions of DNA strands can be sequenced in parallel (Nature.com, 2015). Today's testing procedures allow examination of the DNA sequence of just a few genes up to many genes, which may lead to the identification of an alteration that could be driving the cancer and/or affecting cancer signaling pathways (National Genetics and Genomics Education Centre, n.d.). Cancer Signaling Pathways is when a group of molecules in a cell work together to control one or more abnormal functions, such as cell proliferation. In normal cell function, signaling pathways are key for homeostatic processes in which an initial molecule in a pathway receives a signal, and then activates other molecules. This process is repeated until the activation of the necessary molecules is completed and the cell function is carried out. In cancer, due to genomic alterations, the signaling pathways are abnormal (NCI, n.d.a; Yap, Omlin, & Bono, 2013). The aim of genomic profiling is to detect the tumor's driving alteration(s) since they are responsible for the proliferation and survival of the cancer cell (McDermott et al., 2011). The ultimate goal is to match therapies that potentially target and interfere with that particular alteration and/or cancer cell-signaling pathway.

An example of a cancer genomic profile test used in clinical practice is the CLIA-certified FoundationOne assay, which uses next generation sequencing, is provided by the company Foundation Medicine, and has been available since October 2013. Some insurance

companies cover the cost of the FoundationOne assay and, if insurance denies coverage, the company works with the individual to complete the testing at a reasonable price. Besides the FoundationOne assay, other cancer genomic profile tests exist, but each have a slightly different approach in terms of what kind of alterations are reported, and how the test is performed.

Results obtained from genomic profiling may also indicate that the tumor is sensitive or resistant to a certain type of chemotherapy. For instance, an alteration called ARID1A may indicate that that a tumor is resistant to a class of chemotherapies called platinums. Another alteration, called TOP2A, may indicate a tumor is sensitive to a class of chemotherapies called anthracyclines. Finding alterations indicating sensitivity or resistance to a chemotherapy is less common in practice, thus alterations are predominantly matched to therapies that specifically target the alteration.

Prospective studies comparing matched therapy to not matched therapy are ongoing or in development, but retrospective studies have indicated that the matched therapy yields superior outcomes (Schwaederle et al., 2015; Tsimberidou et al., 2012; 2014). Schwaederle et al. (2015) performed a retrospective study evaluating the clinical outcomes of $N = 392$ patients with a variety of cancer types who had genomic profile testing on their cancer tumor. The most common primary tumor sites were gastrointestinal (23%) followed by breast (21%), brain (14%), gynecologic (8%), head and neck (8%), and hematologic (8%). The remaining 18% of patients had melanoma, lung, and other cancers. Of the $N = 246$ patients evaluated, $n = 53$ patients were treated with agents that were matched to genomic alterations found on genomic profiling. The researchers showed that progression free survival (PFS) was significantly longer in patients who received matched therapy versus those who did not ($p = 0.042$). Progression free survival refers to the time elapsed between initiation of any type of treatment modality and tumor progression or death from any cause (NCI, n.d.a) and is a common endpoint used in cancer clinical trials

observing treatment modality efficacy (Booth & Eisenhauer, 2012). The measure allows for a smaller sample size and shorter follow up time period. Because hormone positive and HER2 positive breast cancer patients were included in the matched therapy group, a Cox regression analysis was performed including matched therapy vs. non-matched and breast histology (hormone and HER2 status) as variables. The matched therapy approach was the only variable independently predicting a longer PFS ($p = 0.028$) (Schwaederle et al., 2015).

Researchers in a Phase I program at MD Anderson Cancer Center examined the outcomes of patients receiving matched therapy based on genomic profiling (this genomic profiling test covered 20 genes) versus therapies that were not matched (Tsimberidou et al., 2012; 2014). Two separate analyses were performed. Patients in both analyses had advanced or metastatic disease, had exhausted other therapy options, and had been referred to the Phase I Program at the University of Texas MD Anderson Cancer Center for treatment of their cancer. Therapy was considered matched if a drug known to inhibit the activity of at least one of the patient's tumor alterations was used. Therapy that did not satisfy this definition was considered unmatched. In the first analysis, 175 patients were treated with matched therapy while 116 received not matched therapy (Tsimberidou et al., 2012). Breast cancer patients represented 6% of the sample ($n = 14$ matched; $n = 2$ not matched) while gynecologic cancers represented almost 10% ($n = 17$ matched; $n = 11$ not matched). The majority of the sample was comprised of patients with melanoma (25%), colorectal (21%), and thyroid (12%) cancers. Endpoints included overall response rate, which is complete response (complete resolution of disease) plus partial response (≥ 30% reduction in disease but < 100%), and overall survival. Matched therapy was associated with a significantly higher overall response rate ($p < 0.001$) and longer survival ($p = 0.017$). Multivariate analysis found that in patients with at least one genomic alteration, matched therapy was an independent factor predicting overall response ($p = 0.001$; OR 6.33)

(Tsimberidou et al., 2012). To validate these findings, data from an additional 379 patients enrolled in the Phase I program between 2011 and 2012 were analyzed (Tsimberidou et al., 2014). Patients with colorectal (22%), lung (12%), ovarian (9%), melanoma (9%), and breast (9%) cancers represented a majority of the sample. The validation analysis revealed that patients receiving matched therapy ($n = 143$) had a significantly higher overall response rate ($p < 0.001$), and longer survival ($p = 0.04$) than patients receiving not matched therapy. Multivariate analysis found matched therapy to be an independent factor predicting overall response ($p = 0.015$; OR 1.91).

To date, one prospective clinical trial has been published with the primary aim of establishing the feasibility of identifying genomic alterations in breast cancer patients, with the intention of providing targeted therapy matched to the individuals' alterations (Andre et al., 2014). In this trial, breast cancer patients with metastatic disease underwent a biopsy of their cancer, which was subsequently analyzed for genomic alterations. Therapeutic decisions were then made based on the identified alterations. Among the 423 patients initially enrolled, 195 patients had at least one genomic alteration that could be matched to a targeted agent. Of the 195, 43 patients had been on matching therapy for at least 16 weeks and were able to be evaluated for disease response at the time the data were reported. Among these 43 patients, four patients had an objective response to therapy while the remaining had stable disease, indicating that the tumor(s) did not grow or shrink (Andre et al., 2014). Objective response was operationally defined in the study as a reduction in tumor size on imaging such as CT scan. Although the results may seem underwhelming, it should be noted that the patients included in this study had advanced disease and were heavily pretreated, thus decreasing the chance of any response in this setting. Moreover, it was the first prospective trial to show that matching therapy based on an individual's genomic profile was feasible.

In summary, the treatment of cancer is increasingly being personalized and based on the genomic alterations exhibited by the tumor versus the primary site of the tumor. Recent research show promising results with this more personalized approach, and prospective trials are ongoing to validate the findings.

Cancer Therapy-Related Symptom Occurrence and Severity

In general, cancer therapy is associated with frequent and potentially severe toxicities and associated symptoms. A systematic literature review examining the prevalence of symptoms in patients with varying cancer diagnoses undergoing treatment of their cancer identified 47 separate symptoms across 21 studies (Miller-Reilly et al., 2013). Of the 47 symptoms, a distinct set of symptoms emerged that were common across cancer types including fatigue, insomnia, anorexia, dry mouth, pain, cognitive changes, and nausea. Building upon this review, the NCI's Symptom Management and Health-Related Qualify of Life Steering Committee set out to identify a core list of symptoms to assess across oncology trials that were 1) present across diverse cancer populations, 2) impacted health outcomes and HRQOL, and 3) could be attributed to the disease or to cancer treatment modalities (Reeve et al., 2014). The methods employed to accomplish this included expanding on the Miller-Reilly (2013) literature review, analyzing two NCI clinical trial databases and four other large datasets across the United States and Europe, and forming an expert panel to review the evidence and provide consensus. This large undertaking culminated in the recommendation that a core set of 12 symptoms be considered for inclusion in oncology clinical trials. The 12 symptoms include fatigue, insomnia, pain, anorexia, dyspnea, cognitive problems, anxiety, nausea, depression, sensory neuropathy, constipation, and diarrhea (Reeve et al., 2014). It should be noted that these data used to conclude this core list of symptoms were collected between the years 2000-2011. While some of the core symptoms are

likely related to the disease, many are therapy-related. New therapies may produce different symptoms that are not part of the core assessment, which can lead to bias and under-reporting.

Numerous individual studies have quantified the number of these cancer therapy-related symptoms across cancer types (Chen & Tseng, 2006; Janz et al., 2007; Kenne-Sarenmalm, Ohlen, Jonsson, & Gaston-Johansson, 2007; Kirkova et al., 2011; Lopez, Williams, & Larkin, 2015; Spichiger et al., 2011). In a large study of breast cancer patients (*N*=1372), Janz et al. (2007) found that the average number of symptoms experienced by the participants who had completed surgery and radiation and/or chemotherapy was seven. In this study, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the Breast Cancer-Specific Quality of Life Questionnaire (QLQ-BR23) were used to assess symptoms. Both the EORTC QLQ-C30 and QLQ-BR23 include symptom domain-specific questions within a QOL assessment, but the QLQ-BR23 has added breast cancer specific items such as body image, sexual functioning, and breast specific-symptoms (e.g. pain, lymphedema) (Janz et al., 2007). Spichiger et al. (2011) assessed the number and type of therapy-related symptoms longitudinally using the Memorial Symptom Assessment Scale (MSAS) in a small sample of patients (*N*=58) with lymphoma, lung, breast, or colorectal cancer receiving chemotherapy and found the number of symptoms experienced to be as high as 14. Spichiger and colleague's (2011) findings were corroborated by Keene-Sarenmalm et al. (2007), who also found that the average number of symptoms experienced when measured by the MSAS was 14 in a sample ($N = 56$) of breast cancer patients on chemotherapy or radiation therapy. Similarly, Chen and Tseng (2006) found that the average number of symptoms experienced by patients with a variety of cancer diagnoses receiving chemotherapy ($N = 329$) was seven. In this secondary analysis of cross-sectional data study, the M.D. Anderson Symptom Inventory (MDSAI) was used to assess the cancer therapy-related symptoms. A more recent cross-

sectional study by Williams, Mowlazadeh, Sisler, and Williams (2015a) used the TRSC to assess symptoms in a sample of (N = 100) patients with varying cancer types who were receiving chemotherapy and/or radiation and found the mean symptoms reported to be eight.

Huang et al. (2013) conducted a study among a sample (N = 121) of breast cancer patients with HER2 overexpression aimed at assessing potential differences in symptoms during therapy with chemotherapy and targeted cancer therapy (trastuzumab). Patients in this study received 12 weeks of chemotherapy, followed by 12 weeks of chemotherapy and trastuzumab (targeted therapy) combined, followed by one year of trastuzumab (targeted therapy) alone. Data on cancer therapy-related symptoms were collected using the MDASI at baseline (prior to any therapy), and at four weeks, and twelve weeks after initiation of the therapy in each group. Results showed no significant differences in symptom occurrence and severity among patients receiving chemotherapy, combined therapy, or trastuzumab alone (Huang et al., 2013). An important limitation of this study is that patients received the therapies sequentially, meaning those receiving chemotherapy and trastuzumab combined had prior experience with chemotherapy, and those receiving trastuzumab alone had prior experience with chemotherapy alone and chemotherapy and trastuzumab combined, which were not accounted for in the analysis. These results are contrasted with prior studies showing that patients treated with chemotherapy and trastuzumab combined or trastuzumab alone experienced less severe symptoms than those receiving chemotherapy alone, particularly in regard to fatigue (Osoba, Slamon, Burchmore, & Murphy, 2002; Rugo, Brammer, Zhang, & Lalla, 2010).

Clearly cancer therapy-related symptoms are pervasive, although all of these studies but one (Huang et al., 2013) relate to symptoms experienced by patients undergoing chemotherapy. The study by Huang et al. (2013) compared chemotherapy to targeted therapy (e.g. trastuzumab), however, the use of trastuzumab is standard when HER2 is overexpressed. The symptoms

experienced by a broader range of patients who are on matched therapy based on comprehensive genomic profiling, needs to be examined. Matched therapy based on genomic profiling results involve using therapies that have not been extensively studied in combination or may use therapies at different doses. Currently the symptom experience of patients receiving therapies that are matched based on genomic profiling results is largely unknown.

Reviewing studies that examine the prevalence of symptoms in matched cancer therapy is challenging for several reasons; the largest being many of the published clinical trials using targeted therapies may not have been specifically matched to genomic profiling results. This is emphasized in a meta-analysis conducted by Niraula et al. (2012), which analyzed serious toxicities of newly approved cancer drugs (including chemotherapy and targeted therapies) between January 2000 and December 2010. Findings showed that therapy-related toxicities were more severe with the newly approved therapies ($p < 0.001$) many of which were targeted therapies (Niraula et al., 2012). The authors did not disclose whether any of the therapies used were matched to genomic profiling results. However, given the time frame (2000-2010) of this study, it is unlikely that genomic profiling was routinely being performed prospectively. Thus, it is currently unclear if the occurrence or severity of cancer therapy-related symptoms will differ when therapies are matched based on genomic profile testing.

Gaining knowledge about symptoms experienced by patients may guide clinicians in their management. For instance, some symptoms/side effects (e.g. skin rash) have been correlated with improved responses to specific therapies, especially when they are “on-target” or matched (Dy & Adjei, 2013; Liu & Kurzrock, 2014). Accordingly, it is crucial to begin to examine symptom occurrence and severity of patients receiving matched therapy, which can assist in identifying potential risks and benefits, and will ultimately contribute to symptom science in the context of current oncology care.

Symptom Measurement Tools

Studies that have examined cancer therapy-related symptoms have used a variety of measurement tools, which can be global, condition-specific, or symptom-specific (Ferrans et al., 2005). Since cancer patients, regardless of the cancer type, typically experience multiple symptoms simultaneously, measures that capture the most commonly experienced symptoms, are easy for patients to understand and complete, are valid and reliable, and improve assessment and control of symptoms are particularly useful (Kirkova et al., 2006). A brief summary of the more commonly used tools in oncology are discussed.

M.D. Anderson Symptom Inventory. The M.D. Anderson Symptom Inventory (MDASI) is a brief measure of the severity of cancer-related symptoms and their impact on the individual (Cleeland et al., 2000). Thirteen symptoms common among all cancer types are listed on the MDASI in addition to six items that measure how symptoms have interfered with the individual's life. The MDASI has demonstrated good psychometric properties with Cronbach's alpha reported as ranging from 0.82 - 0.94, and construct and discriminant validity indicated by inverse correlations with performance status (Cleeland et al., 2000). Other versions have been developed and validated for a variety of cancer types (Jones et al., 2013).

Memorial Symptom Assessment Scale. The Memorial Symptom Assessment Scale (MSAS) evaluates the frequency, severity, and distress of 32 physical and psychological symptoms (Portenoy et al., 1994). Three symptom subscales have been identified in the MSAS including the mood-cognitive symptom subscale, the sickness behavior subscale, and the treatment-related symptom subscale. The MSAS has been used in various clinical trials to assess symptom distress but has been criticized for its length and complicated ratings (Cleeland et al., 2000).

Oncology Treatment Toxicity Assessment Tool. In 1994, Youngblood, Williams, Eyles, Waring, and Runyon developed a self-report checklist, the Oncology Treatment Toxicity Assessment Tool (OTTAT), after noticing a significant underreporting of symptoms during treatments for cancer with the usual assessment method. The original study compared the OTTAT, a 37-item self-report instrument rating symptom severity on a scale from zero to four (four being the most severe) to the usual assessment. Findings showed that the number of symptoms reported with the usual assessment (*Mean* = 1.5; *SD* = 1.6; *range* = 0-9) was significantly lower than the mean number of symptoms reported, with the OTTAT (*Mean* = 11.5; *SD* = 8; *range* = 0-37; $p = 0.001$). The OTTAT was found to be inversely correlated with the Quality of Life Index, (QLI) developed by Ferrans (1992) and Padilla et al. (1983).

Therapy-Related Symptom Checklist. In subsequent instrument development, a principal components analysis reduced the OTTAT into the 25-item checklist that was named the Therapy-Related Symptom Checklist (TRSC). The OTTAT and the TRSC are highly correlated ($r = 0.97$) (Williams et al., 1997; 2001; 2014). The TRSC has fourteen subscales; two subscales contain 'clusters' of four items each. The Fatigue subscale consists of the items feeling sluggish, depression, difficulty concentrating, and difficulty sleeping. The Eating subscale includes the TRSC 'cluster' symptoms of taste change, loss of appetite, weight loss, and difficulty swallowing. A three-item subscale or 'cluster', designated as Oropharyngeal, includes sore mouth, sore throat, and jaw pain. The remaining three subscales or 'clusters' include two items each: Nausea (nausea and vomiting), Fever (fever and bruising), and Respiratory (cough and shortness of breath). Eight of the subscales are single item scales (Pain, Numbness in Fingers and/or Toes, Bleeding, Hair Loss, Skin Changes, Constipation, Soreness in Vein, and Decreased Interest in Sexual Activity). Like the OTTAT, symptom severity is rated on a scale from zero to four, with four being the most severe.

Multiple studies using the TRSC have been conducted within the United States, as well as in Europe, Asia, and Puerto Rico. The samples included in these studies were all receiving not matched therapy. For example, Williams et al. (2006a) conducted a descriptive study with adults ($N = 37$) receiving chemotherapy or radiation therapy for breast cancer, head and neck cancer, leukemia, or lymphoma at a Midwestern cancer center. Results showed that 15 patients reported 17 of the 25 symptoms or more on the TRSC. Patients receiving chemotherapy generally experienced more severe symptoms in the following TRSC subscales: Fatigue, Nausea, Eating, Pain, Hair loss, Numbness in fingers/toes, and Constipation (Williams et al., 2006a). Patients receiving radiation therapy were noted to have more severe symptoms in the following subscales: Eating, Fatigue, Skin changes, Oropharynx, Constipation, and Decreased interest in sexual activity. This study was replicated in cancer centers in China (Williams et al., 2010b), the Philippines (Williams et al., 2010a), and Thailand (Piamjariyakul et al., 2010) with appropriate translation methods. Findings in each study were similar to the results from the Midwestern, United States study in regard to symptom occurrence and severity. For example, the study completed in China examined patient-reported symptoms in $N = 222$ patients receiving chemotherapy and/or radiation therapy for a variety of cancers including breast cancer, gastrointestinal tract cancer, lung cancer, gynecologic cancers, and head and neck cancer (Williams et al., 2010b). Patients receiving combined chemotherapy and radiation therapy reported more symptoms with greater severity on the 25-item TRSC than those receiving either therapy alone ($F = 3.08$, $p < .05$) while patients on either treatment modality reported severe symptoms on the TRSC subscales of Eating, Oropharynx, Nausea, Fatigue, and Pain (Williams et al., 2010b). The study in Manila, Philippines, examined $N = 100$ patients undergoing combined radiation therapy and chemotherapy or chemotherapy alone for the following cancers: breast cancer, gynecologic cancers, lung cancer, colon/rectal cancer, and head and neck cancer

(Williams et al., 2010a). Again, patients on the combined radiation and chemotherapy reported greater symptoms with higher severity on the 25-item TRSC, while 30% of the sample overall reported the occurrence of at least 22 symptoms. Piamjariyakul et al (2010) used the TRSC to examine patient-reported symptoms in a sample of $N = 202$ patients in Thailand receiving chemotherapy and/or radiation therapy for gastrointestinal tract cancers, head and neck cancer, lung cancer, breast cancer, and gynecologic cancers. As in the other studies, results showed that patients receiving the combined radiation and chemotherapy reported more symptoms with greater severity ($F = 7.2$; $p < 0.01$) on the 25-item TRSC, with more severe symptoms reported in the Eating, Oropharynx, Nausea, and Fatigue subscales (Piamjariyakul et al., 2010). The TRSC was also reported to have good reliability and validity in each translated language. Originally developed in paper format, online versions have been used (Heinze et al., 2015) and currently the TRSC is being piloted in a variety of electronic health applications (Williams et al., 2015b). Additionally, the TRSC has been calibrated for a pediatric version, the Therapy-Related Symptom Checklist-Children (TRSC-C) (Williams et al., 2012; Williams et al., 2014).

Summary of Symptom Measurement Tools. There are several limitations of the measures discussed. The MSAS has been criticized for its length and its complicated rating method (Cleeland et al., 2000; Williams et al., 1997; 2000; 2001). The MDASI is shorter and easier to complete, but the limited number of symptoms may not adequately capture the range of symptoms experienced by the patient. The TRSC (a precursor of the OTTAT) is shorter than the MSAS, and includes spaces at the bottom of the checklist that allow patients to write in additional symptoms and rate their severity. None of the symptom measurement tools discussed have been used to examine patient-reported symptoms in the context of matched therapy.

Other Variables Influencing Effects While Receiving Treatments for Cancer

This section will discuss factors or variables that may influence symptom occurrence/severity while receiving treatment for cancer, as reported in the literature. These factors include age, cancer stage, cancer type, length of therapy, prior cancer therapies, and comorbidities.

Age. Age as a factor in the experience of symptoms among cancer patients has been shown in several studies (Cataldo et al., 2013; Kirkova, Rybicki, Walsh, & Aktas, 2012; Smith et al., 2013). In a secondary analysis of three separate studies regarding symptom assessment in oncology patients, older patients (≥ 60 years of age) reported significantly lower occurrence rates of symptoms, severity of symptoms, frequency, and distress of symptoms when compared to patients that were ≤ 60 years of age (Cataldo et al., 2013). Multiple symptoms were reported among adolescents and young adults through a population-based survey of patients aged 15 - 39 years of age (Smith et al., 2013). Eighty-five percent of respondents reported experiencing at least one symptom, and 51% reported experiencing three or more symptoms (Smith et al., 2013). Kirkova et al. (2012) also found age to be an important variable in assessing differences in symptom prevalence in patients with cancer while conducting a secondary analysis of a symptom database. The eight most frequent symptoms found among $N = 1000$ patients decreased in prevalence with older age (Kirkova et al., 2012)

Stage of disease. Stage of disease has been shown to influence the symptom experience. Patients with advanced cancer have been found to experience multiple symptoms (Chen & Lin, 2007; Fan, Filipczack, & Chow, 2007; Walsh, Donnelly, & Rybicki, 2000), which can be attributed to the combined effects of the disease and the treatment of the disease. Interestingly, an analysis by Valeberg and Grov (2013) revealed that symptom burden was basically equal when comparing cancer patients that were in the curative phase versus palliative phase. The

authors concluded that this could be related to the acute symptoms experienced by the patients in the curative phase group, who were undergoing chemotherapy (Valeberg & Grov, 2013). Additionally, the number of patients within the curative phase was relatively small (n = 32) and may indicate an inadequately powered study. Other studies have associated a higher symptom burden in advanced stages of cancer (Kirkova et al., 2011; Walsh, et al., 2000). Patients with advanced disease have higher disease related symptoms and have received multiple treatment modalities for their cancer thereby leading to increased side effects and symptoms.

Cancer types. Traditionally different cancer types have received different cancer therapy regimens yet the symptoms experienced among patients overlap. The NCI Symptom Management and Health-Related Quality of Life Steering Committee previously mentioned identified additional ovarian cancer specific symptoms: abdominal pain, bloating, cramping, fear of recurrence, indigestion, sexual dysfunction, vomiting, weight gain, and weight loss. The NCI recommends adding the 12 core symptoms previously discussed, and eight additional symptoms in ovarian cancer as patient reported outcomes in cancer clinical trials, which will allow for the consistent assessment of common and relevant symptoms and comparisons across trials (Donavan et al., 2014). The TRSC addresses a majority of these symptoms, and patients can add additional symptoms in with the space provided at the bottom.

Length of therapy. Intuitively, length of therapy, or how long an individual has been receiving cancer therapy, will influence symptom occurrence and severity. Spichiger et al. (2011) evaluated symptom prevalence of patients undergoing chemotherapy at three time points - prior to the initiation of chemotherapy, one week prior to the third cycle of chemotherapy and one week prior to the fourth cycle of chemotherapy. The second and third time points translate to approximately eight to 11 weeks, and 11 to 15 weeks post initiation of chemotherapy, respectively. Results from the study showed a significant increase in symptoms over time. This

has been corroborated in other observational studies (Servaes, Verhagen, & Bleijenberg, 2002; Williams et al., 1997). Also, patients with metastatic or advanced stages of disease require chronic treatment of their cancer, which in conjunction with the disease can lead to accumulated symptoms. However, other studies have found an improvement in certain symptoms over time (Visser, Smets, Sprangers, & de Haes, 2000) although this may be attributed to the symptom-management interventions performed (Dujit, Faber, Oldenburg, va Beurden, & Aaronson, 2011; Given et al., 2002; Williams et al., 2013; Williams et al., 2011).

Prior lines of cancer therapy. Prior lines of therapy likely influence symptom prevalence due to the accumulated therapy-related toxicities, and may also indicate advanced disease. Lewis et al. (2015) for example found that neuropathy, a common therapy-related symptom, was significantly higher among patients ($N = 3106$) that had received prior chemotherapy for a variety of cancers. Boland et al. (2013) examined symptom prevalence in a small sample ($N = 32$) of patients with multiple myeloma who had received a median of three prior lines of chemotherapy. The patients were found to have a high symptom burden, which impacted physical functioning and HRQOL (Boland et al., 2013). Evaluating data from clinical trials that involve first line versus multiple lines of prior therapy can reveal differences in symptom occurrence and severity (Kaufman, 2015; Palmieri, 2015) although this can be somewhat deceiving given that many inclusion criteria for clinical trials requires that symptoms/toxicities are ≤ grade 1 or grade 2.

Comorbidities. Comorbidities may influence therapy-related symptom occurrence. Researchers showed that a higher number of comorbidities equated to more severe grades of graft versus host disease after patients ($N = 2985$) underwent hematopoietic cell transplantation (Sorror et al., 2014). Specific to breast and gynecologic malignancies, Hamaker et al. (2014) found that in a sample of breast cancer patients 65 years of age and older, ($N = 73$) higher

numbers of comorbidities were significantly associated with grade 3 or 4 chemotherapy related toxicities including fatigue, mouth sores, and skin conditions. An increased number of comorbidities was also a significant predictor of dose reductions of curative chemotherapy (due to toxicities) in a sample ($N = 3707$) of early stage breast cancer patients (Shayne, Crawford, Dale, Culakova, & Lyman, 2006). Number of comorbidities was also significantly associated with greater symptom distress scores in a sample of cancer patients ($N = 326$) including gynecologic cancer diagnoses (Van Cleave, Egleston, Ercolano, & McCorkle, 2013).

Health-Related Quality of Life (HRQOL)

In general, cancer patients experience decreased HRQOL, either due to the disease itself or due to the treatment modalities they endure (Yarbroff et al., 2007). Clinical experience and numerous studies have confirmed the association between symptoms and HRQOL. An increase in symptoms generally decreases HRQOL (Ferreira et al., 2008; Garrison, Overcash, & McMillan, 2011; Hyland & Sodergren, 1996; Janz et al., 2007; Miaskowski et al., 2006; Montazeri, 2008; Sloan, Cella, & Hays, 2005). For instance, Montazeri (2008) conducted an extensive literature review that included 27 studies linking the impact of common symptoms of breast cancer patients such as fatigue, pain, and insomnia on quality of life. The studies indicated that increased symptoms lowered patient's QOL, particularly the symptom of fatigue (Montazeri, 2008). Garrison et al. (2011) performed a secondary analysis to examine predictors of QOL in a sample of $N = 533$ adult patients with cancer receiving hospice care. Findings showed that symptom occurrence, symptom severity, and functional status accounted for 46% of the variance in QOL (Garrison et al., 2011).

Many studies examining HRQOL concurrently measure symptoms given the overlapping nature of these two concepts. For instance, Huang et al. (2013) also evaluated QOL along with symptoms. Physical and mental QOL component scores were assessed using the 36-Item Short

Form Survey (SF-36). While the physical component scores were significantly worse during therapy in all groups (chemotherapy alone, chemotherapy plus trastuzumab, and trastuzumab alone) compared to baseline, the mental component scores were significantly higher during the trastuzumab alone phase versus the chemotherapy alone phase (Huang et al., 2013). Patients with higher symptom severity had worse physical and mental component scores regardless of the phase (Huang et al., 2013).

Williams et al. (2013) assessed whether the use of the TRSC with oncology outpatients receiving chemotherapy and/or radiation therapy increased the number of symptoms documented and managed and whether this improved patients' HRQOL. Fifty-five oncology outpatients receiving either or both treatment modality received standard of care (group 1 [G1]). At the same clinic, another cohort of 58 patients (group 2[G2]) received standard of care in addition to self-reporting symptoms on the TRSC prior to their clinical consultation. This was a sequential cohort trial. Repeated measures (2-11 visits) were obtained of the number of patient symptoms documented (medical records G1 and TRSC G2), HRQOL scores, and Karnofsky scores, for a total of 696 observations (328 G1 and 368 G2). Results showed that a greater number of symptoms were identified and managed in G2 compared to the standard of care group (6.14 symptoms vs. 2.84, $P < .0001$), and in G2, the number of symptoms declined by approximately 1.5 every 100 days post-baseline more than in the standard of care cohort (Williams et al., 2013).

Janz et al. (2007) reported that sociodemographic, prior health status, clinical, and diagnosis factors accounted for 9% - 27% of the variance of QOL outcomes in breast cancer patients ($N = 1372$) that had completed surgery, chemotherapy, and/or radiation. When symptoms related to the treatment of their cancer were added to the model, the percent of variance explained rose to 18% - 60%. Ferreira et al. (2008) assessed HRQOL in 115 outpatients with cancer who were not receiving any type of treatment for their cancer. Through cluster

analysis, the researchers found that patients with multiple and severe symptoms were four times as likely as those with lower symptoms/severity to have poor HRQOL (Ferreira et al., 2008). Smith et al. (2013) reported significantly worse HRQOL scores in young adults undergoing treatment of their cancer when they were experiencing ongoing symptoms. Williams et al. (2011) conducted a Stetler model evidenced-based study to explore the effects of a nursing intervention on symptom management in 20 cancer patients that included 10 in the intervention group and 10 in the control group. A two group repeated measures design was used. In the intervention group, patient-reported symptoms on the TRSC were assessed and used as basis for education and counseling. Outcomes were measured by the HRQOL-LASA scale and the Karnofsky performance/functional status scale and health form. In the intervention group, patient education and counseling based on the TRSC, and nurse follow-up over time, were associated with a decrease in patient self- reported symptom occurrence and severity, and a trend that reflected improvement in HRQOL (Williams et al., 2011).

Including patient reported outcomes such as HRQOL is fundamental to understanding the patient's experience in receiving treatment for their cancer, and over the past 20 years assessments of HRQOL have been increasingly included in cancer clinical trials. While survival endpoints in cancer therapy clinical trials are predominant, HRQOL has been added to aid in the understanding of new therapies such as what additional survival means to patients (Bottomley et al., 2005). This information may be useful to clinicians and patients when making therapy decisions. For example, a phase III trial comparing different regimens of paclitaxel and carboplatin (both chemotherapies) for ovarian cancer found no statistically significant differences in terms of outcomes (Pignata et al., 2014), yet significant differences were found in terms of HRQOL between women who received weekly chemotherapy versus every three weeks. Unique to this trial, the researchers included QOL as a co-primary endpoint along with PFS. In a

phase II trial that evaluated two different doses of interferon for the treatment of metastatic renal cell carcinoma, Tannir et al. (2006) found no significant differences in PFS and overall survival (OS) between the two treatment arms. However, QOL was significantly better in the patients receiving the lower dose of interferon.

Perhaps one of the most innovative trials to date is the PISCES study, which used patient reported outcomes to help inform the choice of therapy in advanced metastatic renal cell carcinoma (RCC) (Escudier et al., 2014). During this trial, 114 patients were randomly and blindly assigned to one of two approved targeted therapies for RCC - sunitinib and pazopanib. It should be noted that these drugs are approved for RCC regardless of any genomic profiling results. Therapy was switched after 10 weeks so that all patients were exposed to both drugs, and subsequently patients' preferences and HRQOL were measured. Findings showed that the patients preferred the pazopanib to sunitinib, reporting higher HRQOL scores (Escudier et al., 2014). Limitations included the attrition rate (33%) although this is not unexpected in a population with such advanced disease. Also, patients' preference and HRQOL were only assessed once during the trial and may not have captured the variations in the patients' experience.

Studies specifically examining potential differences in HRQOL between patients who are receiving matched therapy and those who are not are lacking. To date, there has been no study found in the literature specifically examining HRQOL in patients receiving therapy that has been selected based on genomic profiling results. Given the changing paradigm of how cancer is being treated, this is an essential concept study in order to better understand how patients may be affected by novel regimens.

HRQOL Measures

Health-related quality of life is a measure of an individual's perception of health-related well-being based on principle health components (Ferrans, Zerwic, Wilbur, & Larson, 2005) that typically include physical, emotional, mental, social and/or functional, and spiritual domains. Many tools are available to measure QOL and HRQOL. In cancer clinical research trials, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy-General (FACT-G) are often used. Both questionnaires are self-reported measures and were specifically developed to assess the quality of life of cancer patients (EORTC Quality of Life, n.d.; FACIT.org, 2010). The EORTC QLQ-C30 contains 30 items that address the physical, functional, social domains as well as specific questions regarding symptoms (EORTC Quality of Life, n.d.). The FACT-G contains 27 items, which address the physical, social, emotional, and functional well-being domains (FACIT.org, 2010).

The EORTC QLQ-C30 and the FACT-G are lengthy and both have been criticized for the potential burden on patients, which may result in poor completion rates (Locke et al., 2007). In a busy clinic setting, questionnaires that are short yet comprehensive, and easy to complete are desired elements. The HRQOL-LASA was created and validated by Bretscher et al. (1999) for that purpose – to measure HRQOL with brief, multiple-item scales (Locke et al., 2007). The HRQOL-LASA contains six items that cover the mental, social, spiritual, emotional, physical, and overall QOL domains. Previous studies found a strong, inverse correlations between total HRQOL-LASA scores and total TRSC scores (Gonzalez et al., 2011; Heinze, 2012; Williams et al., 2013; Williams et al., 2011). Studies conducted by Williams et al. (2011, 2012) showed that by using the TRSC, more symptoms were documented and thus managed, thereby increasing HRQOL as evidenced by higher HRQOL-LASA scores.

Summary

The symptom experience of patients undergoing treatment for their cancer and corresponding impact on HRQOL has been reviewed. Discussion included how cancer treatment is increasingly being personalized using genomic profililng. This study will fill a gap in knowledge regarding the symptom experience and potential impact on HRQOL for patients undergoing matched therapy not previously explored. Knowledge gained will not only inform nurses and other clinicians of possible sequelae of matched therapy but will also serve as a first step in improving symptom management and HRQOL.

Chapter Three

Methodology

The purpose of this study was to describe the characteristics of patients with breast or gynecologic cancer undergoing matched therapy or not matched therapy, as well as to describe cancer therapy-related symptom occurrence and severity, and overall HRQOL for patients undergoing matched therapy and not matched therapy. Associations between type of therapy (matched or not matched) and cancer therapy-related symptom occurrence and severity as well as HRQOL were examined after controlling for person and health/illness factors. In this chapter, the design, study setting and sample are described and also the methodology that was used to collect and analyze the data.

Research Design

This study used a descriptive correlational research design to examine existing data on patients with either breast cancer or gynecologic cancer who are receiving care at a cancer center located in the upper Midwest. A descriptive design was appropriate for this study because no studies have been found regarding symptom occurrence and severity and HRQOL for patients undergoing matched therapy. This study examined the relationships among selected study variables, conceptually identified in the SMT. Strengths of the descriptive correlational design included using existing data, which presents an inexpensive and cost-efficient opportunity to expand research opportunities that answer important research questions (Bullock, 2007; Vance, 2012). Using existing data are particularly useful for studying situations or events in real-life settings, and can provide groundwork for further studies (Castle, 2003).

Study Setting and Sample

The study setting was a single-site, community, outpatient cancer center located in the upper Midwest. This cancer center has the greatest volume of new breast and gynecologic cancer patients within a 200-mile radius. Approximately 300 new breast cancer patients are seen each year, and roughly one-half of these patients require treatment with chemotherapy due to advanced or high-grade disease. There are around 150 new gynecologic cancer patients seen each year. Of these, about 70 will require therapy. The cancer center routinely performs genomic profiling and uses these results to help match therapy decisions in appropriate cases as determined by the primary oncologists. Approximately 450 patients with breast or gynecologic cancer received matched therapy from March 2014 to September 2016.

The sample for this study was derived from breast cancer patients who are enrolled in the ongoing research trial *Using Metformin to Reduce Cardiac Toxicity in Breast Cancer Patients,* and patients who are enrolled in the ongoing research trial *Identifying Molecular Drivers of Cancer.* The purpose of the *Using Metformin to Reduce Cardiac Toxicity in Breast Cancer Patients* research trial is to determine if co-administration of metformin and doxorubicin (chemotherapy) in breast cancer patients who are receiving neoadjuvant or adjuvant therapy will reduce the number of patients who develop a significant change in left ventricle ejection fraction. This study began enrolling patients in August 2014. The purpose of the *Identifying Molecular Drivers of Cancer* research trial is to identify mutational drivers of cancer by performing multiple molecular tests on the patient's cancer tissue. This study began enrolling patients in July 2015. Enrollment and study procedures for both of these studies will continue until target enrollments are achieved (44 patients for *Using Metformin to Reduce Cardiac Toxicity in Breast Cancer Patients;* 1000 patients for *Identifying Molecular Drivers of Cancer*).

Criteria for inclusion in the current study were female patients that: (a) were enrolled in at least one of the parent studies, (b) have documented breast or gynecologic cancer, (c) were receiving cancer therapy that was either matched or not matched, and (d) who completed the TRSC and HRQOL-LASA questionnaire at least four weeks post initiation of the cancer therapy but no longer than 12 weeks after therapy began. This time frame was chosen since cancer therapy-related symptoms and any potential impact on HRQOL may not be evident before four weeks. Between four to 12 weeks, therapy-related symptoms and impact on HRQOL would be most evident. After 12 weeks, symptoms typically stabilize and/or interventions have occurred that ameliorate symptoms and subsequent effects on HRQOL. Additionally, staying within a range of four to 12 weeks was meant to minimize the variability and potential for significant differences between the groups that could be due to length of time on therapy. Exclusion criteria included those patients: (a) not enrolled in either parent study, (b) for whom TRSC and HRQOL-LASA were not gathered during the four to 12-week period post initiation of the matched or not matched therapy, or (c) missing TRSC and/or HRQOL-LASA data, or (d) for whom TRSC and HRQOL-LASA data were not gathered at the same time (e.g. TRSC gathered at four weeks post initiation of therapy and HRQOL-LASA gathered at five weeks post initiation of therapy).

A priori Power Analysis for Sampling

An appropriately powered study is essential for valid results. A statistical power analysis involves the relationships among sample size, significance criterion (α), statistical power, and population effect size (Cohen, 1992). An unadjusted comparison of groups based on a student's *t* test at the 0.05 level of significance would require approximately 128 subjects to detect a medium effect ($d = 0.5$). This study adjusted for several covariates (e.g., therapy type, age, length of therapy, prior lines of therapy, type and stage of disease, and comorbidities).

Considering all research questions, equations based on Cohen's (as cited in Green, 1991) power analytic approach ($N \geq L/f^2$ where $f^2=R^2/(1-R^2)$ were used to estimate an adequate sample size.

$$L = 6.4 + 1.65(\text{m}) - 0.05(\text{m}^2)$$

$$f^2=R^2/(1-R^2) = .13/1-.13 = .15$$

$$N \geq 19/.15 = 127 \text{ subjects}$$

Assuming a medium effect size of $R^2 = 0.13$, $\alpha = .05$, m (independent variables) = 12, and desired power of 0.80 a total of 127 participants were estimated as sufficient. Additionally, it was important to achieve relatively equal numbers of patients receiving matched therapy and patients receiving not matched therapy.

Study Measures and Procedures

Study data included patient-reported information on cancer therapy-related symptoms occurrence and severity according to the TRSC, health-related quality of life according to the HRQOL-LASA, age and ethnicity (demographic data), and other measures including therapy type, concurrent therapy, length of therapy, prior lines of therapy, cancer type, cancer stage, and comorbidities.

Therapy-Related Symptoms Checklist (TRSC) and Health-Related Quality of Life-Linear Analogue Self Assessment (HRQOL-LASA) Measures

Therapy-Related Symptoms Checklist (TRSC). Symptoms within the checklist are conceptually defined as "a subjective experience in the biopsychosocial functioning, sensations, or cognition of an individual" (Dodd et al., 2001, p. 669). Measurement of symptom occurrence and severity were collected in the parent study *Identifying Molecular Drivers of Cancer* using the Therapy-Related Symptoms Checklist (TRSC). Patients were asked to complete the TRSC each time they meet with the provider, which may vary based on the provider's preference and on the patient's regimen. For example, the therapy may be administered every three or four weeks and

the provider meets with the patient prior to each administration. Some oral chemotherapies or targeted agents were consumed daily. Therefore, patients may be assessed every two to four weeks, depending on how often the provider deems necessary.

Measurement of symptom occurrence and severity in the parent study*, Using Metformin to Reduce Cardiac Toxicity in Breast Cancer Patients,* were also collected using the TRSC. Patients were asked to complete the TRSC each time they meet with their provider, which is approximately every two to three weeks. In both studies, trained research personnel give the paper form TRSC to the patients after they checked in to the clinic and while they are waiting to be seen by the provider. Patients were instructed by the research personnel to check the symptoms they have experienced/are experiencing, and then circle the severity of the symptoms according to the scale provided. The research personnel were available during the interval to answer questions. Once completed, participants return the paper form to the research coordinator, which was then placed in a binder with other study-related documents.

The TRSC is a patient self-report instrument that subjectively measures cancer therapy-related symptom severity (Williams et al., 1997; 2001). Twenty-five physical and psychological symptoms commonly experienced during cancer therapy are included on the TRSC. The severity of each symptom is rated by the patient using a 5-point scale ranging from 0 (not present) to 4 (severe) and scores are summated to reflect the total TRSC score. A higher total score indicates higher symptom occurrence and severity as perceived by the patient (Williams et al., 1997; Williams et al, 2001). Space exists at the bottom of the measure so that symptoms can be added if necessary, however, past studies have shown that fewer than 2% of patients have added symptoms (Piamjariyakul et al., 2010; Williams et al., 2001; Williams et al., 2006a; Williams et al., 2010a; 2010b; 2011; 2013; 2015). The range of total scores is from 0-125 unless symptoms are added, in which case scores could theoretically exceed 125 (Appendix C).

Good psychometric properties have been reported for the TRSC in previous studies across a variety of settings (Gonzalez, Williams, Tirado, & Williams, 2011; Heinze, 2012; Piamjariyakul et al., 2010; Williams et al., 2001; Williams et al., 2006a; Williams, Williams, & Doolittle, 2006b; Williams et al., 2010a; 2010b). Cronbach's alpha, which measures internal consistency, has been reported as ranging from 0.70 to 0.83 or higher in prior studies using the paper format (Gonzalez et al., 2011; Piamjariyakul et al., 2010; Williams et al., 2001; Williams et al., 2006a; 2006b; Williams et al., 2010a; 2010b; Williams et al., 2011; Williams et al., 2013; Williams et al., 2015a). Construct validity and discriminant validity (up to 80% correctly classified) have been shown in adult patients receiving chemotherapy versus radiation therapy (Williams et al., 2001) and various populations within and outside the USA (Gonzalez et al., 2011; Heinze, 2012; 2014; Piamjariyakul et al., 2010; Mische-Lawson et al., 2012; Williams et al., 2010a; 2010b; 2014). Its use also has been tested in a cancer center health care delivery system and shown to impact HRQOL, number of symptoms identified and managed, and functional status (Williams et al., 2011; 2013).

In the current study, data on each TRSC response item and extra responses were extracted from the paper form completed by each patient. Some patients in the parent study completed the TRSC more than once during their course of cancer therapy. To minimize variation, TRSCs completed within a four to 12-week timeframe from the start of the current therapy were used. Meaning, for matched therapy, the first TRSC completed during the four to 12-week time period after beginning matched therapy was extracted and used in the analysis. For not matched therapy, the first TRSC completed during the four to 12-week time period after beginning not matched therapy was extracted and used in the analysis. The time of TRSC completion since the initiation of the cancer therapy was recorded in weeks.

Health-Related Quality of Life-Linear Analogue Self Assessment (HRQOL-LASA). Health-related quality of life is a measure of an individual's perception of health-related well-being based on principle health components (Ferrans, Zerwic, Wilbur, & Larson, 2005) including the physical, emotional, mental, social, spiritual, and overall QOL (Bretscher et al., 1999). Measurement of HRQOL is collected in both parent studies using the Health-Related Quality of Life-Linear Analogue Self-Assessment (HRQOL-LASA) tool. For the parent studies, the HRQOL-LASAs were collected at the same time points as the TRSCs. While patients waited to see their provider, trained research personnel provided the paper form HRQOL-LASA with instructions for completion. Once the patients completed the form, they returned it to the research personnel, which was then placed in the patient's research binder.

The HRQOL-LASA is a six-item questionnaire that represents overall QOL and overall physical, emotional, mental, social, and spiritual wellbeing (one item for each component). Each item is self-rated on a 10-point scale from 0 (as bad as it can be) to 10 (as good as it can be). When item scores are summated, total scores can range from 0-60 (Appendix D). A high score on the HRQOL-LASA indicates a high quality of life.

The HRQOL-LASA was initially validated in patients with cancer receiving hospice care (Bretscher 1999). Also, items within the questionnaire have been validated as general measures of global QOL dimensional constructs in multiple settings (Grunberg, Groshe, Steingass, Zaretsky, & Meyerowicz, 1996; Gudex, Dolan, Kind, & Williams, 1996; Hyland & Sodergren, 1996). Cronbach's alpha, a measure of the scale's internal consistency, has recently been reported as 0.83 in a study of patients with brain cancer (Locke et al., 2007), and 0.93 in a study of breast cancer patients who had completed primary treatment with surgery, radiation therapy, and/or chemotherapy (Heinze, 2012). The HRQOL-LASA has been used in numerous studies that also use the TRSC. Strong, inverse correlations (r = -0.29 to -0.47) between scores on the

HRQOL-LASA and total TRSC scores have been reported showing construct and discriminant validity (Gonzalez et al., 2011; Heinze, 2012; Williams et al., 2013; Williams et al., 2011).

For the current study, HRQOL-LASA item scores as well as the total score were extracted from the patient paper forms and entered into the dataset. Some patients in the study completed the HRQOL-LASA more than once during their course of cancer therapy. To minimize variation, data from the first HRQOL-LASA completed during the four to 12-week time period from the start of the current therapy (matched or not matched) were extracted and used in the analysis. The time of HRQOL-LASA completion since the initiation of the cancer therapy was recorded in weeks.

Other Measures for the Proposed Study

Demographic data. Demographic data on patient age and ethnicity were obtained to appropriately describe the sample characteristics in the research report. Typically, demographic data including patient birthdate, age, and ethnicity, are recorded in the patient's electronic health record (EHR) when the patient is admitted to the service. Age was defined as age in years when the patients completed the TRSC and HRQOL-LASA; the date the TRSC and HRQOL-LASA were completed is recorded on each form. For this study, data on age and ethnicity were extracted from the EHR and/or the patient's study binder (from either parent study) and entered into the dataset by the investigator. Data on ethnicity was used to describe the sample.

Socioeconomic data. Socioeconomic data on patient health insurance type and drug coverage were obtained to describe the sample characteristics. Health insurance type conceptually referred to third party coverage for the individual's health/illness related expenses. Operationally health insurance type was defined as no insurance/self-pay, Medicare, Medicaid, or commercial insurance. Commercial insurance was any private insurance that the patient paid for, or shared in the cost of with their employer. Drug coverage was conceptually defined as

how the costs of a patient's cancer drugs (therapies) were covered. Operationally, drug coverage was defined as health insurance, samples, patient assistance programs, self-pay, or a combination of these possibilities. For this study, data on health insurance type and drug coverage were extracted from the EHR and/or the patient's study binder (from either parent study) and entered into the dataset by the investigator.

Family cancer history. Family cancer history referred to whether or not the patient had relatives that had been diagnosed with cancer. Operationally this variable was categorized as family history of breast cancer, gynecological cancer, any cancer, or none. Data on family cancer history were extracted from the EHR and entered into the dataset by the investigator during this study. These data were used to describe the sample.

Therapy type. Therapy type referred to matched therapy or not matched therapy. Conceptually, matched therapy was defined as matching a specific cancer therapy or therapies that is/are known to target a genomic alteration(s) to the patient's genomic alteration(s), which is/are found on genomic profiling. For this study, matched therapy was operationally defined as the use of at least one drug that is known to target the genomic alteration of at least one of the patient's genomic alterations found on genomic profile testing.

Conceptually not matched therapy referred to therapy or therapies used to treat cancer that is/are not matched to specific genomic alteration(s). For this study, not matched therapy was operationally defined as the use of drugs that were not specifically matched to the patient's genomic alterations. Patients receiving not matched therapy may or may not have had genomic profile testing. If a patient had undergone genomic profile testing, several factors may have influenced whether or not they received matched therapy. One factor is that 10% to 15% of the time, a genomic alteration is found on testing that does not have a drug that will target it. If this occurred, patients would receive not matched therapy only. Another factor influencing type of

therapy is insurance coverage. Many cancer therapies are very expensive and may not be approved for the type of cancer it is being requested. For example, an ovarian tumor may exhibit an alteration that is commonly seen in breast cancer. Even if a therapy specifically targeting that alteration is FDA approved for breast cancer, many insurances will not allow a patient with ovarian cancer to obtain this drug. If the drug(s) was/were not obtained through insurance or other means (i.e. patient assistance programs, self-pay), then patients would receive not matched therapy. Patients receiving not matched therapy who did not undergo genomic profile testing, may or may not have received other testing on their cancer, and may have received or be receiving a drug that targets a pathway in tumor growth (e.g. testing for hormone status [ER/PR] in breast cancer).

The investigator searched the patient record to extract information on therapy type, which was readily available since information regarding therapy type is not blinded in the parent study. Therapy type was operationally defined as the type of therapy being received at the time the first TRSC and HRQOL-LASA were completed during the four to 12-week time period after the start of the current therapy. Documenting the therapy type patients received when completing the questionnaires was important since patients may change regimens upon progression of disease, or if they are unable to tolerate the therapies (e.g. allergic to therapy, intolerable side effects). For verification purposes, a random reassessment of 20% of patients was performed.

At the outpatient cancer center, genomic profiling is performed with the FoundationOne assay which uses the Illumina HiSeq 2000 platform for next generation sequencing. The FoundationOne assay indicates a patient's particular cancer genomic profile, and from these findings, recommendations can be made based on therapies available to match the specific alterations found. Briefly, DNA is first extracted from cancer tissue that is taken from routine biopsy or surgical specimens. Then, the extracted DNA's entire coding sequence of over 4,500

exons of 315 cancer-related genes is interrogated, in addition to approximately 50 introns (segments of a DNA or RNA molecule that does not code for proteins but interrupts the sequence of genes [Intron, n.d.]) from 28 genes that are often altered in cancer. Results of the FoundtionOne assay are available in 14-21 days (FoundationOne, 2014; Framptom et al., 2013). Most types of genomic alterations are detected with the FoundationOne assay, which include: a) Base substitutions, where one base is exchanged for another (i.e. an A switching to a G); b) Indels, which refers to insertions – when extra base pairs are inserted into a new place in the DNA, or deletions – when a section of DNA is lost; c) Copy number alterations, which refers to an abnormal variation in the number of copies in one or more sections of the DNA; and d) Rearrangements, which refers to a change in the structure of the native gene and includes selected gene fusions. Validation of the assay was completed in several ways, which was necessary given the different alteration types being detected. Validation of the assay included creating pools of normal cell lines as well as tumor cell lines to model key determinants of accuracy including allele frequency, indel length, and amplitude of copy change. Concordance between the FoundationOne assay and a variety of current clinical technologies was examined, such as HER2 FISH testing, (Frampton et al., 2013). Reproducibility was validated by examining specimens independently. Results showed that this assay reports high sensitivity (≥ 90%) and specificity (≥ 99%) (FoundationOne, 2014; Frampton et al., 2013). Table 3 provides information regarding the validity of the FoundationOne assay.

Table 3

Sensitivity, Specificity, and Positive Predictive Value (PPV) of the FoundationOne Assay

	Base Substitutions	**Indels**	**Copy Number Alterations**	**Rearrangements**
Sensitivity	> 99%	> 97%	> 95%	≥ 90%
Specificity	> 99%	> 99%	> 99%	> 99%
PPV	> 99%	> 99%	> 99%	> 99%

Concurrent therapy. Concurrent therapy referred to the specific information regarding all types of therapy the patient was receiving at the time the TRSC and HRQOL-LASA questionnaires were completed (surgery, chemotherapy, radiation therapy, and targeted therapy). Patients with metastatic cancer may have been receiving matched therapy based on their genomic alterations, but may have also received chemotherapy depending on the context. For instance, many agents targeting genomic alterations are cytostatic, therefore, in the case of an aggressive tumor, it may be best to add chemotherapy (which is cytotoxic). The patient's overall clinical situation is also incorporated into the decision of recommended therapy. If patients do not have metastatic disease, they will receive chemotherapy according to established guidelines plus or minus matched therapy based on their genomic alterations. For example, a breast cancer patient receiving neoadjuvant therapy may receive chemotherapy plus a matched therapy for 12 weeks prior to receiving surgery. A patient with gynecologic cancer (non-metastatic) may have surgery first, followed by chemotherapy plus a matched therapy based on the genomic alterations. The type of therapy (surgery, chemotherapy, radiation therapy, and targeted therapy) was extracted from the EHR to the study dataset by the investigator.

Length of therapy. Length of therapy conceptually referred to the amount of time in weeks a patient had been on the current therapy (matched or not matched) when the TRSC and HRQOL-LASA were completed (see earlier discussion of TRSC and HRQOL-LASA completion time points). Length of therapy was operationally defined as the number of weeks that patients were receiving the designated therapy at the time the TRSC and HRQOL-LASA were administered. The research investigator calculated this based on the number of days from the start of therapy date as recorded in the EHR, and the date on which the TRSC and HRQOL-LASA were administered.

Prior lines of therapy. Conceptually, prior lines of therapy referred to the number of regimens a patient received to treat their cancer prior to the therapy upon which therapy type was determined (matched or not matched). Regimens for different treatment modalities, specifically chemotherapy, are generally changed in response to disease progression or due to lack of tolerability. Prior lines of therapy were operationally defined as the number of regimens the patient received prior to the therapy received during the administration of the TRSC and HRQOL-LASA. Data on prior lines of therapy were retrieved from the patient's record by the research investigator. Additionally, the type of therapy received in prior lines (i.e. surgery – type of procedure; radiation - anatomical location, chemotherapy and/or targeted therapy – specific drug) was extracted from the EHR to the dataset.

Cancer type and stage. Cancer type is defined by the tissue or organ where the cancer originated from (NCI, 2015b) and in this study was categorized as breast cancer or gynecologic cancer. Cancer type is entered in the EHR by the treating oncologist upon diagnosis. Cancer type was determined from the EHR for this study after verifying the diagnosis on pathology reports in the patients' EHR.

Cancer stage describes the severity of the cancer, which is based on the location, size, and extent of the primary cancer tumor (AJCC, 2015). The primary oncologist determines the cancer stage at diagnosis, which is entered into the patient's EHR. For the current study, the stage of the cancer (stage 1, 2, 3, or 4), was obtained from the EHR. Additionally, information regarding whether the disease was metastatic or not was obtained from the EHR and recorded in the study dataset. Metastatic disease was confirmed by pathology or radiological reports showing that the primary site of cancer (e.g. breast, gynecologic) had spread to other tissues or organs in the body (NCI, n.d.a).

Comorbidities. Comorbidities are the presence of one or more additional diseases occurring with the primary disease (cancer) (Comorbidity, 2009). Operationally, comorbidities were defined as patient diagnoses other than cancer as defined by the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) diagnosis code (ICD-10-CM Official Guidelines for Coding and Reporting, 2016). Existing data of study patient comorbidities including ICD-10 code and descriptor were extracted from the EHR and recorded for each patient in the study dataset. The number of categories per patient were used in the regression analyses.

Ethical Considerations

No study-related procedures occurred until the study was fully reviewed and approved by the Avera Oncology Institutional Review Board (IRB). Since the study was being conducted at Avera, the University of Kansas Medical Center's IRB reviewed and agreed to rely on Avera IRB approval of the study. A Memorandum of Understanding was signed between the two institutions, which established an agreement for the designation of IRB responsibilities. The study investigator had access to patient electronic health care records in the clinic. The study variables were recorded in an excel spreadsheet, which was contained on the password protected Q-drive at the cancer center. Participants were given a unique de-identifiable numeric code on the spreadsheet. Once all variables were recorded, patient identifying information including patient name was removed and the excel file was transferred to the study investigator's password-protected personal computer. The file linking patient name to the de-identifiable numeric code is maintained on the password protected Q-drive of the cancer center. Study-related paper forms for this study will be destroyed after the study has ended. The data file will be maintained in a secured file for a minimum of seven years, which is the requirement of KUMC's IRB. This is longer than what is required from Avera's Oncology IRB, whose policy

requires data to be maintained on site for three years, followed by three years off site (total of six years). Any publications from the study will not contain participant identifiers; results will be reported in aggregate. The study investigator has maintained Health Insurance Portability and Accountability Act (HIPAA) and human protection subjects training.

Data Analysis

Data Preparation and Management

The research investigator was responsible for extracting the necessary data for this study as well as maintaining the data in an excel spreadsheet. The research investigator maintained a log of any analytic decisions as well as a codebook, which contained demographic and other study variables with corresponding level of measurement. The codebook also included recoding decisions that occurred during the course of the study.

Data for the study were collected from May 2016 to September 2016. Intra-rater reliability of the extracted data was established by re-extracting data from a random 10% of the patients with the exception of the therapy type variable, on which a random reassessment of 20% of the patients was performed. The audit of therapy type revealed 100% agreement. Intra-rater reliability of the remaining variables was 85%. Most of the disagreement occurred in comorbidity and family cancer history data and was due to EHR anomalies. For instance, comorbidities were typically included in progress notes, but were frequently not recorded as comorbidities or other diagnoses per ICD-10 in the EHR. Additionally, comorbidities listed by the clinician in the progress notes varied based on the patient's changing condition (e.g. development of a GI ulcer). Furthermore, the outpatient cancer center site uses a different EHR than the hospital, which required looking for data in two different EHRs for accuracy. The decision was made to record family cancer history and comorbidities that were listed in at least one of the EHRs at the time closest to when the questionnaires were completed. After the first

audit, comorbidities and family cancer histories were reviewed and updated if necessary for each subject, referencing both EHRs. A random reassessment on comorbidities and family cancer history for 20% of the patients revealed 100% agreement. The data were reviewed for outliers and if any values appeared to be extreme, they were re-checked against the EHR, TRSC, and/or HRQOL-LASA. There were no missing data.

In order to prepare the data for analysis, categorical and ordinal data were recoded as appropriate. For example, data on ethnicity yielded an initial four categories. These data were recoded into three groups: Caucasian, Hispanic, and Asian/Native American. Insurance type was recoded as no insurance/self-pay, Medicare, Medicaid, or commercial. Drug coverage was recoded as health insurance, samples, patient assistance programs, or a combination of health insurance/samples, health insurance/patient assistance, samples/patient assistance, or insurance/samples/patient assistance. Data recorded for family history of cancer was coded as yes or no for breast cancer, gynecologic cancer, and other cancer. Concurrent therapy type was recoded as yes or no for chemotherapy, targeted therapy, or a combination of chemotherapy/targeted therapy. The type of prior therapy was also recoded as yes or no under the following treatment modality categories: Surgery, radiation, chemotherapy, or targeted therapy. The number of treatment modality categories was then summed for each patient. Data recorded for metastatic disease were recoded as yes or no. For each patient, the ICD-10 codes were grouped by ICM-10-CM category (ICD-10-CM Official Guidelines for Coding and Reporting, 2016). The comorbidities were recoded as yes or no for each corresponding ICD-10-CM code (ICD-10-CM Official Guidelines for Coding and Reporting, 2016). The number of categories were then counted to obtain the total number of comorbidities for the patient.

A number of decisions were made during the data preparation phase. For the variable "number of prior lines of therapy", each therapy and/or different treatment modality was counted

as a line. For example, the treatment plan for a patient with breast cancer receiving neoadjuvant therapy may include chemotherapy, surgery, radiation therapy and targeted therapy. For this study, each of these modalities was counted as a line of therapy due to the nature of therapy-related symptoms compounding each other. Also, the investigator discovered that several patients, who were being treated for gynecologic cancer, had previously been treated for breast cancer. In these instances, therapies received for their breast cancer were counted as a prior line of therapy.

A potentially important variable, previously not recognized, emerged during the data preparation and analysis phase. It was noted that the timing of the most recent prior line of therapy was not being accounted for, but that this conceptually could influence patient symptom occurrence and severity and/or HRQOL. For example, a prior line of therapy for one patient may have been months or even years ago, while a prior line of therapy for another patient may have been weeks ago. Since a large portion of the symptoms on the TRSC are a result of acute sequelae from therapy, patients whose prior therapy occurred shortly before their current therapy (e.g. within three months) may not have had complete resolution of these acute symptoms. Therefore, the decision was made to include the timing of the prior line of therapy as a variable for description in research question #1, and a control variable in the regression model for research questions #3 and #4. For those patients that had undergone prior therapy for their cancer, this variable was conceptually defined as the timing of the most immediate prior therapy. Operationally the timing of the prior line of therapy was extracted from the EHR and categorized in the dataset as immediate (zero to less than three months), three months (three months to less than one year), and one year or greater. These categories were chosen based on the anticipated differences in symptom occurrence and severity at the different time points. For instance, acute symptoms from therapy such as nausea and vomiting would be expected to resolve shortly

(within weeks) after therapy completion, while certain symptoms such as fatigue may persist six months or more past therapy completion. Study power was recalculated (equations based on Cohen's as cited in Green, 1991) to confirm adequate sample size with the additional variable.

$$L = 6.4 + 1.65(\text{m}) - 0.05(\text{m}^2)$$

$$f^2 = R^2/(1\text{-}R^2) = .13/1\text{-}.13 = .15$$

$$N \geq 19.4/.15 = 129 \text{ subjects}$$

Assuming a medium effect size of $R^2 = 0.13$, $\alpha = .05$, m (independent variables) = 13, and desired power of 0.80 a total of 129 participants were estimated as sufficient. Other decisions made during the data preparation phase included noting that some patients in the sample were diagnosed with bilateral, simultaneous breast cancers that were different stages. For this study, the breast cancer with the highest stage was recorded in the dataset, since the therapy plan would be based on the higher stage. Finally, the number of days for the length of current therapy variable, as calculated from the start of therapy date recorded in the EHR, and the date on which the TRSC and HRQOL-LASA were administered, was rounded up or down to weeks. For example, if the patient had been on therapy for six weeks and five days, then the number of weeks recorded in the dataset was seven weeks. Once the dataset was recoded, reviewed, and complete, it was uploaded to SPSS version 22 (IBM Corp. SPSS, Armonk, NY, USA). All analyses were performed in SPSS.

Data analysis for research question #1. The first research question for the study was: *What are the characteristics (demographic data, socioeconomic data, length of therapy, concurrent therapy, prior lines of therapy [number, type, and timing], cancer type and stage, and number of comorbidities) of patients by type of therapy (matched therapy, not matched therapy)?* Descriptive statistics were used to summarize the characteristics of the patients by the type of therapy. Categorical and ordinal data (ethnicity, insurance type, drug coverage, family

cancer history, concurrent therapy, prior treatment modalities, cancer type, cancer stage, and timing of prior line of therapy) were reported as frequencies and distributions. Results for continuous variables (age, length of therapy, prior lines of therapy, comorbidities) were reported as a mean and standard deviation.

Data analysis for research question #2. The second research question was as follows: *What is the occurrence and severity of cancer therapy-related symptoms as reported on the Therapy-Related Symptom Checklist (TRSC) and overall HRQOL as reported on the Health-Related Quality of Life – Linear Analogue Self Assessment (HRQOL-LASA) for patients receiving matched therapy and those receiving not matched therapy?* Descriptive statistics were used to report the TRSC and HRQOL-LASA individual item scores and total scores for patients receiving matched and not matched therapy. The TRSC total score was obtained by summating the 25 symptom severity scores, and the HRQOL-LASA total score was obtained by summating the score of the six items. Both the TRSC total score and HRQOL-LASA total score were reported as a mean and standard deviation. The frequency and distribution of TRSC and HRQOL-LASA item scores were also reported.

Symptoms added to the TRSC by patients were evaluated for appropriate placement in existing categories. For instance, several patients added "nosebleed" to the list of symptoms instead of selecting "bleeding" from the existing TRSC items. Therefore, the investigator reclassified "nosebleed" as "bleeding" on the TRSC and moved the intensity rating for "nosebleed" to the TRSC item "bleeding." Similarly, two patients rated the "pain" item as zero, but added "feet tenderness" and "aches" to the list of symptoms. In both cases, the investigator reclassified "feet tenderness" and "aches" as "pain" on the TRSC and moved the intensity ratings for "feet tenderness" and "aches" to the TRSC item "pain". "Blurry vision" and "vision changes" were added to the list of symptoms by two patients, and, in this case, the investigator

reclassified these as “other - vision changes”. One patient claimed the TRSC item symptom “skin changes,” and rated the intensity of this symptom as “four”” The patient also added “rash,” “skin peeling”, and “cracked heels” to the list of symptoms. Since these were in addition to the “skin changes” item, the investigator decided to keep these as separate symptoms. They were reclassified as “other - rash,” “other - skin peeling”, and “other - cracked heels”. In further instances, “loose BM” was reclassified as “other - diarrhea”, while “toe nail” was reclassified as “other - nail changes”. One patient added “diarrhea” to the list of symptoms but did not rate the severity, therefore the severity was left blank. Two other symptoms – “right side upper hip” and “toe” – were added to the list of symptoms but were unclear as to what they were referencing. Therefore they were reclassified as “other – right side upper hip,” and “other – toe”. Altogether, 21 symptoms were added.

Evaluation of the scale’s reliability was accomplished by performing the Cronbach’s alpha, which evaluates the consistency with which a measure assigns scores to subjects, and the extent to which the measure leads to similar results regardless of the variations that may occur (internal consistency) (Ferketich, 1990). A Cronbach’s alpha was performed on the original 25-item TRSC as well as the six-item HRQOL-LASA. Additionally, a Cronbach’s alpha was run on the TRSC with the added “Other” item scores.

Multiple Linear Regression Analysis

Data analysis for research question #3. The third research question was: *What is the association between type of therapy (matched therapy versus not matched therapy) and overall occurrence and severity of cancer therapy-related symptoms as reported on the TRSC after controlling for person (age) and health/illness factors (cancer type, cancer stage, length of therapy, number of prior lines of therapy, timing of prior line of therapy, and number of comorbidities)?* Symptom occurrence and severity as reported on the TRSC was the dependent

variable for this research question. The total TRSC score was used, which was summated from the original 25 TRSC items. To examine the association between therapy type and symptoms, a multiple linear regression model was built. Multiple linear regression is used when the dependent variable is measured with a continuous (interval or ratio) level measure (Institution for Digital Research and Education, 2017; Sousa, 2010), as is the case in the current study.

First, procedures to examine model assumptions were conducted and included normality testing, evaluation of potential multicollinearity, and assessing independence of the data. The continuous data were evaluated for normality by reviewing histograms, Q-Q plots, skew, and kurtosis values. Indices for acceptable values of skewness and kurtosis were set at -2 to +2 (Field, 2013). Values for skewness in this study ranged from -0.27 to 0.96 and values for kurtosis ranged from 0.98 to 0.41 indicating sufficient normal distribution. Correlations between variables were evaluated and generally ranged from 0.003 to 0.48. The highest correlation of 0.55 was between cancer stage 3 and cancer type (see Table 4). However, variance inflation factors (VIF) values for all variables were less than 10 (range 1.1 to 3.04) and tolerance values for all variables were greater than .10 (range 0.33 to 0.90) indicating little multicollinearity (Mendenhall & Sincich, 2012; Sousa, 2010). Independence of observations was checked by the Durbin-Watson statistic (Sousa, 2010). In this study and for this analysis, the Durbin-Watson statistic value was 1.9, which was within the 1.5 to 2.5 range for independence of observations.

Table 4

Pearson's Correlations of Variables for Research Question # 3

	TRSC total	Therapy type	Age	Length current therapy	No. prior lines therapy	Cancer type	Comorbidities	Stage 2	Stage 3	Stage 4	Last therapy <3 months	Last therapy 3 months - 1 year	Last therapy >1 year
TRSC total	1.0	-.067	.012	-.010	.027	.166	.094	-.067	.072	-.112	.163	-.003	.006
Therapy type		1.0	.048	-.181	.331	-.006	.087	-.095	.072	-.112	.163	-.003	.006
Age			1.0	-.107	.226	.383	.370	-.208	.117	.190	.039	.111	.110
Length current therapy				1.0	-.184	-.017	-.005	-.034	.234	-.261	-.034	-.033	-.014
No. prior lines therapy					1.0	.227	.057	-.400	.044	.452	.479	.042	-.032
Cancer type						1.0	.092	-.295	.547	-.238	.108	.239	.193
Comorbidities							1.0	-.097	-.003	.132	.088	.115	-.012
Stage 2								1.0	-.362	-.382	-.148	-.015	-.098
Stage 3									1.0	-.457	.109	.043	-.118
Stage 4										1.0	.100	.032	.067
Last therapy <3months											1.0	-.323	-.288
Last therapy 3 months – 1 year												1.0	-.036
Last therapy >1 year													1.0

Note. TRSC = Therapy Related Symptom Checklist

After assessing the model assumptions, a multiple linear regression analysis was performed. The independent variable, therapy type, was modeled using a categorical indicator variable ($x = 0$ for not matched therapy, $x = 1$ for matched therapy) and included covariates age, cancer type and stage, length of therapy in weeks, number of prior lines of therapy, timing of prior line of therapy, and number of comorbidity categories. Table 5 shows the variables that were included in the regression model. Three dummy variables were created for the variable cancer stage (stage 2, stage 3, stage 4) with stage 1 as the reference variable, and three dummy variables were created for the variable prior line of therapy timing (< 3 months, > 3months but < 1 year, > 1 year), with no prior therapy as the reference variable.

Table 5

Variables for Research Question #3

Independent variable	Dependent variable
Therapy type (categorical)	Symptom occurrence/severity (TRSC scores – continuous)
Control variables	**Type of data**
Age	Continuous
Cancer type	Categorical
Cancer stage	Categorical
Length of therapy	Continuous
Prior lines of therapy	Continuous
Timing of prior line of therapy	Categorical
Comorbidities	Continuous

Note. TRSC = Therapy-Related Symptom Checklist

Independent variables were entered into the model by step. In the first step, therapy type was added. The remaining independent variables were added to the model in the second step. Two-tailed significance tests (*F*-test) for each step in the model were performed and reported. Additionally, the *t*-value and corresponding probability (*p*)-value, as well as the unstandardized B, and the standard error of the estimate (*SE)* for each variable were determined and reported. Level of significance was set at alpha ≤ 0.05.

Data analysis for research question #4. The fourth research question was: *What is the association between type of therapy (matched therapy versus not matched therapy) and overall HRQOL as reported on the HRQOL-LASA after controlling for person (age) and health/illness factors (cancer type, cancer stage, length of therapy, number of prior lines of therapy, number of comorbidities, and overall symptom occurrence and severity)?* Health-related quality of life was the dependent variable for this research question as defined by the total HRQOL-LASA, which was summated from individual item scores. To examine the association between therapy type and HRQOL, a multiple linear regression model was built.

Procedures to examine model assumptions were conducted first, and included normality testing, evaluation of potential multicollinearity, and assessing independence of the data. The continuous data were evaluated for normality by reviewing histograms, Q-Q plots, skew, and kurtosis values. Indices for acceptable values of skewness and kurtosis were set at -2 to +2 (Field, 2013). Values for skewness ranged from -0.70 to 0.962, and values for kurtosis ranged from 0.98 to 0.41, indicating sufficient normal distribution. Correlations between variables were evaluated and generally ranged from 0.002 to 0.48. The highest correlation of 0.55 was between cancer stage 3 and cancer type (see Table 6). However, variance inflation factors (VIF) values for all variables were less than 10 (range 1.1 to 3.1) and tolerance values for all variables were greater than 0.10 (range 0.32 to 0.90) indicating little concern for multicollinearity (Mendenhall & Sincich, 2012; Sousa, 2010). Independence of observations was checked by the Durbin-Watson statistic (Sousa, 2010). In this study and for this analysis, the Durbin-Watson statistic value was 1.9, which was within the 1.5 to 2.5 range for independence of observations.

Table 6

Pearson's Correlations of Variables for Research Question # 4

	HRQOL-LASA	Therapy type	Age	Length current therapy	No. prior lines therapy	Cancer type	Comorbidities	Stage 2	Stage 3	Stage 4	Last therapy <3 months	Last therapy 3 months–1 year	Last therapy >1 year	TRSC total
HRQOL-LASA	1.0	.166	.061	-.002	.144	-.139	-.053	-.015	-.016	.093	.034	-.168	.021	-.491
Therapy type		1.0	.048	-.181	.331	-.006	.087	-.095	-.110	.271	.335	.032	.083	-.067
Age			1.0	-.107	.226	.383	.370	-.208	.117	.190	.039	.111	.110	.012
Length current therapy				1.0	-.184	-.017	-.005	-.034	.234	-.261	-.034	-.033	-.014	-.010
No. prior lines therapy					1.0	.227	.057	-.400	.044	.452	.479	.042	-.032	.027
Cancer type						1.0	.092	-.295	.547	-.238	.108	.239	.193	.166
Comorbidities							1.0	-.097	-.003	.132	.088	.115	-.012	.094
Stage 2								1.0	-.362	-.382	-.148	-.015	-.098	-.067
Stage 3									1.0	-.457	.109	.043	-.118	.072
Stage 4										1.0	.100	.032	.067	-.112
Last therapy <3months											1.0	-.323	-.288	.163
Last therapy 3 months – 1 year												1.0	-.036	-.003
Last therapy >1 year													1.0	.006
TRSC total														1.0

Note. HRQOL-LASA = Health Related Quality of Life – Linear Analogue Self Assessment; TRSC = Therapy Related Symptom Checklist.

After assessing the model assumptions, a multiple linear regression analysis was performed. The independent variable, therapy type, was modeled using a categorical indicator variable ($x = 0$ for not matched therapy, $x = 1$ for matched therapy), and included covariates age, type and stage of disease, length of therapy, prior lines of therapy, timing of prior line of therapy, comorbidities, and symptoms (TRSC scores). Table 7 shows the variables that were included in the regression model. The three dummy variables created for the variable cancer stage (stage 2, stage 3, stage 4) with stage 1 as the reference variable and the three dummy variables created for the variable prior line of therapy timing (< 3 months, > 3months but < 1 year, > 1 year) with no prior therapy as the reference variable were also used in the analysis.

Table 7

Variables for Research Question #4

Independent variable	Dependent variable
Therapy type (categorical)	HRQOL (HRQOL-LASA scores – continuous)
Control variables	Type of data
Age	Continuous
Cancer type	Categorical
Cancer stage	Categorical
Length of therapy	Continuous
Prior lines of therapy	Continuous
Timing of prior line of therapy	Categorical
Comorbidities	Continuous
Symptoms (TRSC scores)	Continuous

Note. HRQOL-LASA = Health-Related Quality of Life – Linear Analogue Self Assessment, TRSC = Therapy-Related Symptom Checklist;

Independent variables were entered into the model by step. After careful consideration, it was decided to enter the variables in three steps instead of the previously planned two step model to better characterize the contribution of the TRSC score. In the first step, therapy type was added. The variables age, cancer type, cancer stage, length of therapy, prior lines of therapy, timing of prior line of therapy, and number of comorbidities were added in the second step. Symptoms (TRSC scores) were added in the final step. Two-tailed significance tests (F-test) for

each step in the model were performed and reported. Additionally, the *t*-value and corresponding *p*-value, as well as the unstandardized B, and *SE* for each variable were determined and reported; level of significance was also set at ≤ 0.05.

Summary

This chapter presented an overview of the methods used to analyze symptom occurrence and severity as well as HRQOL in patients with breast or gynecologic cancer receiving matched or not matched therapy. These analyses of existing data are the first known for this population, and will provide a better understanding of the association between the type of therapy (matched or not matched) and symptom experience and HRQOL. This study utilizes descriptive and multiple linear regression statistical methods to answer the questions proposed. Chapter Four will present the findings from these described analyses.

Chapter Four

Results

This chapter presents the findings of the analyses performed on existing data of breast and gynecologic cancer patients to assess symptom occurrence and HRQOL among those receiving matched or not matched therapy. Specifically, the following results will be discussed: a) The characteristics of the study sample by type of therapy, b) Symptom occurrence and severity and HRQOL by type of therapy, c) The association between type of therapy and overall symptom occurrence and severity as reported on the TRSC while controlling for person and health/illness factors, and d) The association between type of therapy and HRQOL as reported on the HRQOL-LASA after controlling for person and health/illness factors.

Description of Study Sample

The final study sample was comprised of 129 female patients. The overwhelming majority of the sample was Caucasian (n = 124, 96%), and their mean age was 56 years (SD = 10.8). Among the study women, 73% (n = 94) had a diagnosis of breast cancer while 27% (n = 35) had a diagnosis of gynecologic cancer. Only 15% (n = 19) patients in the sample reported no family history of cancer. Among those that did have a family history of cancer, 80 patients (62%) had more than one family member with a cancer history. Fifty-four percent (n = 70) were considered to have metastatic disease at the time of this study, and most of the patients in the sample (n = 102, 79%) had undergone prior cancer therapy for their cancer diagnosis. Of the patients who had had prior cancer therapy, the mean number of prior lines of therapy was 3.3 (SD = 3.2), and the most frequent prior treatment modalities were surgery (n = 79, 61%) and chemotherapy (n = 81, 63%). All but one patient had health insurance of some type; most patients had commercial insurance (n = 88, 68%), and most of their drug coverage was provided

by health insurance (n = 102, 79%). The mean length of current therapy for the entire sample was 7.2 weeks (SD = 2.3).

Research Question #1

Among the sample, 67 patients (52%) received matched therapy and 62 patients (48%) did not receive matched therapy. The demographic and clinical profiles of the patients receiving matched and not matched therapy in this study are shown in Table 8. Patients receiving matched therapy were slightly older on average (57 years, SD = 12.1) than those patients receiving not matched therapy (55 years, SD = 13.4). The ethnicity of both groups was mainly Caucasian. Although the majority of patients had commercial insurance and drug coverage was largely provided by the patients' insurances, more patients receiving matched therapy required additional assistance for drug coverage in the form of drug samples and/or patient assistance programs compared to those not receiving matched therapy. The percentage of patients with a family history of cancer was nearly equal between groups.

Most patients receiving matched therapy were receiving a combination of chemotherapy and targeted therapy representing a total of 55% (n = 37). Patients may have received more than one targeted therapy concomitantly, and the combination of therapies for patients receiving matched therapy varied. Table 9 shows the compiled list of targeted therapies used to target the genomic alteration(s) among patients receiving matched therapy. Eight of the 15 targeted therapies listed are currently approved by the FDA for the treatment of cancer types other than breast or gynecologic cancer, including renal cell cancer, melanoma, lung cancer, leukemia, and prostate cancer. Only two of the 15 targeted therapies listed (temsirolimus, olaparib) are currently approved by the FDA for the treatment of gynecologic cancer, and six of the 15 (everolimus, palbociclib, lapatinib, pertuzumab, trastuzumab, TDM1) are currently approved by the FDA for breast cancer.

Table 8

Characteristics of Patients Receiving Matched and Not Matched Therapy

Characteristic	Matched Therapy (n = 67)	Not Matched Therapy (n = 62)
Age (Mean years/*SD*)	56.6 (12.1)	55.4 (13.4)
Length of current therapy (Mean weeks/*SD*)	6.8 (2.3)	7.6 (2.3)
No. of prior lines of therapy (Mean weeks/*SD*)	4.3 (3.2)	2.2 (2.9)
Comorbidity categories Mean/*SD*)	2.2 (1.5)	2.0 (1.6)
Ethnicity (*n*/percent)		
Caucasian	64 (95.5%)	60 (96.8%)
Hispanic	1(1.5%)	2 (3.2%)
Asian/Native American	2 (3%)	0
Insurance type (*n*/percent)		
No insurance/self-pay	0	1 (1.6%)
Medicaid	0	2 (3.2%)
Medicare	20 (29.9%)	18 (29%)
Commercial	47 (70.1%)	41(66.1%)
Drug coverage (*n*/percent)		
Health insurance	42 (62.7%)	60 (96.8%)
Patient assistance programs	8 (11.9%)	2 (3.2%)
Samples	6 (9%)	0
Health insurance/samples	4 (6%)	0
Health insurance/patient assistance	5 (7.5%)	0
Samples/patient assistance	1 (1.5%)	0
Insurance/samples/patient assistance	1 (1.5%)	0
Family history (*n*/percent)[a]		
Breast cancer	34 (50.7%)	31 (50%)
Gynecologic cancer	16 (23.9%)	16 (25.8%)
Other cancer	41 (61.2%)	38 (61.3%)
Concurrent therapy type (*n*/percent)		
Chemotherapy	0	39 (62.9%)
Targeted therapy	30 (44.8%)	6 (9.7%)
Chemotherapy/targeted therapy	37 (55%)	17 (27.4%)
Prior treatment modalities (*n*/percent)[b]		
Surgery	46 (68.7%)	33 (53.2%)
Radiation	23 (34.3%)	12 (19.4%)
Chemotherapy	54 (80.6%)	27 (43.5%)
Targeted	41 (61.2%)	14 (22.6%)
No prior therapy	3 (4.5%)	24 (38.7%)
Cancer stage (*n*/percent)		
Stage 1	7 (10.4%)	11 (17.7%)
Stage 2	13 (19.4%)	17 (27.4%)
Stage 3	17 (25.4%)	22 (35.5%)
Stage 4	30 (44.8%)	12 (19.4%)
Cancer type (*n*/percent)		
Breast	49 (73.1%)	45 (72.6%)
Gynecologic	18 (26.9%)	17 (27.4%)
Timing prior line therapy (*n*/percent)		
No prior therapy	3 (4.5%)	24 (38.7%)
<3 months	58 (86.6%)	35 (56.5%)
>3 months, < 1 year	3 (4.5%)	2 (3.2%)
> 1 year	3 (4.5%)	1 (1.6%)

Note. *SD* = Standard Deviation

[a] Frequency of family history of cancers exceed sample size since multiple subjects reported family history of >1 type of cancer. [b] Frequency of prior treatment modalities exceed sample size since multiple subjects had >1 prior treatment modality.

Table 9

Targeted Therapies Used for Patients Receiving Matched Therapy

List of Targeted Therapies	No. of Patients Receiving Each Targeted Therapy[a]
Trametinib	15
Everolimus	42
Temsirolimus	4
Pazopanib	12
Palbociclib	7
Olaparib	1
Crizotinib	2
Lapatinib	2
Dabrafenib	1
Ponatinib	1
Enzalutamide	1
Pertuzumab	3
Trastuzumab	10
TDM1	1
Pembrolizumab (immunotherapy)	4

Note. TDM1 = ado-trastuzumab emtansine

[a] Total of no. of patients receiving each targeted therapy exceeds the sample size of patients receiving matched therapy since many patients received more than one type of targeted therapy.

Most patients receiving not matched therapy were receiving chemotherapy only (63%). Mean length of current therapy for patients receiving matched therapy was 6.8 weeks (*SD* = 2.3) compared to 7.6 weeks (*SD* = 2.3) for patients receiving not matched therapy. Patients receiving matched therapy had more prior lines of therapy on average (*M* = 4.3, *SD* = 3.2) compared to patients receiving not matched therapy (*M* = 2.2, *SD* = 2.9). Thirty nine percent (*n* = 24) of patients receiving not matched therapy had no prior line of therapy compared to just 5% (*n* = 3) of the patients receiving matched therapy. The number of different types of treatment modalities used in the prior lines of therapy (surgery, radiation, chemotherapy, or targeted therapy) were higher for patients receiving matched therapy (*M* = 2.5, *SD* = 1.2) compared to patients receiving not matched therapy (*M* = 1.4, *SD* = 1.4). The mean number of comorbidities was slightly higher for patients receiving matched therapy (*M* = 2.2, *SD* = 1.5) compared to patients receiving not matched therapy (*M* = 2.0, *SD* = 1.6). Endocrine diseases were the most common comorbidity for patients receiving matched therapy (*n* = 28, 42%) while circulatory diseases were the most

frequent comorbidity for patients receiving not matched therapy (n = 25, 40%). See Table 10 for the distribution of comorbid conditions among the sample by therapy type.

Table 10

Distribution of Comorbid Conditions by Therapy Type

Comorbidity categories	Corresponding ICD-10 Codes[a]	Matched Therapy (n=67) *n (%)*	Not Matched Therapy (n=62) *n* (%)
Diseases of Genitourinary System	N00-N19	2 (3%)	3 (4.8%)
Other Diseases of Urinary System and Female Pelvic Organs	N25-N99	4 (6%)	7 (11.3%)
Diseases of the Circulatory System	I00-I199	24 (35.8%)	25 (40.3%)
Congenital Malformations, Deformations and Chromosomal Abnormalities	Q00-Q99	2 (3%)	1 (1.6%)
Diseases of the Digestive System	K00-K95	22 (32.8%)	14 (22.6%)
Mental, Behavioral and Neurodevelopmental Disorders	F01-F99	12 (17.9%)	11 (17.7%)
Endocrine, Nutritional and Metabolic Diseases	E00-E89	28 (41.8%)	22 (35.5%)
Diseases of the Skin	L00-L99	6 (9%)	4 (6.5%)
Diseases of the Blood and Blood-Forming Organs and Certain Disorders Involving the Immune Mechanism	D50-D89	4 (6%)	0
Disease of the Respiratory System	J00-J99	10 (14.9%)	8 (12.9%)
Diseases of the Eye	H00-H59	3 (4.5%)	2 (3.2%)
Diseases of the Musculoskeletal System	M00-M99	17 (25.4%)	14 (22.6%)
Diseases of the Ear and Mastoid Process	H60-H95	2 (3%)	0
Diseases of the Nervous System	G00-G99	11 (16.4%)	6 (9.7%)
Neoplasms	C00-D49	2 (3%)	3 (4.8%)
Certain Infectious and Parasitic Diseases	A00-B99	0	2 (3.2%)
Persons with Potential Health Hazards Related to Family and Personal History and Certain Conditions Influencing Health Status (Food Allergies)	Z77-Z99	1 (1.5%)	0
Persons Encountering Health Services in Other Circumstances (Tobacco Use)	Z69-Z76	1 (1.5%)	0

Note, ICD-10 = International Statistical Classification of Diseases – 10th revision.
[a] ICD-10-CM official guidelines for coding and reporting (2016). Retrieved from http://www.cdc.gov/nchs/data/icd/10cmguidelines_2016_final.pdf

The rate of breast and gynecologic cancers were evenly distributed between patients receiving matched therapy and patients receiving not matched therapy. By stage, there were more stage 3 cancers in patients receiving not matched therapy (n = 22, 36%) than patients receiving matched therapy (n = 17, 25%). Conversely there were more stage 4 cancers in patients receiving matched therapy (n = 30, 45%) than in patients receiving not matched therapy (n = 12, 19%).

Research Question #2

Therapy-Related Symptom Checklist (TRSC) Scores

The mean number of symptoms reported on the original 25-item TRSC across all 129 subjects was 8.2 (SD = 4.9). Patients receiving matched therapy reported a mean number of 8.0 symptoms (SD = 4.9), and patients receiving not matched therapy reported a mean number of 8.4 symptoms (SD = 5.2). In regard to overall symptom occurrence and severity, the mean total TRSC score for the patients receiving matched therapy was 14.7 (SD = 10.1), which was lower than the mean total TRSC score for patients receiving not matched therapy (M = 16.1, SD = 11.6).

Table 11 shows the count (frequency of occurrence) of each symptom, the mean rating of severity for each symptom, and the rank of occurrence by therapy type on the original 25-item TRSC.

Table 11

Symptom Occurrence, Mean Rating of Severity, and Rank of Symptom Occurrence on the TRSC by Therapy Type

	Matched Therapy				Not Matched Therapy			
Symptoms and Subscales	Count (%)	*Mean* Severity Rating	*SD* Severity Rating	Rank of Occurrence	Count (%)	*Mean* Severity Rating	*SD* Severity Rating	Rank of Occurrence
Fatigue								
Feeling sluggish	46 (69%)	1.3	1.1	1	45 (73%)	1.5	1.2	1
Depression	14 (21%)	0.36	0.79	12	17 (27%)	0.44	0.80	11
Difficulty concentrating	24 (36%)	0.63	0.95	9	35 (56%)	0.87	0.93	3
Difficulty sleeping	35 (52%)	1.0	1.2	3	34 (55%)	1.1	1.2	4
Eating								
Taste changes	35 (52%)	1.1	1.3	3	38 (61%)	1.1	1.1	2
Loss of appetite	29 (43%)	0.78	1.1	5	34 (55%)	1.0	1.1	4
Weight loss	19 (28%)	0.40	0.72	11	18 (29%)	0.48	0.90	10
Difficulty swallowing	8 (12%)	0.15	0.44	16	9 (15%)	0.26	0.72	15
Oropharynx								
Sore mouth	24 (36%)	0.75	1.2	9	19 (31%)	0.53	0.94	9
Sore throat	10 (15%)	0.28	0.71	15	11 (18%)	0.37	0.93	14
Jaw pain	4 (6%)	0.13	0.58	18	4 (6%)	0.08	0.33	18
Fever								
Fever	7 (10%)	0.15	0.47	17	4 (6%)	0.16	0.62	18
Bruising	13 (19%)	0.27	0.59	13	12 (19%)	0.27	0.61	13
Nausea								
Nausea	27 (40%)	0.73	1.1	7	32 (52%)	0.95	1.2	5
Vomiting	11 (16%)	0.21	0.54	14	11 (18%)	0.35	0.93	14
Respiratory								
Cough	19 (28%)	0.36	0.64	11	15 (24%)	0.42	0.92	12
Shortness of breath	26 (39%)	0.55	0.84	8	19 (31%)	0.44	0.76	9
Pain	34 (51%)	0.91	1.2	4	17 (27%)	0.56	1.1	11
Numbness in fingers and/or toes	37 (55%)	0.97	1.1	2	23 (37%)	0.82	1.3	8
Bleeding	11 (16%)	0.24	0.65	14	7 (11%)	0.23	0.78	16
Hair loss	20 (30%)	0.70	1.3	10	35 (56%)	1.8	1.8	3
Skin changes	28 (42%)	0.78	1.1	6	19 (31%)	0.52	0.97	9
Constipation	24 (36%)	0.78	1.2	9	29 (47%)	0.89	1.1	6
Sore vein	7 (10%)	0.18	0.65	17	6 (10%)	0.11	0.34	17
Decreased interest in sexual activity	27 (40%)	0.94	1.3	7	25 (40%)	0.94	1.3	7

Note. TRSC = Therapy-Related Symptom Checklist, *SD* = Standard Deviation

The symptom with the highest occurrence as reported by patients receiving matched and not matched therapy was "feeling sluggish." Most of the other symptoms were reported at similar rates of occurrences, with the following exceptions: a) "numbness in fingers and/or toes" was the second highest occurring symptom as reported by patients receiving matched therapy, compared to the eighth highest occurring symptom as reported by patients receiving not matched therapy; b) "pain" was the fourth highest occurring symptom as reported by patients receiving matched therapy compared to the 11th as reported by patients receiving not matched therapy; c) "difficulty concentrating" was the ninth highest occurring symptom as reported by patients receiving matched therapy compared to the third as reported by patients receiving not matched therapy; and, d) "hair loss," which was the 10th highest occurring symptom as reported by patients receiving matched therapy compared to, again, the third as reported by patients receiving not matched therapy.

Evaluation of the severity of each item on the original 25-item TRSC revealed that eight symptoms had higher mean severity ratings for patients receiving matched therapy compared to patients receiving not matched therapy. The eight higher mean severity ratings included the following symptoms: "sore mouth", "jaw pain", "shortness of breath", "pain", "numbness in fingers and/or toes", "bleeding", "skin changes", and "soreness in vein". Of these eight symptoms, "pain" was notably higher in terms of both occurrence and severity for patients receiving matched therapy (see Figure 2).

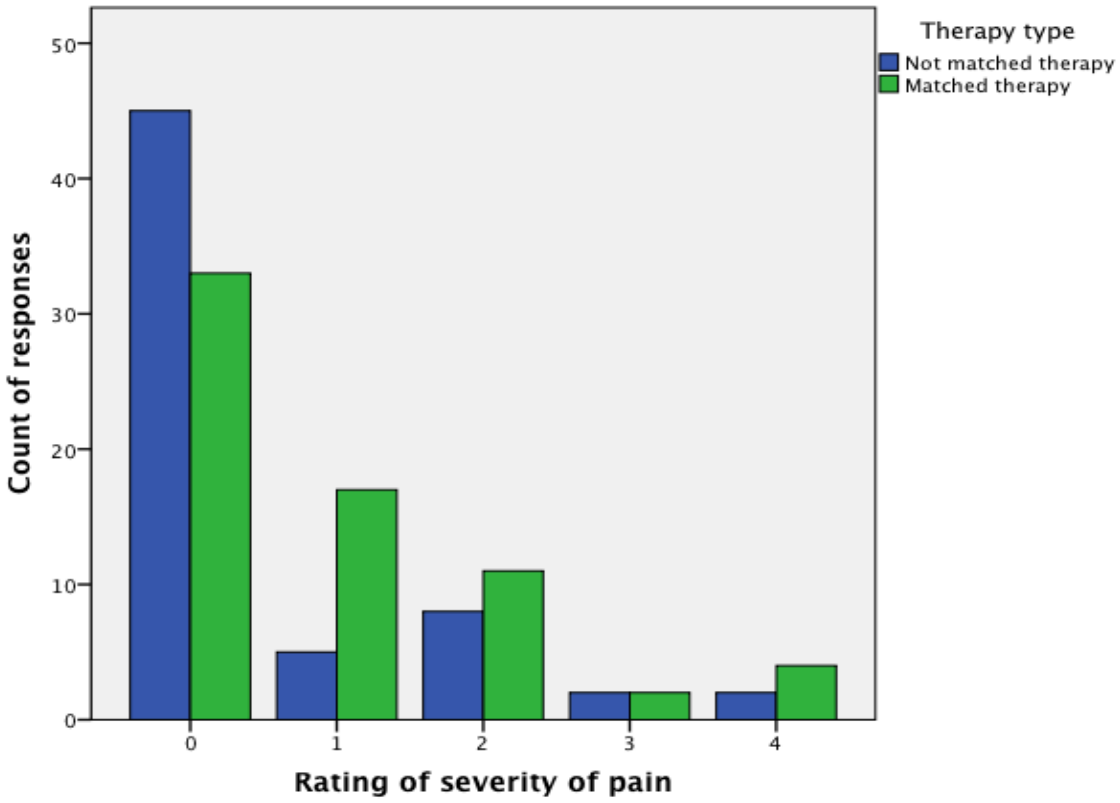

Figure 2. Occurrence and severity of pain on the TRSC as self-reported by patients receiving matched therapy or not matched therapy.

Patients receiving matched therapy had higher occurrence but slightly lower mean severity ratings for six other symptoms when compared to patients receiving not matched therapy, and included the following: “feeling sluggish”, “difficulty sleeping”, “weight loss”, “fever”, “bruising”, and “cough”. The remaining symptoms on the 25-item TRSC had higher occurrence and/or mean severity ratings for patients receiving not matched therapy. Of these, “hair loss” was notably higher in terms of occurrence and severity for patients receiving not matched therapy compared to the patients receiving matched therapy (see Figure 3). The overall Cronbach’s alpha value for the TRSC with the original 25 items was 0.83.

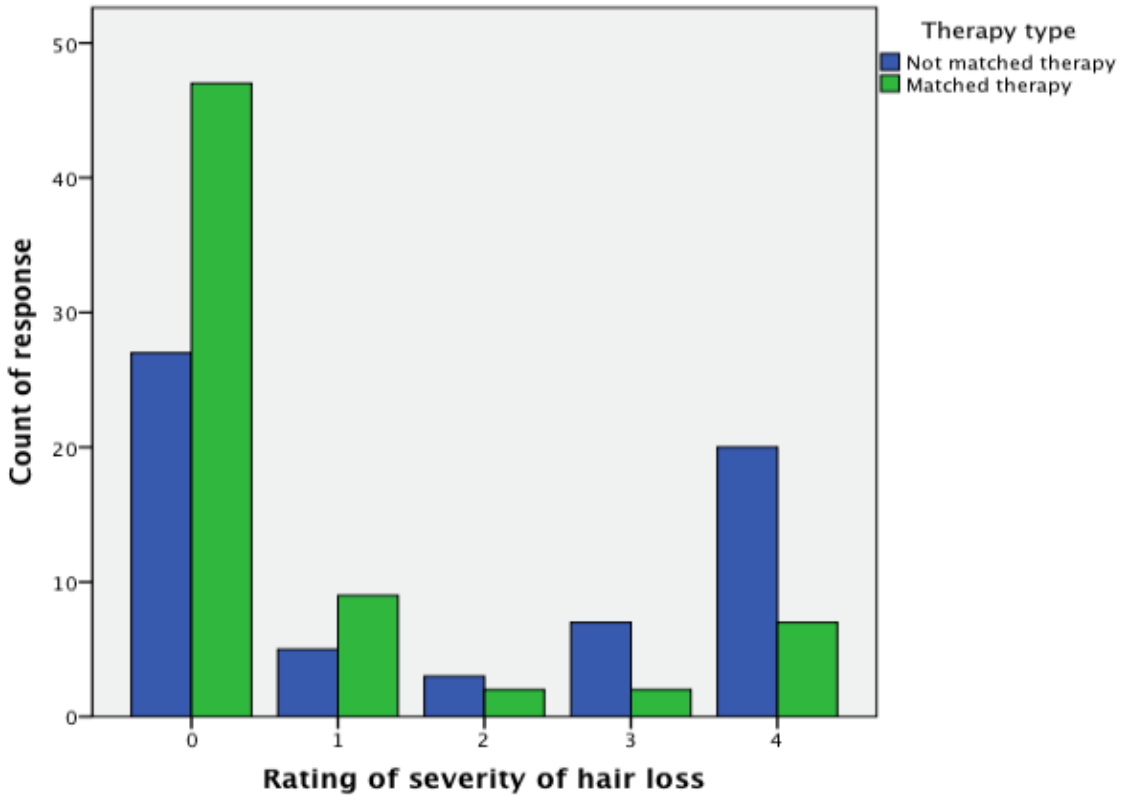

Figure 3. Occurrence and severity of hair loss on the TRSC as self-reported by patients receiving matched therapy or not matched therapy.

Fourteen (25%) of the patients receiving matched therapy added symptoms to the TRSC and 23 (37%) of the patients receiving not matched therapy added symptoms to the TRSC (see Table 12). In all, 37 patients (29%) added symptoms to the TRSC, which is much higher relative to past TRSC studies where less than 2% of patients added symptoms to the TRSC (Williams et al., 2013). Consequently, mean total TRSC scores by therapy type that included the additional symptoms were also calculated. For patients receiving matched therapy the mean TRSC score with the added symptoms was 15.2 (*SD* = 10.5), which was lower than the mean TRSC score for patients receiving not matched therapy (*M* = 17.0, *SD* = 12). When the added symptoms were included in the analysis, the overall Cronbach's alpha value was 0.81.

Table 12

Additional 21 Items Added to the TRSC by Patients Receiving Matched (n = 67) or Not Matched (n = 62) Therapy

	Matched No. Patients that Added the Item	Not Matched No. Patients that Added the Item
Diarrhea	6	7
Anxiety	1	0
Hot flashes	1	0
Right upper hip	0	1
Vision change	0	2
Unsteady	0	1
Cold symptoms	1	0
Nail changes	1	1
Rash	1	1
Peeling skin	1	0
Cracks in heels	1	0
Toe	0	1
Delayed wound healing	0	1
Neutropenia	0	1
Dry mouth	1	0
Dry eyes	0	2
Headache	0	1
Watery eyes	0	1
Weakness	0	1
Leg cramps	0	1
Foods don't sit well	0	1
Total	14 (21%)	23 (37%)

Note. TRSC = Therapy-Related Symptom Checklist

Health-Related Quality of Life – Linear Analogue Self Assessment (HRQOL-LASA) Scores

Overall, patients rated their HRQOL relatively high, with a combined mean total HRQOL-LASA score of 46.8 (*SD* = 8.4). The mean total HRQOL-LASA score for patients receiving matched therapy was 48.1 (*SD* = 7.5) which was higher than the mean score of 45.4 for patients receiving not matched therapy (*SD* = 9.1). The Cronbach's alpha for the HRQOL-LASA was 0.89.

Evaluation of the individual HRQOL-LASA item responses revealed that ratings on the overall QOL item ranged from three to 10 for patients receiving matched therapy and for patients receiving not matched therapy. The distribution of ratings for this item is shown in Figure 4. The mean score for overall QOL was slightly higher for patients receiving matched therapy (*M* = 7.93, *SD* = 1.57) versus patients receiving not matched therapy (*M* = 7.53, *SD* = 1.73).

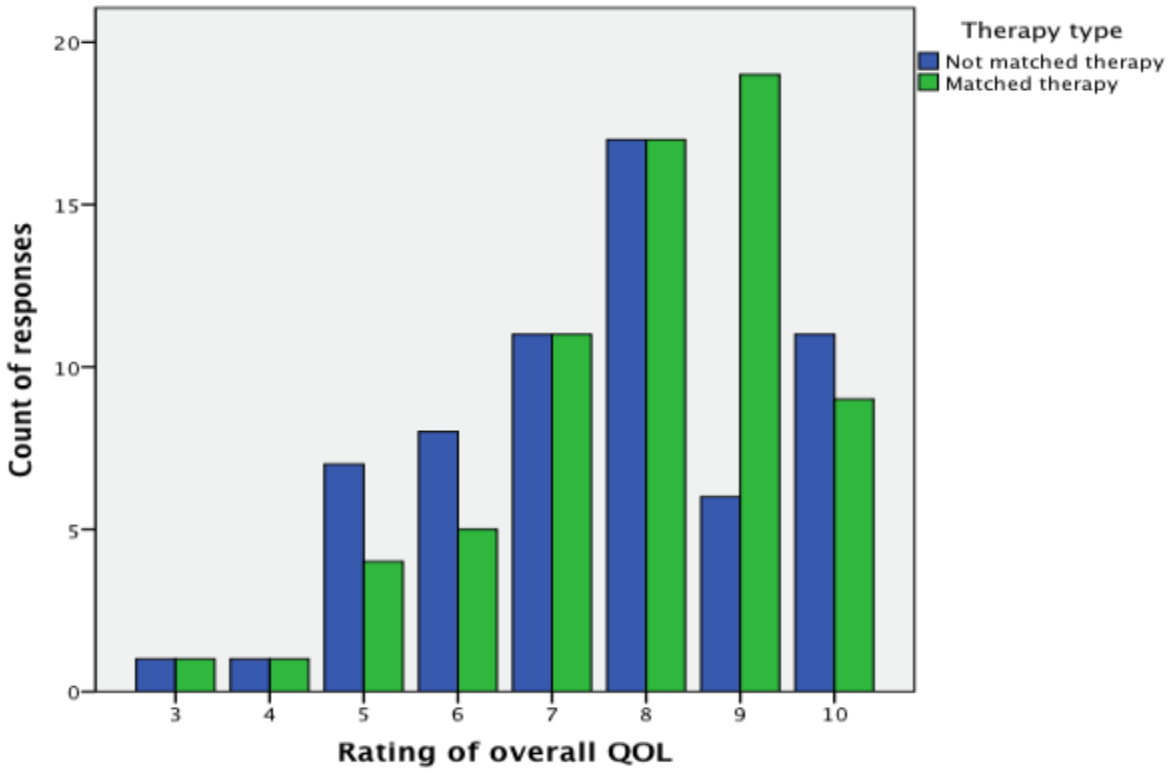

Figure 4. Perception of overall QOL as reported by patients receiving matched therapy or not matched therapy.

Ratings on the mental well-being item ranged from five to 10 for patients receiving matched therapy, compared to a range of four to 10 for patients receiving not matched therapy. The distribution of ratings for overall mental health well-being by therapy type is shown in Figure 5. The mean score for overall mental well-being was higher for patients receiving matched therapy (M = 8.28, SD = 1.25) compared to patients receiving not matched therapy (M = 7.95, SD = 1.52).

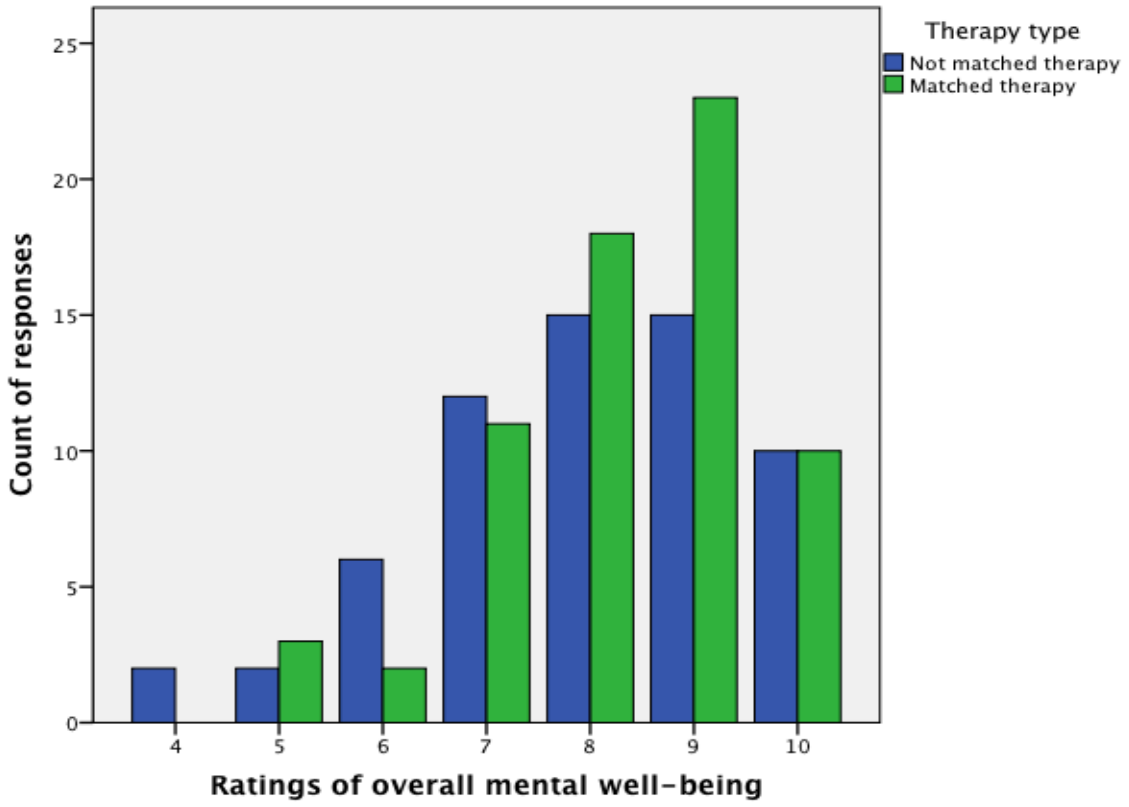

Figure 5. Perception of overall mental well-being as reported by patients receiving matched therapy or not matched therapy.

Ratings on the overall physical well-being item ranged from four to 10 for patients receiving matched therapy compared to a range of two to 10 for patients receiving not matched therapy. The distribution of ratings for overall physical well-being is shown in Figure 6. The

mean score for overall physical well-being for patients receiving matched therapy was slightly higher (M = 7.33, SD = 1.78) than patients receiving not matched therapy (M = 7.26, SD = 1.78).

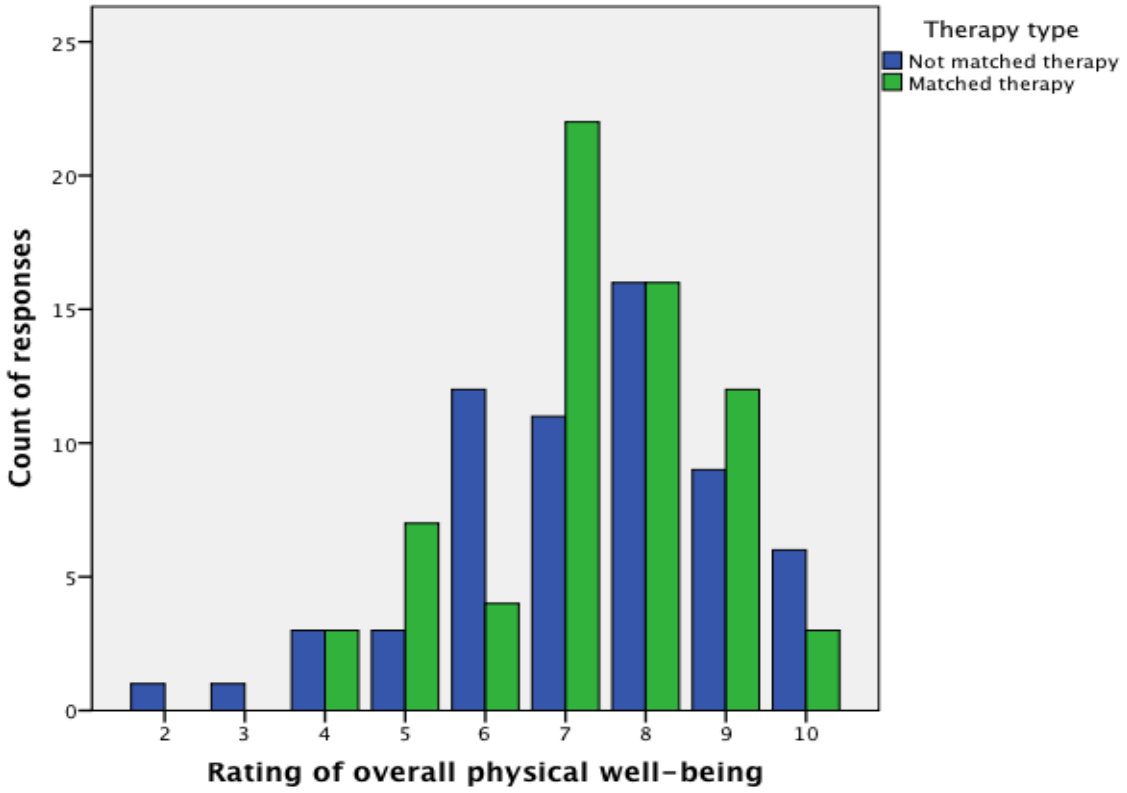

Figure 6. Perception of overall physical well-being as reported by patients receiving matched therapy or not matched therapy.

Ratings on the overall emotional well-being item ranged from four to 10 for patients receiving matched therapy compared to a range of three to 10 for patients receiving not matched therapy. The distribution of ratings for overall emotional well-being is shown in Figure 7. The mean score for overall emotional well-being was higher for patients receiving matched therapy (M = 7.97, SD = 1.42) compared to patients receiving not matched therapy (M = 7.61, SD = 1.59).

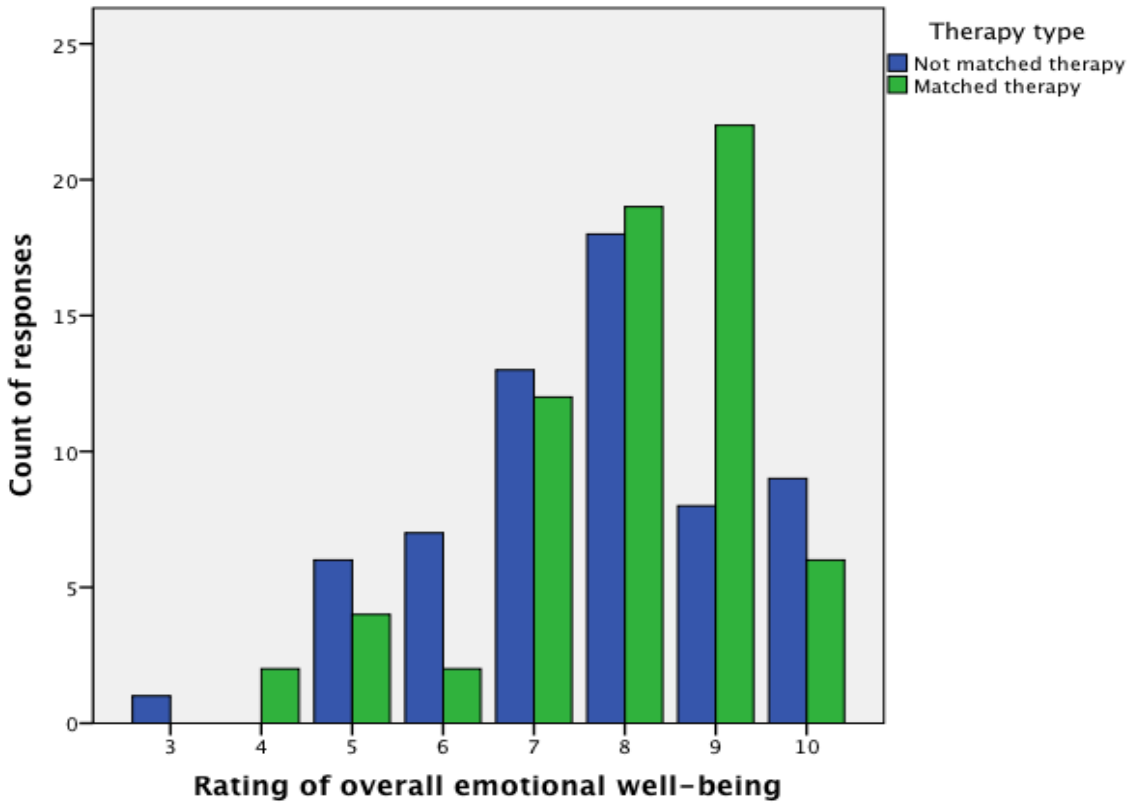

Figure 7. Perception of overall emotional well-being as reported by patients receiving matched therapy or not matched therapy.

Ratings on the level of social activity item for patients receiving matched therapy ranged from zero to 10 compared to a range of two to 10 for patients receiving not matched therapy. The distribution of ratings for level of social activity is shown in Figure 8. The mean score for level of social activity for patients receiving matched therapy was notably higher (M = 7.85, SD = 1.89) compared to patients receiving not matched therapy (M = 6.77, SD = 2.32).

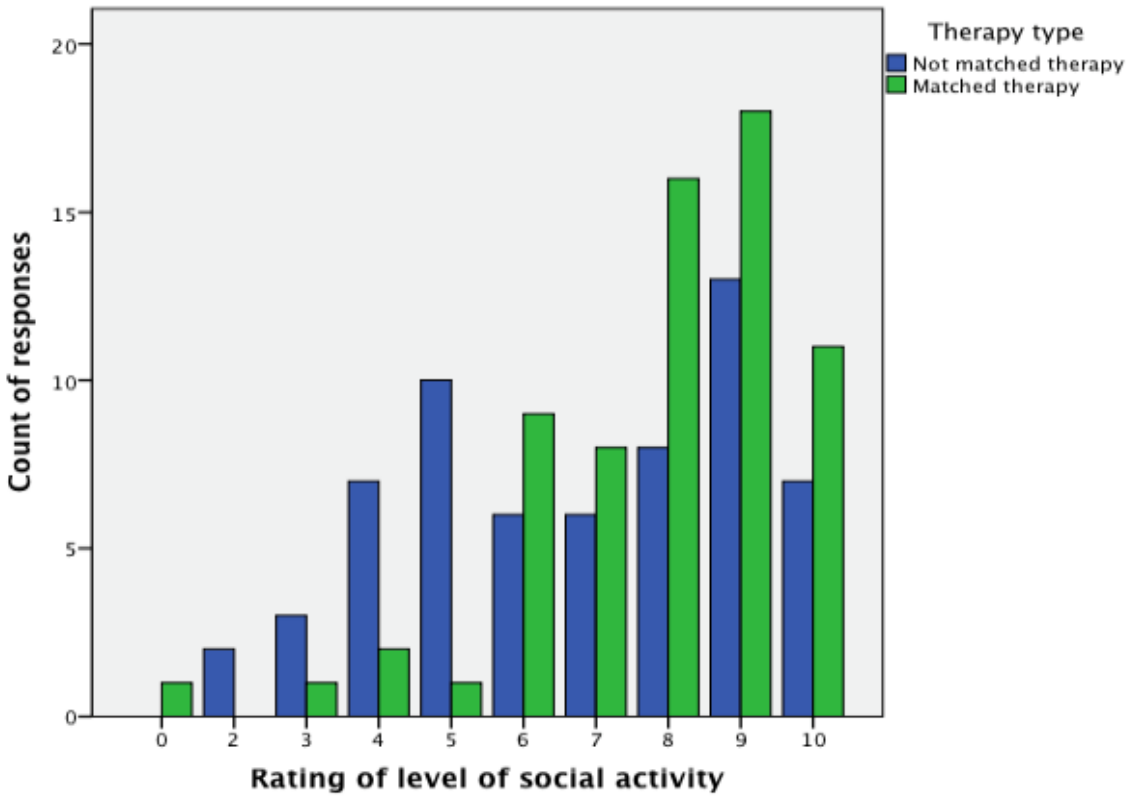

Figure 8. Perception of level of social activity as reported by patients receiving matched therapy or not matched therapy.

Finally, ratings on the overall spiritual well-being item ranged from zero to ten for patients receiving matched therapy compared to a range of one to 10 for patients receiving not matched therapy. The distribution of ratings for overall spiritual well-being is shown in Figure 9. The mean score for overall spiritual well-being was higher for patients receiving matched therapy (M = 8.63, SD = 1.76) compared to patients receiving not matched therapy (M = 8.23, SD = 1.94).

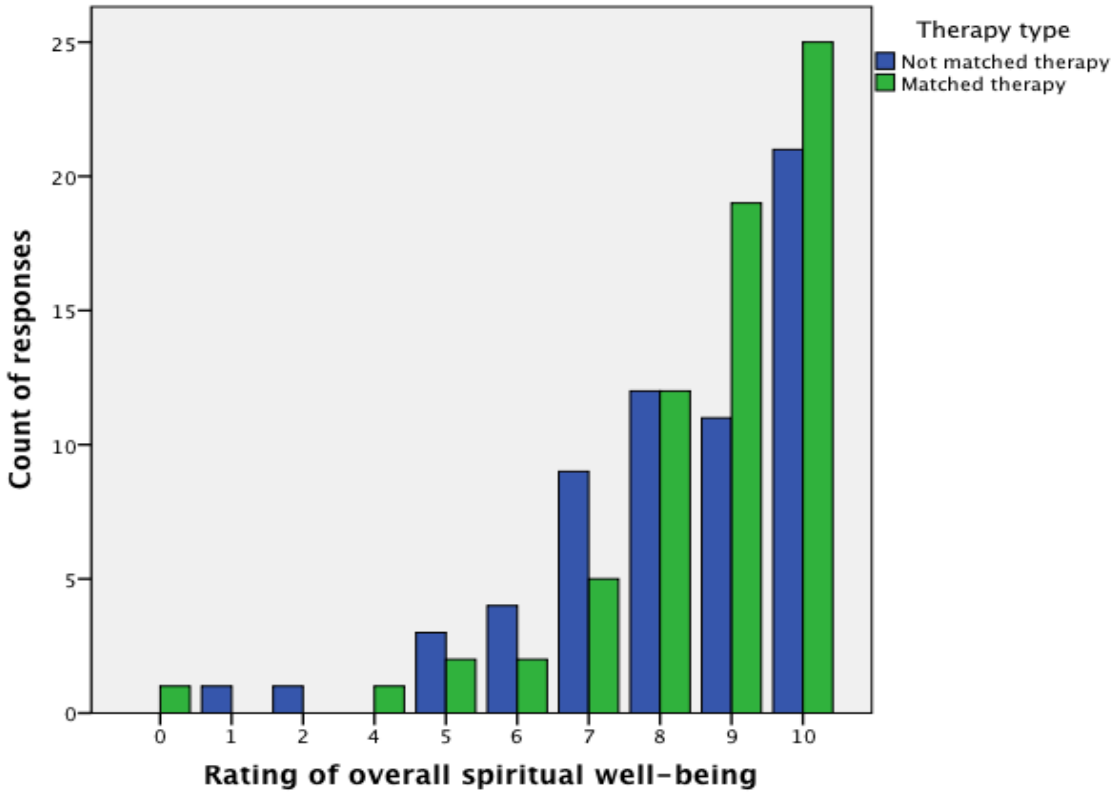

Figure 9. Perception of overall spiritual well-being as reported by patients receiving matched therapy or not matched therapy.

Research Question #3.

Multiple linear regression modeling to determine the relationship between study variables and total TRSC scores (Table 13) revealed that less than 1% of the variance in symptom occurrence and severity was explained by therapy type alone (matched versus not matched), $\Delta R^2 = 0.004$, $\Delta F = 0.57$, $p = 0.45$, which was not statistically significant.

Table 13

Regression Results with TRSC as Dependent Variable

	Step 1					Step 2				
Variable	B	*SE*	*β*	*t*	Sig.	B	*SE*	*β*	*t*	Sig.
Therapy Type	-1.44	1.91	-0.067	-0.754	0.452	-2.96	2.2	-0.137	-1.35	0.181
Age						-0.05	0.09	-0.06	-0.567	0.572
Cancer type						3.2	3.3	0.13	0.984	0.327
Cancer Stage										
Stage 1 (reference category)						0.00	0.00	0.00	0.00	0.00
Stage 2						-4.2	3.3	-0.16	-1.25	0.212
Stage 3						-4.1	3.4	-0.16	-1.19	0.237
Stage 4						-4.9	3.5	-0.21	-1.38	0.169
Length of current therapy						-0.26	0.45	-0.06	-0.586	0.559
Timing of prior line of therapy										
No prior therapy (reference category)						0.00	0.00	0.00	0.00	0.00
< 3 months						6.2	3.1	0.26	2.03	0.045*
> 3 months to < 1 year						3.5	5.96	0.06	0.581	0.562
> 1 year						3.2	6.6	0.05	0.487	0.627
Prior lines of therapy						-0.16	0.42	-0.05	-0.376	0.708
Comorbidities						0.70	0.67	0.10	1.04	0.299

Note. TRSC = Therapy Related Symptom Checklist, B = Unstandardized coefficient, *SE* = Standard error, *β* = Standardized coefficient, *t* = *t*-test, Sig. = Statistical significance

* Indicates significant at $p \leq 0.05$

About 10.3% of the variance in symptom occurrence and severity was explained by the linear combination of all the variables in the model (e.g., therapy type [matched versus not matched], age, cancer type, cancer stage, length of therapy in weeks, number of prior lines of therapy, timing of prior lines of therapy, and number of comorbidities), $\Delta R^2 = 0.10$, $\Delta F = 1.2$, $p = 0.35$, which was not statistically significant.

Type of therapy (matched therapy versus not matched therapy) was not significantly associated with the total TRSC scores after controlling for person (age) and health/illness factors (cancer type, cancer stage, length of therapy, number of prior lines of therapy, timing of prior line of therapy, and number of comorbidities). Patients who had prior therapy less than three months before the onset of the current therapy type had a significantly higher TRSC total score relative to patients with no prior therapy (B = 6.2, $p = 0.045$) after controlling for all other variables in the model. The remaining variables – cancer type, cancer stage, length of therapy, number of prior lines of therapy, and number of comorbidities – were not significantly associated with a higher or lower TRSC total score.

Research Question #4

Multiple linear regression modeling to determine the relationship between study variables and total HRQOL-LASA scores (Table 14) revealed that 3% percent of the variance in HRQOL was explained by therapy type (matched versus not matched), $\Delta R^2 = 0.03$, $\Delta F = 3.6$, $p = 0.06$, which was not statistically significant.

Table 14

Regression Results with HRQOL-LASA scores as Dependent Variable

	Step 1					Step 2					Step 3				
Variable	B	*SE*	*β*	*t*	Sig.	B	*SE*	*β*	*t*	Sig.	B	*SE*	*β*	*t*	Sig.
Therapy Type	2.77	1.46	0.166	1.89	0.060	3.05	1.67	0.183	1.83	0.069	1.99	1.48	0.119	1.34	0.183
Age						0.097	0.070	0.148	1.40	0.165	0.078	0.062	0.119	1.28	0.205
Cancer type						-4.51	2.49	-0.241	-1.82	0.072	-3.35	2.20	-0.179	-1.52	0.132
Cancer Stage															
Stage 1 (reference category)						0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Stage 2						1.48	2.54	0.075	0.583	0.561	-0.035	2.26	-0.002	-0.016	0.988
Stage 3						2.74	2.61	0.151	1.05	0.296	1.27	2.32	0.070	0.544	0.587
Stage 4						-0.165	2.680	-0.009	-0.061	0.951	-1.93	2.39	-0.108	-0.808	0.421
Length of current therapy						0.139	0.338	0.039	0.410	0.682	0.044	0.299	0.012	0.149	0.882
Timing of prior line of therapy															
No prior therapy (reference category)						0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
< 3 months						-3.32	2.34	-0.179	-1.42	0.158	-1.07	2.10	-0.057	-0.508	0.612
> 3 months to < 1 year						-8.49	4.52	-0.197	-1.88	0.063	-7.24	4.001	-0.168	-1.81	0.073
> 1 year						0.496	5.03	0.010	0.099	0.922	1.66	4.45	0.035	0.373	0.710
Prior lines of therapy						0.620	0.322	0.238	1.92	0.057	0.562	0.285	0.216	1.97	0.051*
Comorbidities						-0.361	0.509	-0.068	-0.710	0.479	-0.109	0.452	-0.020	-0.240	0.811
TRSC score											-0.361	0.062	-0.468	-5.80	0.000*

Note. HRQOL-LASA = Health-Related Quality of Life – Linear Analogue Self Assessment, TRSC = Therapy Related Symptom Checklist, B = Unstandardized coefficient, *SE* = Standard error, *β* = Standardized coefficient, *t* = *t*-test, Sig. = Statistical significance

* Indicates significant at $p \leq 0.05$

An additional 11% of the variance in HRQOL was explained by the addition of age, cancer type, cancer stage, length of current therapy, timing of prior line of therapy, number of lines of prior therapy, and comorbidities to the model, $\Delta R^2 = 0.11$, $\Delta F = 1.3$, $p = 0.137$, which was not statistically significant. After adding total TRSC scores to the model, 33% of the variance in HRQOL was explained by the linear combination of all the variables in the model (e.g. therapy type [matched versus not matched], age, cancer type, cancer stage, length of current therapy, number of lines of prior therapy, timing of prior line of therapy, number of comorbidities, and total TRSC score). Twenty percent of the variance in HRQOL was explained by the TRSC score alone, $\Delta R^2 = 0.20$, $\Delta F = 33.6$, $p = < 0.001$, which was statistically significant.

Patients who had a higher number of prior lines of therapy had significantly higher HRQOL-LASA scores (B = 0.56, $p = 0.05$) after controlling for all other variables in the model. Patients who had higher TRSC scores had significantly lower HRQOL-LASA scores (B = -0.361, $p = < 0.001$) after controlling for all other variables in the model. The remaining study variables – age, cancer type, cancer stage, length of therapy, timing of prior line of therapy, and comorbidities – were not significantly associated with a higher or lower HRQOL-LASA total score.

Summary

This chapter has presented the results of this descriptive correlational study using existing data. The results of the first and second research questions addressed the descriptive data of the sample characteristics and specific questionnaire-related data by therapy type respectively. The results of the third and fourth research questions addressed the associations between type of therapy and symptom occurrence and severity and HRQOL respectively, while controlling for relevant variables. Chapter Five will discuss the results as well as their implications for practice, theory, and research.

Chapter Five

Discussion, Conclusions, and Recommendations

This chapter discusses findings relevant to the study and how the results contribute to the knowledge of the symptom experience and HRQOL in patients receiving matched cancer therapy. The study examined the characteristics of patients with breast or gynecologic cancer receiving matched or not matched therapy, their symptom occurrence and severity and HRQOL, as well as associations between type of therapy, symptoms, HRQOL, and person and health/illness factors. Implications for practice and theory will be addressed as well as unanswered questions that are suitable for future research questions.

Significance of the Study

This study is believed to be the first to describe symptom severity and occurrence and HRQOL in patients who received matched therapy and not matched therapy, and to investigate potential associations among person and health/illness factors. Matched cancer therapy as a treatment option for cancer is becoming more common due to the increased availability of genomic profiling in the clinical setting. Patients and clinicians alike desire information about the symptoms associated with matched therapy, their potential severity, and their impact on HRQOL. The study aligns with national research objectives set forth by the NINR, Healthy People 2020, and the NCI to advance the science of symptoms and QOL in the context of chronic diseases and precision medicine (Grady & Gough, 2015; Healthy People, 2015; NINR, n.d.; 2016; Reeve et al., 2014).

Discussion of the Results

Characteristics of Patients by Type of Therapy

The sample of patients in this study was overwhelmingly Caucasian, presumably because the setting was South Dakota where Caucasians represent 86% of the state population (United

States Census Bureau, 2015). The mean age for the entire sample (matched and not matched) was 56 years (*SD* = 10.8), which is comparable to the age of participants in studies examining matched therapy in terms of progression free survival (PFS) (Schwaederle 2015, Andre et al., 2014), but lower than national statistics indicating an average age of 60 years for patients with breast and gynecologic cancers (Howlander et al., 2016). However, patients receiving matched therapy in this study were slightly older on average compared to the patients receiving not matched therapy. This is in contrast to the study by Tsimberidou and colleagues (2014) in which patients receiving matched therapy were proportionately younger compared to patients receiving not matched therapy.

The sample was representative of the patients served at the Cancer Center in which the study was conducted. Breast cancer patients comprised a majority of the sample, which is reflective of the higher number of breast cancer patients seen at the study site as well as of the higher incidence of breast cancers compared to gynecologic cancers (ACS, 2015). Most of the patients in this study had commercial insurance, a finding that is reflective of the mean age of the sample, assuming many switch to Medicare at age 65. Nevertheless, 37% of the patients receiving matched therapy required assistance in addition to their insurance to obtain their drugs compared to just 2% of patients receiving not matched therapy. The finding is understandable given the increased likelihood of drug(s) being prescribed for patients with a type of cancer other than what the drug was originally approved for. This is often referred to as off-label use, which is common in matched therapy as indicated by the list of targeted therapies used in this study (Table 9), most of which are currently approved for cancers other than breast and gynecologic cancer. Currently, for a drug to be approved by the FDA it must have a disease indication (e.g. breast cancer). Even if the drug approved was developed to target a specific alteration that is seen in a variety of different cancers, that drug will still only be approved in a specific type or

types of cancer. Although the FDA does not control provider decisions about which drugs should be prescribed for their patients, insurance companies including Medicare frequently deny coverage of the drug(s) when it/they are used off label. As a result, the lack of insurance coverage for off-label use is a major barrier in the implementation of matched therapy. Even if insurance companies approve the (off-label) use of the matched therapy, Medicare and other insurances have placed many of these targeted cancer therapies on "specialty tiers", which requires payments that are 20% to 40% or more of the drug cost regardless of their income (Balch, 2015). As an example, the drug everolimus costs approximately $10,000 per month. Patients would thus be required to pay $2000 to $4000 for a one month supply, rendering the therapy virtually inaccessible for most without additional assistance outside of patients' insurance. Various foundations in the form of non-profit organizations and patient assistance programs through the pharmaceutical companies exist to assist patients with drug acquisition and/or co-pay help (Association of Community Cancer Centers [ACCC], 2017). However, many organizations will only provide financial assistance if the drug being requested is approved for use in the type of cancer in which it is FDA approved. The need to address these barriers and improve access to drugs is currently being discussed among national organizations like the American Society of Clinical Oncology, and is part of the Cancer Moonshot ^{SM} agenda (NCI, 2016a).

The majority of patients in the study had a family history of cancer. The NCI (2016b) estimates that nearly 40% of men and women will experience a diagnosis of cancer at some point during their lifetime, yet familial patterns of cancers due to inherited genetic alterations (germline alterations) comprise just 5% - 10% of these cancers (NCI, 2015e). A majority of cancers, therefore are due to somatic alterations. Interestingly, there were several study patients with an extensive family history of breast, gynecologic, and/or other cancer(s), suggesting a

pattern of potential germline alterations. Although these patients were referred for genetic counseling during their care, studies have found that cancer patients who meet the criteria for genetic counseling (e.g. extensive family history, young age at diagnosis) are often not referred for genetic testing despite the current guidelines and known importance of this counseling (Meyer et al., 2010; Murff, Byren, & Syngal, 2004; Wood et al., 2014). Even when a patient has already developed cancer, genetic testing is still critical since a germline alteration may suggest that a certain therapy will be beneficial for the patient. Additionally, other family members may be at risk of developing cancer and should be given the opportunity to learn about potential risk mitigation strategies.

All patients receiving matched therapy were receiving targeted therapy, which are listed in Table 9. The patients in this study were not co-enrolled to phase I clinical trials because they were receiving targeted therapy/therapies that were already FDA approved for treatment of some type of cancer. In contrast, previous studies examining matched therapy were phase I or phase II clinical trials testing targeted therapies that were not yet FDA approved (Andre et al., 2014; Schwaederle et al., 2015; Tsimberidou et al., 2012; 2014). About half (51%) of the patients in this study were receiving chemotherapy in addition to the targeted therapy, which is similar to other studies comparing matched and not matched therapy (Schwaederle et al., 2015; Tsimberidou et al., 2012; 2014).

Patients receiving matched therapy had received nearly twice as many prior lines of therapy compared to patients receiving not matched therapy. Studies by Andre et al. (2014) and Tsimeridou (2012; 2014) also showed that patients receiving matched therapy had higher numbers of prior lines of therapy. More than likely, these patients have tried traditional cancer therapies that failed, and were willing to try novel therapies (Rubin, 2015). Conversely, patients receiving not matched therapy were more likely than patients receiving matched therapy to have

no prior therapy. This may be because criteria for inclusion in one of the parent studies (*Using Metformin to Reduce Cardiac Toxicity in Breast Cancer Patients*) was a history of zero to one prior line of therapy. Also, patients who have never received therapy before are expected to receive traditional therapies before receiving matched therapy. Before any new cancer therapy/therapies becomes part of usual care, data must indicate that the therapy/therapies are safe and superior to the usual care. It is typical that new therapies are trialed in patients with more advanced disease. It was therefore not unanticipated that there were more patients with stage 3 disease receiving not matched therapy and more patients with stage 4 disease that were receiving matched therapy.

In this study, patients receiving matched therapy had more comorbidities than patients receiving not matched therapy. Previous studies have found that patients with more advanced cancer and who have lived with cancer for longer periods of time have an increase in comorbidities (Ah et al., 2015; Land, Dalton, Joregensen, & Ewertz, 2012; Morice, Leary, Creutzberg, Abu-Rustum, & Darai, 2016; Patnaik, Byers, DiGuiseppi, & Dabelea, 2011; Urban et al., 2016), but these studies were not conducted within the context of matched therapy. This study found that circulatory diseases and endocrine diseases were the most frequently reported comorbidities, which was also found in other studies of patients with breast and gynecologic cancers (Land et al., 2012; Siegelmann-Daneili et al., 2006; Shah et al., 2014). Known relationships between circulatory diseases and in particular breast cancer exist due to breast cancer therapy-related cardiotoxicities from certain chemotherapies (e.g. anthracyclines), radiation therapy, and targeted therapies (e.g. trastuzumab) (Vo, Nolan, Vance, Patrician, & Meneses, 2017). Relationships between gynecologic and breast cancers and hyperglycemia/hyperinsulinemia have been proposed but not fully characterized (Shah et al., 2014; Sun et al., 2016; Vrachnis et al., 2016).

Symptom Occurrence and Severity

Therapy-Related Symptom Checklist (TRSC) scores. This study found that cancer therapy is associated with a variety of adverse symptoms, which is consistent with prior study reports (Chen & Tseng, 2006; Janz et al., 2007; Kenne-Sarenmalm et al., 2007; Kirkova et al., 2011; Lopez, et al., 2015; Miller-Reilly et al., 2013; Reeve et al., 2014). In this study, the average number of symptoms reported across the sample was eight (M = 8.2), which was essentially equal to the average number of symptoms experienced by patients receiving matched therapy (M = 8.0), and not matched therapy (M = 8.4). Results are similar to those by Janz et al. (2007) who found the average number of symptoms reported in a sample of breast cancer patients that had recently completed cancer therapy was seven. Likewise, Chen and Tseng (2006) reported that the average number of symptoms among patients with a variety of cancers receiving chemotherapy was seven, while Williams et al. (2015a) found the average number of symptoms reported by a sample of patients with different cancer types receiving chemotherapy and/or radiation therapy to be eight. It is noted that, like this study, Williams et al. (2015a) used the TRSC for symptom occurrence and severity assessment in a cross-sectional manner. Other studies have found that patients receiving chemotherapy and/or radiation therapy reported a higher number of symptoms. Spichiger et al. (2011) and Keene-Sarenmalm et al. (2007) found the average number of symptoms to be 14.

Symptom occurrence as reported on the TRSC for this study was similar to that found in past studies using the TRSC (Lopez et al., 2015; Piamjarijakul et al., 2010; Williams et al, 2010a; Williams et al., 2001; Williams et al., 2013; Williams et al., 2010b; Williams et al., 2015a; Williams et al., 2006a; Williams et al., 1997; Williams et al., 2011). For example, the following symptoms—"taste change", "loss of appetite", "nausea", "numbness in fingers and/or toes", "feeling sluggish", and "difficulty sleeping", were symptoms with high reports of

occurrence by patients receiving matched and not matched therapy in this study, as was the case in the Williams et al. (2010a) and Williams et al., (2015a) studies. The symptom with the highest occurrence as reported by patients receiving matched and not matched therapy was "feeling sluggish." Results parallel those from Williams et al. (2010a), Williams et al. (2015a), and Williams et al. (2006a) that also found "feeling sluggish" was the most frequently reported symptom.

In this study, there was little difference in symptom occurrence and/or severity between patients receiving matched or not matched therapy except for "numbness in fingers and/or toes", "difficulty concentrating", "pain", and "hair loss". For patients receiving matched therapy, the second highest occurring symptom was "numbness in fingers and/or toes". It is noted that these patients also had a higher number of prior lines of therapy compared to patients receiving not matched therapy. This is consistent with findings by Lewis et al. (2015), who reported that patients who had received chemotherapy in prior lines of therapy had significantly higher levels of neuropathy (Lewis et al., 2015). Many of the patients receiving matched therapy in this study were currently receiving or had previously received chemotherapy for their cancer, and many of these agents are known to cause nerve damage (Majithia, Loprinzi, & Smith, 2016).

The occurrence of the symptom "difficulty concentrating" was higher for patients receiving not matched therapy, which was interesting since patients receiving matched therapy had a higher number of prior lines of therapy on average. Cognitive impairments such as difficulty concentrating, thinking, and/or memory problems are commonly experienced by patients undergoing cancer therapy (ACS, 2016). The cause of cognitive impairment in cancer patients is likely multifactorial, and prior studies have found links between cognitive impairment and specific chemotherapies (Majithia et al., 2016), anxiety, and depression (Janelsins et al., 2016). It may be that patients receiving not matched therapy in this study were more anxious

about their treatment given less experience with cancer therapy (2.2 previous lines of therapy on average), and thus experienced more difficulty concentrating.

Pain occurrence was higher for patients receiving matched therapy as was its severity. This is perhaps because more patients receiving matched therapy had stage 4 disease, and patients with metastatic disease (where the primary site of cancer has spread to other tissues or organs in the body) frequently experience pain (Gilbertson-White et al., 2011; Kim, Dodd, Aouizerat, Jahan, & Miaskowski, 2009; Reeve et al., 2014). Hair loss occurrence was higher for patients receiving not matched therapy as was its severity, which was related to the higher number of these patients that were receiving chemotherapy. Hair loss is a known side effect of certain chemotherapies, particularly the types of chemotherapies used to treat breast and gynecologic cancers.

Higher TRSC scores correspond to higher symptom occurrence and severity, and in this study, total TRSC scores reported for the 25-item TRSC were 14.7 on average for patients receiving matched therapy, and 16.1 on average for patients receiving not matched therapy. The average TRSC score for patients receiving not matched therapy is similar to findings by Williams et al. (2011) in which patients receiving chemotherapy showed a mean TRSC score of 16.5. Other studies using the TRSC found the mean TRSC scores to be slightly higher compared to mean TRSC scores in this study (Piamjarijakul et al., 2010; Williams et al., 2010b). Piamjarijakul and colleagues (2010) found that the mean TRSC score was 17.9 among a sample of cancer patients in Thailand who were receiving chemotherapy, while Williams and colleagues (2010b) found that the mean TRSC score was 17.7 among a sample of cancer patients in China who were receiving chemotherapy. It is again noted that prior studies using the TRSC were conducted in samples of patients who were receiving not matched therapy. The higher TRSC scores found in the Piamjarijakul et al. (2010) and Williams et al. (2010b) studies could

substantiate prior research showing that Asian women receiving chemotherapy report greater side effects (Bordeanu et al., 2012; Ma, Yeo, Hui, Wing, & Johnson, 2002). Higher TRSC scores may also be related to differences in supportive care measures in other countries compared to the United States. Nonetheless, the average TRSC scores for patients receiving matched therapy in this study were lower compared to previous studies of patients receiving not matched therapy (Piamjarijakul et al., 2010; Williams et al., 2010b; Williams et al., 2011).

In this study, patients receiving matched therapy had a higher number of prior lines of therapy on average and a higher occurrence of stage 4 disease. These patients had lower TRSC scores, which conflicts with previously reported findings that patients who have received multiple lines of therapy, and/or have advanced stages of cancer have higher symptom burdens (Boland et al., 2013; Kaufman, 2015; Kirkova et al., 2011; Lewis et al., 2015; Palmieri, 2015; Walsh et al., 2000). Potentially, this could be because many of the patients had tried traditional therapies, failed, and were running short on further treatment options. These patients may under-report symptoms out of fear that they will be taken off a potentially life-extending therapy, and although clinicians admit concern about this based on the investigator's experience, there is no existing data to support this concern. Results may also be because patients receiving matched therapy had prior cancer therapy-related symptom experience as indicated by a higher number of stage 4 cancers (more advanced disease) and a higher mean number of prior lines of therapy. Consequently, the patients and/or their clinicians may have become more proficient at managing symptoms over time. This is supported by the findings of Williams et al. (2011) in a study conducted among a sample of patients receiving chemotherapy and/or radiation therapy who completed the TRSC at three time points: baseline, approximately three weeks after starting therapy, and approximately six weeks after starting therapy. After an initial rise in mean TRSC scores at the second time point (compared to baseline), mean TRSC scores decreased at the third

time point. Stabilization or improvement of symptoms over time is congruent with findings by other investigators including Dujit et al. (2011), Given et al. (2002); Visser et al. (2000), and Williams et al. (2013), but is in contrast to Spichiger et al., (2011), who found that compared to baseline, symptoms of patients receiving chemotherapy significantly increased when assessed two and three months after the start of chemotherapy. These divergent results may be related to the interventions performed to alleviate the symptoms in the studies showing symptom improvement over time (Dujit et al, 2011; Given et al. 2002; Williams et al., 2013). For this study, the assessment of symptoms in both groups occurred at similar time points to each other (6.8 weeks for patients receiving matched therapy versus 7.6 weeks for patients receiving not matched therapy), which is comparable to the second and third time points of symptom assessments in the Spichiger et al. (2011) and Williams et al. (2011) studies respectively. Since symptom assessments were not performed longitudinally in this study, it is unknown whether symptoms had initially worsened and improved over time, or became more severe over time after the start of matched or not matched therapy.

The TRSC was developed in 1997 and much has changed in cancer care over the past 20 years. Although many symptom items are still relevant to today's therapies, several items were not frequently experienced including "jaw pain" (6%), "fever" (9%), and "soreness in vein where chemotherapy was given" (10%). Jaw pain is a potential side effect of a small number of chemotherapies; chemotherapies that are not used to treat breast or gynecologic cancers. Soreness in the vein where the chemotherapy is administered also may have less relevance than previously since most patients have central venous lines for infusions versus peripheral intravenous catheters. Also, many contemporary cancer therapies are taken orally. Future studies should determine the relevance of these items in a broader cancer population.

A substantial number of patients added symptoms to the TRSC compared to prior studies, suggesting the TRSC may not fully capture the symptoms related to newer treatment modalities. In all, 21 patients added symptoms to the TRSC, and surprisingly more patients receiving not matched therapy added symptoms compared to patients receiving matched therapy. This could be because many patients receiving not matched therapy had less experience with cancer treatment and were therefore motivated to report their symptoms in greater detail. All patients, regardless of the type of therapy they received, knew that they were in a research study and were fully informed of the therapies they were receiving for their treatment regimen. This may have led to the patients' increased motivation for reporting detailed symptom information, since they were aware that researchers were seeking this information.

The mean TRSC score with the added symptoms was lower for patients receiving matched therapy compared to patients receiving not matched therapy. This was unexpected since patients receiving matched therapy were receiving novel combinations of therapy. Results may suggest that symptoms are not significantly different between matched or not matched therapy, or results may suggest that symptoms are not fully captured on the TRSC. Diarrhea was the most common symptom added for both groups. Other studies using the TRSC also reported the addition of diarrhea (Williams et al.2010; Williams et al., 2015a), which suggests it is a symptom that should be considered for inclusion in a revised version of the TRSC. This addition is supported by the work previously described by Miller-Reilly (2013) and Reeve et al. (2014), in which diarrhea was identified as one of 12 core symptoms that should be assessed in oncology clinical trials. Skin changes was another symptom frequently added by participants in this study. Conceptually, the added symptoms: "rash", "peeling skin", and "nail changes", could be collapsed under skin changes. Providing a descriptor for each TRSC symptom or allowing space along side of each existing symptoms for patients to add their variation of the TRSC symptom

would be beneficial. In this study, several added symptoms had unclear meanings such as "toe," or "right upper hip." It would have been helpful if the meaning of these added symptoms items were clarified in real time with the patient, at which time a descriptor could be added, or the item correctly classified. It is worth noting that several symptoms added by the patients were objective side effects rather than subjective, including "neutropenia" and "delayed wound healing." The patient reporting neutropenia was reporting an objective toxicity of the therapy, but she was not *experiencing* the symptom of neutropenia. Clarification by the research coordinator would have been helpful to understand if the patient was reporting neutropenia or delayed wound healing because the patient was experiencing symptoms stemming from these side effects (e.g. fever related to neutropenia, or pain related to delayed wound healing).

The TRSC demonstrated good reliability in this study. Desired values for Cronbach's alpha are 0.70 or higher in an instrument's early development stages, while a value of at least 0.80 is appropriate for instruments in later stages of development (Ferketich, 1990). Cronbach's alpha for the original 25-item TRSC was 0.83, and 0.81 with the added symptoms, indicating good reliability/internal consistency. This is consistent with other studies using the TRSC, that reported Cronbach's alpha from 0.70 to 0.83 (Gonzalez et al., 2011; Piamjariyakul et al., 2010; Williams et al., 2001; Williams et al., 2006a; 2006b; Williams et al., 2010a; 2010b; Williams et al., 2011; Williams et al., 2013; Williams et al., 2015a).

Health-Related Quality of Life

Health-Related Quality of Life – Linear Analogue Self Assessment (HRQOL-LASA) scores. As a whole, the sample reported relatively high HRQOL with a combined mean HRQOL-LASA score of 46.8 (SD = 8.4). In a study by Sreedhar (2016), mean HRQOL-LASA scores for patients undergoing chemotherapy and/or radiation therapy were lower (M = 44.2) compared to this study. Other studies using instruments to measure HRQOL other than the

HRQOL-LASA have shown that HRQOL levels among cancer patients are similar to healthy controls (DeBoer et al., 2000; Ganz et al., 2004; Hammerlid & Taft, 2001; Rudberg et al., 2002). Results from this study suggest that despite a life-threatening illness and pervasive symptoms, cancer patients maintain a reasonably high HRQOL.

This study found that the average total HRQOL-LASA score was higher for patients receiving matched therapy ($M = 48.1$, $SD = 7.5$) than the average total HRQOL-LASA score for patients receiving not matched therapy ($M = 45.4$, $SD = 9.1$). Patients receiving matched therapy had lower mean TRSC scores in this study, therefore it was not surprising to see that they also had higher HRQOL-LASA scores. This is consistent with prior studies showing that patients who reported lower TRSC scores also reported higher HRQOL-LASA scores (Gonzalez et al., 2011; Heinze, 2012; Williams et al., 2013; Williams et al., 2011). Since patients receiving matched therapy also had a higher number of prior lines of therapy, results may have been related to an increased efficacy in symptom management over time and thus improvement in HRQOL.

Improvement in cancer patients' HRQOL over time was not measured in this cross-sectional study, but is supported in multiple other studies (Burkett & Cleeland, 2007; Hess & Stehman, 2012; Huang et al., 2013; Jeffe, Perez, Cole, Liu, & Schootman, 2016; Leung, Pachana, & McLaughin, 2014; Taira et al., 2011). Longitudinal studies have shown that despite short-term decreases in QOL during chemotherapy (Ganz et al., 2011; Jeffe, et al, 2016; Taira et al., 2011), QOL often improves significantly over time (Burkett & Cleeland, 2007; Hess & Stehman, 2012; Huang et al., 2013; Jeffe et al., 2016; Leung et al., 2014). Many of these studies, however, contained a population that was being treated for curative intent, and thus had a finite treatment period. Other longitudinal studies of patients with metastatic disease found that patients reported lower HRQOL around the time of diagnosis, but that over time, their HRQOL

improved (Anderson, Carpenter, Yang, & Shapiro, 2007; Willis, Lewis, Ng, & Wilson, 2015). These findings are consistent with those by Meisel et al. (2012) who showed that women living with metastatic breast cancer for greater than five years reported higher overall QOL compared to women newly diagnosed with metastatic disease. These studies may indicate increased coping strategies or resiliency, which has been associated with increased HRQOL in other studies (Chirico et al., 2017; Filazoglu & Griva, 2008). In this study, patients receiving matched therapy may have had greater coping strategies and thus higher HRQOL. Although this study did not capture the patients' time since diagnosis, it can be inferred that patients receiving matched therapy had been diagnosed for a longer period since there was a higher frequency of stage 4 disease and a higher number of prior lines of therapy in this group. Patients who were receiving not matched therapy may still be adjusting to the emotional and physical changes that a cancer diagnosis brings, thereby reflecting a lower HRQOL-LASA score.

Another potential reason for higher reports of HRQOL in patients receiving matched therapy is that patients gained hope from a novel therapy. Several qualitative-based studies have indicated that hope is an indicator of higher QOL (Luoma & Hakamies-Blomqvist, 2004; Sarenmalm, Thoren-Jonsson, Gaston-Johansson, & Ohlen, 2009; Svensson, Brandberg, Einbeigi, Hatschek, & Ahlberg, 2009). Luoma & Hakamies-Blomqvist (2004) found that continuing cancer treatment allowed patients to feel comforted and optimistic about their QOL and longer survival. This was consistent with findings by Sarenmalm et al. (2009) who found that women with breast cancer associated hope with continuing treatment, and that their biggest fear was being told there were no other treatment options. Many patients who seek matched therapy have limited treatment options. Perhaps by being able to continue to fight their cancer with additional therapy, they are more hopeful and thus have higher HRQOL. The investigator's clinical experience confirms that patients who seek matched therapy are hopeful about the potential of

the increased efficacy associated with matched therapy, but there were no existing studies found on this topic. Since patients receiving matched therapy may have been living longer with cancer, they may have participated in support programs to help them cope and foster hope, which led to increased HRQOL. Support programs for patients with cancer include strategies to improve coping skill that have been shown to increase patient hope levels (Lichwala, 2014). Other studies have reported an association between increased hope and decreased distress (Stanton et al., 2000), as well as positive experiences of living with cancer, including personal and spiritual growth (Ahmad, Muhammad, & Abdullah, 2011; Chunlestskul, Carlson, Koopmans, & Angen, 2008; Sarenmalm et al., 2009), having a new perspective on life, and an increased gratitude for their own life (Sarenmalm et al., 2009).

In addition to mean total HRQOL-LASA scores, mean ratings on overall QOL, overall mental well-being, overall physical well-being, overall emotional well-being, level of social activity, and overall spiritual well-being were higher for patients receiving matched therapy than for patients receiving not matched therapy. That the mean score for, "level of social activity" was more than one point higher for patients receiving matched therapy compared to the mean score for patients receiving not matched therapy was surprising in a group where the majority of patients had advanced disease. It could be that patients with advanced disease are more intentional with their social activities or attempt to enrich their relationships (Burkett & Cleeland, 2007). Svensson and colleagues (2009) found that certain actions such as seeking social support positively impacted HRQOL, and served as an important coping mechanism. Leung and colleagues (2014) found social support to be an important influence on HRQOL, which is consistent with other studies (Park, Bae, Jung, & Kim, 2012; So et al., 2012). It should be noted that most of these studies were conducted in the breast cancer population; data on HRQOL in gynecologic patients are sparse and mostly related to surgical outcomes.

Cronbach's alpha for the HRQOL-LASA was 0.89, thereby indicating good reliability/internal consistency. Results align with prior studies using the HRQOL-LASA, that reported Cronbach's alpha from 0.83 to 0.93 (Heinze, 2012; Locke et al., 2007).

Multiple Linear Regression

Associations between type of therapy and symptom occurrence and severity. In this study, therapy type (matched or not matched therapy) was not significantly associated with symptom occurrence and severity (total TRSC score) and only explained 1% of the variance in symptom occurrence and severity when entered into the regression model alone. Although this study did not find a significant association between therapy type and symptom occurrence and severity, the findings have important clinical implications. This study is the first of its kind to demonstrate that, in this sample, symptom occurrence and severity was not any worse for patients receiving matched therapy. Indeed, mean TRSC scores were lower for patients receiving matched therapy. The implementation of matched therapy is a new concept in routine oncology practice, and based on the investigator's clinical experience, many clinicians are fearful of the potential side effects caused by novel drug combinations. Although not specific to matched therapy, this concern was articulated by Dy and Adjei (2013) who cited frequent and severe toxicities associated with targeted therapies. They argued that the toxicities were no less severe, just different compared to chemotherapy. It should be noted that the toxicities discussed by Dy and Adjei (2013) were determined by a clinician and not self-reported by the patient. Understandably, oncology clinicians might be uneasy with implementing matched therapy since it has not been examined in traditional clinical research phased studies (NCI, 2016b) prior to clinical use. However, the average amount of time elapsed during the phased study process is approximately 14 years (ACS, 2016). With the rapid increase of knowledge about cancer biology being gained by genomics, and with the potential promise of improved outcomes with

matched therapy, waiting 14 years is no longer acceptable for many patients or clinicians (DeVita et al., 2014; Mukherjee, 2016). This has led to a larger, societal-wide discussion of using matched therapy in cancer care (Gladwell, 2015; Mukherjee, 2016). Many patients, clinicians, and scientists believe that while protecting patients is vital, there is also an inordinate amount of over-regulation that occurs in both drug development and in conducting clinical trials that ultimately prevents patients accessing the drugs they need (DeVita et al., 2014). Furthermore, traditional cancer clinical trials are meant to find statistical significance between groups of heterogeneous patients, yet with the movement toward personalized medicine the groups will be inherently smaller (DeVita et al., 2014). This is important to recognize when examining statistical significance of symptoms in cancer trials since adequate power to achieve statistical significance may not be attainable in single-studies. Meta-analyses of smaller, single studies may be needed to address this issue. Also, in the context of matched therapy or other personalized medicine initiatives, descriptive statistics can offer important clinical information for the patient and clinicians.

The only variable significantly associated with symptom occurrence and severity in this study was the timing of the prior line of therapy. Patients who had prior therapy less than three months before the onset of the current therapy type had significantly higher TRSC scores compared to patients who had no prior therapy. Surprisingly, data to support the relationship between the timing of the prior line of therapy and symptom occurrence and severity are lacking. Boland et al., (2013) characterized symptom burden in a sample of patients with multiple myeloma and assessed the median number of years since diagnosis as well as number of lines of prior therapies, but did not include the timing of the prior line of therapy. Likewise, Lewis et al. (2015) and Kirkova et al. (2011) examined multiple factors influencing the symptom prevalence of cancer patients, including the number of years since diagnosis and if they had received prior

therapy, but the timing of the prior line of therapy was not included in the model. Janz and colleagues (2007) did collect data regarding the time interval from initial surgical treatment for breast cancer to the time of questionnaire completion (symptom experience and QOL measures), yet the researchers did not control for this variable in the regression model. The results of this study suggest that the timing of the prior line of therapy is an important factor to examine in future studies regarding the symptom experience of cancer patients.

The person and health/illness variables originally chosen for this study (age, cancer type and stage, length of current therapy, number of prior lines of therapy, number of comorbidities) for inclusion in the multiple linear regression were also not significantly associated with TRSC total scores. This conflicts with other studies showing significant associations between higher symptom burdens and younger age (Cataldo et al., 2013; Kirkova et al., 2012), higher symptom burdens and higher stages of disease (Kirkova et al., 2011; Walsh et al., 2000), higher symptom burdens and longer length of therapy (Spichiger et al., 2011), higher symptom burdens and a higher number of prior lines of therapy (Lewis et al., 2015), and higher symptom burdens and a greater number of comorbidities (Hamaker et al., 2014; Shayne et al., 2006; & Van Cleave et al., 2013). Concerning stage of cancer however, findings are consistent with those by Valeberg and Grov (2013) who found no significant association between symptoms and stage of cancer. For this study, results may be because there were differences between how gynecologic and breast cancers were documented in the EHR in terms of stage. Patients with gynecologic cancers were staged at diagnosis (usually at the time of surgery) and that stage did not change even if the disease later became metastatic. For example, a patient who was diagnosed with stage 3 disease and whose cancer later metastasized was still referred to as having stage 3 disease. Patients with breast cancer, however, were staged according to their current state. Thus, a patient with breast cancer diagnosed with stage 3 disease, whose cancer later metastasized, was classified as stage 4.

Still, the overall model explained only 10% of the variance in symptom occurrence and severity, suggesting that the symptom experience is a complex and multifactorial process, and there were other factors that influenced the symptom experience not accounted for in this study.

Potentially, the side effect profile of each individual therapy/drug was an influential factor on TRSC total scores. Patients receiving not matched therapy were generally receiving chemotherapy only, while patients on matched therapy were receiving a combination of chemotherapy and targeted therapy or targeted therapy alone. Each drug class has certain side effects, some of which are unique and some of which overlap with other drug classes. Descriptive data regarding the type of concurrent therapy were collected, but were not included in the linear regression models. This would have been difficult to execute since the drug combinations were vast and the study would have been under-powered to account for every possible combination.

Other person factors not accounted for that may also have influenced symptom occurrence and severity include socioeconomic status (SES), education levels, and symptom management interventions. The type of insurance and type of drug coverage were collected for the descriptive aspect of this study, but were not included in the linear regression models. Income levels were not collected in this study, however, past studies have found that lower income levels were predictive of an increased number of symptoms in cancer patients (Ashing-Giwa & Lim, 2011; Barton-Burke, Smith, Frian, & Loggins, 2010; Bickell & Cohen, 2008; Eversley et al., 2005; Vona-Davis, & Rose, 2009). Education levels may also influence a patient's ability to self-manage symptoms, although there is surprisingly little research found on this topic. A study by Herdon, Kornblith, Holland, and Paskett (2008) revealed that a lower education level was significantly associated with poorer outcomes (e.g. survival) in a secondary analysis of 1,577 patients with lung cancer. The authors also found that lower levels of

education were significantly associated with poorer performance status, which may be due to symptoms, however symptoms were not reported in the study (Herdon et al., 2008). In contrast, the study by Leach and colleagues (2015) did not find education to significantly influence chronic symptoms and comorbidities in a sample (*N*=1527) of long-term cancer survivors, including patients with a history of breast and gynecologic cancers. However, education level may have an impact on the patient's sense of self-advocacy, since patients with higher education levels may be more resourceful and seek out additional information and/or support. A qualitative study by Smith, Dixon, Trevena, Nutbeam, and McCaffery (2009) revealed that compared to patients with higher education levels, patients with lower education levels were less involved in decision making related to their own health care needs and generally relied on the provider to tell them what to do. Future studies should explore additional person factors and their influence on symptom occurrence and severity.

This study also did not collect data on nor control for types of interventions for symptom amelioration, which can influence symptom occurrence and severity. A variety of interventions are typically prescribed and suggested for patients that are receiving cancer therapy. For example, medications to control nausea, pain, sore mouth, numbness in fingers and/or toes, etc. are often prescribed. Other non-medication interventions typically suggested are massage, exercise, acupuncture, and dietary changes. Multiple prior studies using the TRSC also used a companion self-report tool called the Self Care Method (SCM) form (Williams et al., 2010a; 2010b; Williams et al., 2015; Williams et al., 2006a; Piamjariyakul et al., 2010). The SCM form is based on the TRSC so that if symptoms are reported, the patient is asked to also report what self-care method(s) they used to control the symptoms and if the intervention was helpful (Piamjariyakul et al., 2010). As previously mentioned, patients receiving matched therapy had a higher number of prior lines of therapy and therefore may have implemented previously

developed strategies to alleviate symptom occurrence and/or severity. Perhaps by using the SCM in tandem with the TRSC with future studies, categories could be created based on the type of intervention used for the symptom(s) and included in the regression model to examine potential associations between type of intervention and symptom occurrence and severity. This study would have been under powered with the addition of this variable, but could be considered for future research. Overall, findings from this study provide initial evidence that the implementation of matched therapy showed little change in to the patients' symptom experience.

Associations between type of therapy and health-related quality of life. This study found that therapy type (matched versus not matched) was not significantly associated with HRQOL (total HRQOL-LASA score), and alone, only explained 3% of the variance in HRQOL-LASA scores. This is the first known study examining the associations between therapy type (matched or not matched) and HRQOL in a sample of breast and gynecologic cancer. As previously discussed, this is clinically important since there is no prior data documenting the impact on patients who are receiving matched therapy. Understanding the impact of new cancer therapies and treatment modalities on patients not only in terms of survival but also on patient reported outcomes like HRQOL is crucial to patients and clinicians in order to have meaningful discussions about specific therapy-related risks and benefits (Bottomley et al., 2005; McFarland, 2014; Osaba, 2011). Findings from this study showed that HRQOL was no worse when receiving matched therapy, and that even though it was not statistically significant, that the mean total HRQOL-LASA score was higher for patients receiving matched therapy.

The added person and health/illness variables of age, cancer type and stage, length of current therapy, timing of prior lines of therapy, number of prior lines of therapy, and comorbidities to the model explained 11% of the variance in HRQOL, which falls within the 9% to 27% variance in HRQOL found by Janz et al. (2007) for person factors (sociodemographic)

and health/illness factors (prior health status, clinical, and diagnosis factors) among breast cancer patients. On its own, age was not found to be significantly associated with HRQOL, which confirms findings from Gotze, Ernst, Brahler, Romer, and von Klitzing (2015) but differs from findings by Mkanta, Chumbler, Richardson, and Kobb (2007), who found that older patients consistently reported better HRQOL compared to their younger counterparts. The average age of the patients in the Mkanta et al. (2007) study was higher ($M = 63.7$) compared to the average age of patients in this study ($M = 56$) however, and the sample size was small ($N = 48$). Cancer stage was also not significantly associated with HRQOL in this study, which contrasts with findings from other studies (Ferreira et al., 2008; Gotze et al., 2015). Ferreira et al. (2008) for instance found that the presence of metastases was associated with lower HRQOL scores in the physical domain, while Gotze et al. (2015) found that patients with cancer stages from 0 – 2 had higher HRQOL scores in the mental domain compared to patients with cancer stages from 3 – 4. As discussed in the previous section, the differences between how the gynecologic and breast cancers were documented in the EHR in terms of stage is acknowledged, which may have implications for identifying a significant relationship between stage and HRQOL.

Cancer type was not associated with HRQOL in this study. This confirms findings from Popovic et al (2013) who examined predictors of QOL among a sample of cancer patients across 17 total studies using weighted linear regression analysis. However, only three of the 17 studies contained a sample of cancer patients with heterogeneous diagnoses; the majority of the studies in the analysis were patients with the same diagnosis. The number of comorbidities was also not associated with HRQOL in this study. Results are in contrast to those from Wu and Harden (2015) who found that patients with an increased number of comorbidities had significantly poorer QOL. However, patients in this study had a higher symptom burden, thus it is unclear if the higher number of comorbidities or the higher symptom burden was associated with poorer

QOL. It should be noted that the aforementioned comparison studies used HRQOL instruments other than the HRQOL-LASA in their analysis, which does not allow for direct comparisons given the potential differences in the underlying health dimensions assessed.

In this study, higher number of prior lines of therapy was associated with a higher HRQOL. This was an unexpected finding, but could be reflective of the difference in HRQOL between patients who are newly diagnosed and patients who have been diagnosed with cancer for a longer period as previously discussed for TRSC scores. This conflicts with findings by Gotze and colleagues (2015) who found that patients who had been diagnosed with cancer for a longer period had lower physical and mental HRQOL scores. Brothers and Andersen (2009) found that for women who were newly diagnosed with breast cancer, feelings of hopelessness and difficulties in adjusting to their diagnosis were common. Other studies have shown that HRQOL in women with metastatic breast cancer improves over time (Andersen et al., 2007; Oh et al., 2004; Meisel et al., 2012). Longitudinal improvements in self-care and self-symptom management and effect on HRQOL was not measured in this cross-sectional study.

The addition of symptom occurrence and severity (measured by the total TRSC score) to the model explained 20% of the total variance in HRQOL. The analysis showed that symptom occurrence and severity was significantly associated with HRQOL after controlling for all other variables in the model. These findings were confirmed by Janz et al. (2007) who found that symptom burden accounted for 18% to 60% of the variance in QOL outcomes in a sample of breast cancer patients. However, patients in this study had recently completed or stopped cancer therapy, and were not currently on therapy while the symptom assessments were taken. Like this study, Gonzalez et al. (2011) used the same symptom and HRQOL instruments (TRSC, HRQOL-LASA), and found that higher symptom scores were significantly associated with lower HRQOL scores. Other studies have also found that a higher symptom burden from cancer and/or

cancer therapies is significantly associated with poorer HRQOL (Ferreira et al., 2008; Gonzalez et al., 2011; Huang et al., 2013; Hyland & Sodergren, 1996; Miaskowski et al., 2006; Montazeri, 2008; Sloan, Cella, & Hays, 2005; Smith et al., 2013; Williams et al., 2013; Williams et al., 2011). In contrast, a number of other studies have shown that despite persistent cancer therapy-related symptoms, HRQOL isn't always impacted (DeBoer et al., 2000; Ganz et al., 2004; Hammerlid & Taft, 2001; Rudberg, Carlsson, Milsson, & Wikblad, 2005). However, these studies were conducted in samples of patients who had completed their cancer therapy, and with different symptom and HRQOL measures.

Study results suggest that symptom occurrence and severity significantly influences HRQOL among patients receiving matched therapy and not matched therapy, and that symptoms and HRQOL are separate concepts that are influenced by multiple factors. Assessments of HRQOL in cancer care have greatly increased over the years, but patients and clinicians also desire concrete information about what symptoms to anticipate with new therapies. Neither HRQOL nor symptom occurrence and severity can serve as proxies for one another. For novel cancer therapies like matched therapy, it will be important to collect data on the symptoms experienced as well as HRQOL.

Study Limitations

There are a number of limitations to this study. The retrospective, correlational design in addition to the cross-sectional nature of the data limits the study to assessment of association not causation (Shadish et al., 2002). The patients' symptoms (TRSC score) and HRQOL (HRQOL-LASA scores) were unknown at baseline, prior to starting the matched or not matched therapy. Therefore, potentially significant differences in symptoms and HRQOL between patients receiving matched versus not matched therapy at baseline may have existed. After completing the TRSC and HRQOL-LASA measures, patients may have had more difficulty in tolerating

their therapy, which was not captured in this study by repeat measurement of symptoms and HRQOL. In addition, data on the characteristics of patients who did not complete the TRSC and HRQOL during treatment was not collected, thus unknown, thereby possibly decreasing the generalizability of the study. Other limitations to generalizability include the homogenous ethnic and the female-only sample. Differences in symptom occurrence and severity as well as HRQOL may exist among different ethnic groups, between genders, or among patients with different types of cancer and future studies should consider a more diverse population.

Another limitation is that the type of concurrent therapy may have influenced TRSC and HRQOL-LASA scores, which was not measured in this study. Likewise, the type of prior lines of therapy were not included in the regression analysis. Although different therapies and/or treatment modalities can cause different symptoms, accounting for each different combination is probably not feasible for the analysis. However, collapsing the concurrent and/or prior line of therapy drugs into classes (e.g. chemotherapy only, targeted therapy only, combination chemotherapy/targeted therapy) and entering these into the linear regression model could be considered in future studies. It should be noted that the operational definition of the variable, "prior lines of therapy" in this study was different than other research studies and different from their quantification in clinical practice. For example, the treatment plan for a patient with breast cancer receiving neoadjuvant therapy would traditionally be referred to as one line of therapy but may include the following: two phases of chemotherapy, surgery, radiation therapy, and endocrine therapy. A different patient with breast cancer may undergo surgery followed by radiation therapy, which in traditional terms would also be referred to as one line of therapy. To more appropriately examine the effect of prior therapy on symptom occurrence and severity for this study, the decision was made to count each phase as a line of therapy due to the nature of therapy-related symptoms compounding one another. Therefore in the former example, the

number of lines of therapies would be recorded as five, and the latter example would be counted as two. This may have limited the comparison of results between studies. Moreover, prior studies examining outcomes of matched therapy have classified patients receiving endocrine therapy and/or trastuzumab as receiving matched therapy since the therapies are "matched" to the tumor's ER/PR and HER2 status respectively regardless of their genomic profiling results. In this study, endocrine and/or trastuzumab therapy that was *not* chosen based on genomic profiling results was considered not matched, thereby potentially limiting the ability to detect differences between groups and the ability to compare to other studies. Lastly, patients in this study rated their HRQOL relatively high overall which may have limited the ability to detect an association between therapy type and HRQOL.

Implications for Study Conceptual Framework

The conceptual framework used for this study was the SMT (Dodd et al., 2001) and research questions focused on the symptom experience as measured by the TRSC and the outcome of quality of life as measured by the HRQOL-LASA. Person (age, ethnicity) and health/illness (cancer therapy type, cancer type and stage, comorbidities, number of prior lines of therapy, timing of prior line of therapy, and length of therapy) variables were identified from the SMT for inclusion in this study. Results from this research study provided support for the relationship between health/illness factors and the symptom experience and can serve as a hypothesis-generating study to advance symptom and HRQOL-related knowledge in contemporary cancer care. Specifically, this study found a significant relationship between the timing of the prior line of cancer therapy and the symptom experience. That is, patients who had received a prior line of cancer therapy within three months of the current therapy had significantly higher symptom occurrence and severity scores compared to patients with no prior therapy. Consistent with the SMT, this study also found a relationship between the symptom

experience and the outcome of QOL. Specifically, lower symptom occurrence and severity was associated with higher HRQOL. Interestingly the health/illness variable—number of prior lines of therapy—was significantly associated with HRQOL, indicating that perhaps components within the "symptom management strategies" concept may directly or indirectly influence HRQOL, which were not measured in this study. Future research should re-examine the link between the health/illness factor—therapy type (matched or not matched therapy)—and the patient symptom experience as well as HRQOL using a larger number of patients. Additionally, future research should examine the link between the components of symptom management strategies and the symptom experience and HRQOL for patients receiving matched versus not matched therapy.

Recommendations for Future Research

This is the first study to examine symptom occurrence and severity and HRQOL in cancer patients receiving matched therapy. Prospective, longitudinally-designed studies are needed to adjust for baseline differences and to follow changes in symptoms and HRQOL over time. One way to achieve this is to embed symptom and HRQOL collection within cancer treatment clinical trials. In doing so, results from larger sample sizes can be examined and researchers can also investigate the effect symptoms may have on adherence to cancer therapies that may ultimately contribute to overall survival. Most of the studies concerning symptoms and HRQOL have been conducted in samples of Caucasian women with breast cancer, therefore conducting future studies in a more heterogeneous population will also be important for generalizability purposes.

This study classified patients as receiving matched therapy if their therapy was guided by genomic profile results. Other studies examining the efficacy of matched therapy considered therapies targeting hormone receptors (e.g. endocrine therapy) and/or HER2 receptors (e.g.

trastuzumab) as matched therapy even if the patients did not undergo genomic profile testing (Schwaederle et al., 2015). Future studies with larger sample sizes could also take into account personalized therapies that were chosen for reasons other than genomic testing to assist in the ability to detect differences between groups more robust.

Future research should include the evaluation of the adequacy of symptom assessment tools, including the TRSC. The importance of assessing cancer therapy-related symptoms will continue to grow given the rise of targeted therapies, many of which are given orally, continuously, and for longer durations. Symptoms that occur from these therapies may be more chronic in nature and thus under-reported by clinicians (Kluetz et al., 2016). Ongoing qualitative and quantitative studies are paramount to elicit relevant and meaningful cancer therapy-related symptoms. The TRSC was developed over 20 years ago and given the change in cancer therapies, under-reporting of relevant symptoms may occur. The potential for the under-reporting of symptoms is supported by the substantial proportion of the sample that added symptoms to the TRSC for this study (n = 37, 29%). It is important to confirm these findings in future studies since multiple other studies using the TRSC found that fewer than 2% of patients have added symptoms (Piamjariyakul et al., 2010; Williams et al., 2001; Williams et al., 2006a; Williams et al., 2010a; 2010b; 2011; 2013; 2015). Many of the prior studies using the TRSC were conducted outside of the United States, therefore differences in the symptom experience and/or differences in the self report of symptoms may exist due to culturally-related factors and thus warrant further examination in future studies. In addition to the large number of added symptoms, this study also found that several symptoms on the TRSC were infrequently encountered (jaw pain, soreness in vein where chemotherapy was given, fever), suggesting the need for future revisions so that relevant and meaningful symptoms are being assessed. Validation of the revised TRSC should be completed that includes patients receiving matched

therapy. Also, validation of the psychometric properties of the HRQOL-LASA should be performed with patients receiving matched therapy since this instrument has not been previously validated in this population. The Cronbach's alpha for both measures however showed good reliability in this study, and the strong inverse correlation between the measures (B = -0.361, p = 0.000) found in the regression analysis demonstrated construct validity.

Historically, most oncology clinical trials have captured only objective therapy-related side effects, referred to as adverse events (AEs). Capturing AEs is a routine part of any clinical trial and a standardized assessment called the Common Terminology Criteria for Adverse Events (CTCAE) is used. Assessment of these AEs, however, is done by the clinician, even for symptoms like nausea or peripheral neuropathy. Organizations such as the NCI and FDA have advocated for patient reported symptom-assessments since patients are best positioned to report their own symptoms (Kluetz, Chingos, Basch, & Mitchell, 2016). A standardized symptom assessment across oncology clinical trials will be important to compare and examine important information about tolerability of cancer therapies, leading to meaningful discussions about risk-benefit with the patient. Comparing findings across trials may become increasingly necessary since future cancer therapy trials involving matched therapy may not be adequately powered due to the diverse and substantial number of potential therapy combinations. The TRSC is an efficient instrument for patients and clinicians in a clinical setting, but it's completeness for research purposes requires further investigation. Studies using the TRSC plus other symptom assessment tools should be considered for establishing concurrent validity.

Future studies should examine potentially important mediator and moderator variables given the complexity of and multiple influences on the symptom experience and HRQOL. One variable that is becoming increasingly important in cancer care and that deserves further exploration is the financial impact on patients. Medical debt caused by cancer care is an

unfortunate reality (Zafar, 2015) and has been linked to poorer HRQOL (Fenn et al., 2014; Zafa et al., 2015), poorer quality of care, and limited access to contemporary cancer care (Zafar, 2014). Out-of-pocket costs are exceptionally high for cancer patients, often because the cost of their medications require high co-pays. This may include medications used to defray symptoms, which may lead to greater odds of noncompliance (Hershman et al., 2011; Neugut et al., 2011). Examining the influences on the symptom experience and HRQOL due to the cost of cancer care warrants further research.

Another variable to consider in future studies includes the time elapsed since diagnosis. Prior studies have indicated that patients' ability to cope with their symptoms and disease improves over time (Andersen et al., 2007; Andersen et al., 2015; Oh et al., 2004; Meisel et al., 2012) and even though there were more patients with stage 4 disease receiving matched therapy, the stage of disease for this study may not be a reliable indicator for whether the patients are newly diagnosed or have been diagnosed for some time. Future studies could explore the use of the variable "metastatic or not metastatic" versus "cancer stage" since the presence of metastasis has been associated with HRQOL in previous studies (Ferreira et al., 2008; Gotze et al., 2015). Furthermore, examining hope as a variable and its potential relationship with symptoms and HRQOL should be considered in future studies since prior qualitative studies have found hope to be an important indicator of QOL (Luoma & Hakamies-Blomqvist, 2004; Sarenmalm et al., 2009; Svensson et al., 2009). Other variables to include in future studies are length of current therapy, and timing of prior lines of therapy since there are little data examining these variables in relation to symptoms and HRQOL.

Over the past several decades, there has been an exponential increase in the number of cancer studies investigating QOL and HRQOL, but this has seemingly been at the expense of symptom studies. This investigator maintains that symptoms and HRQOL are conceptually

different yet equally important aspects to cancer care and both need to be included in future trials. This will necessitate clear hypotheses and guidance by an appropriate conceptual framework and/or middle range theory in future studies. Furthermore, qualitative studies regarding the perceptions that oncology clinicians have about implementing matched therapy are needed since there were no studies found on this topic and may identify important barriers or challenges. Other qualitative studies are needed to explore the patients' perceptions about novel cancer therapies like matched therapy and symptom occurrence and severity. Knowing what the symptom(s) mean(s) to the patients, how it/they impact the patient, and the type of care the patient desires will be invaluable information. If personalized medicine like matched therapy is intended to tailor treatment to the individual, then tailoring the *care* is also paramount.

Nursing Implications

Nursing science is concerned with the human response to illness and health making symptoms and HRQOL an important area to study. The survival benefits of matched therapy are currently being investigated, therefore the impact of this therapy on the patient is a timely and needed research endeavor. One of the first questions a cancer patient asks during a discussion of any new therapy is how they (the patient) will feel. Results from this study provide foundational evidence of the symptom occurrence and severity and HRQOL in cancer patients receiving matched therapy, which will better prepare nurses and other health care professionals to provide effective cancer care. Nurses caring for cancer patients must incorporate the assessment of symptom occurrence and severity as well as HRQOL into their care. It is important that nurses stay up-to-date in new knowledge related to cancer care since they play an essential role in providing anticipatory guidance on potential therapy-related symptoms and in providing education about symptom management. By staying informed, nurses can help assess the barriers to matched therapy or other new treatment modalities, particularly the barriers to obtaining

potentially life-extending drugs due to costs and insurance coverage issues. Advocating for the expansion of patient assistance programs and supporting policy-changes at the local and national level is necessary to improve the current financial toxicities cancer patients face. These activities are encouraged by the NINR, who emphasizes the important contributions nurses can make in addressing health disparities and social determinants of health (NINR, 2016). Nursing science must continue to generate new knowledge related to symptoms and HRQOL in the context of state-of-the-art cancer care to improve patients' well-being.

Conclusions

Patients with breast and gynecologic cancer receiving matched or not matched therapy experience a variety of symptoms that can impact HRQOL, which was confirmed by this study. Patients who were receiving matched therapy reported lower levels of symptom occurrence and severity compared to patients receiving not matched therapy. However, this study found no significant association between cancer therapy type (matched, not matched) and symptom occurrence and severity while controlling for age, cancer type and stage, length of therapy, number of prior lines of therapy, timing of prior line of therapy, and comorbidities. Patients who had received prior therapy within three months of the current therapy had significantly higher symptom occurrence and severity compared to patients who had not received prior therapy. Further research about factors that influence symptoms, such as symptom management strategies for patients who receive matched therapy versus those that receive not matched therapy is necessary. This study found that more patients added symptoms to the TRSC (29%) compared to prior studies utilizing the TRSC (2%). Additional studies are needed to confirm these findings and to ensure that symptoms that are meaningful to the patient and clinician are being captured.

Patients who were receiving matched therapy had higher HRQOL compared to patients who were receiving not matched therapy. There was not a significant association between

cancer therapy type (matched, not matched) and HRQOL while controlling for person and health/illness variables. Nonetheless there was a significant association between symptom occurrence and severity and HRQOL; an increase in symptoms led to a decrease in HRQOL. Patients who had received an increased number of prior lines surprisingly had significantly higher HRQOL. Further research is needed to understand the important linkage between symptoms and HRQOL, and what factors may mediate or moderate this relationship. Finally, within the context of matched cancer therapy and its potential for increased efficacy, additional research focusing on the patients' symptom experience and impacts on HRQOL is needed.

References

Ah, W., Kurian, A. W., Kwan, M. L., John, E. M., Lu, Y., Keegan, T. H…Vigen, C. (2015). Diabetes and other comorbidities in breast cancer survival by race/ethnicity: The California Breast Cancer Survivorship Consortium (CBCSC). *Cancer Epidemiology, Biomarkers, and Prevention, 24,* 361-368. doi: 10.1158/1055-9965.EPI-14-1140

Ahmad, F., Muhammad, M., & Abdullah, A. A. (2011). Religion and spirituality in coping with advanced breast cancer: Perspectives from Malaysian Muslim women. *Journal of Religion and Health, 50*, 36-45. doi:10.1007/s10943-010-9401-4

American Cancer Society (2015a). Cancer facts & figures 2015. Retrieved from http://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2015/cancer-facts-and-figures-2015.pdf

American Cancer Society. (2016). Clinical trials: What you need to know. Retrieved from http://www.cancer.org/acs/groups/cid/documents/webcontent/003006-pdf.pdf

American Cancer Society. (2016). Chemo Brain. Retrieved from https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/changes-in-mood-or-thinking/chemo-brain.html

American Cancer Society. (2017a). Breast cancer HER2 status. Retrieved from https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-her2-status.html

American Cancer Society. (2017b). Chemo –What it is, how it helps. Retrieved from: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy.html

American Cancer Society. (2014). The history of cancer. Retrieved from http://www.cancer.org/acs/groups/cid/documents/webcontent/002048-pdf.pdf

American Cancer Society. (2015b). What is cancer? Retrieved from http://www.cancer.org/cancer/cancerbasics/what-is-cancer

American Joint Committee on Cancer. (2015). What is Cancer Staging? Retrieved from https://cancerstaging.org/references-tools/Pages/What-is-Cancer-Staging.aspx

American Nurses Association. (2009). *Essentials of genetic and genomic nursing: Competencies, curricula guidelines, and outcome indicators.* (2nd ed.). Retrieved from https://www.genome.gov/pages/careers/healthprofessionaleducation/geneticscompetency.pdf

Andre, F., Bachelot, T., Commo, F., Campone, M., Arnedos, M., Dieras, V…Bonnefoi, H. (2014). Comparative genomic hybridization array and DNA sequencing to direct treatment of metastatic breast cancer: A multicenter, prospective trial (SAFIR01/UNICANCER). *Lancet Oncology, 15*, 267-274. doi: 10.1016/S1470-2045(13)70611-9

Andersen, B. L., Carpenter, K. M., Yang, H. C., & Shapiro, C. L. (2007). Sexual well-being among partnered women with breast cancer recurrence. *Journal of Clinical Oncology, 25*, 3151-3157. doi: 10.1200/JCO.2006.09.6958

Arnould, L., Gelly, M., Penault-Liorca, F., Benoit, L., Bonnetain, F., Migeon, C…Coudert, B. (2006). Trastuzumab-based treatment of HER2-positive breast cancer: An antibody-dependent cellular cytotoxicity mechanism? *British Journal of Cancer, 94*, 259-267. doi: 10.1038/sj.bjc.6602930

Ashing-Giwa, K. T., & Lim, J. W. (2011). Examining emotional outcomes among a multiethnic cohort of breast cancer survivors. *Oncology Nursing Forum, 38*, 279-288. doi:10.1188/11.ONF.279-288

Association of Community Cancer Centers. (2017). Patient assistance and reimbursement guide. Retrieved from http://www.accc-cancer.org/publications/pdf/Patient-Assistance-Guide-2017.pdf

Balch, A. (2015). The need to eliminate barriers to personalized medicine. The American Journal of Managed Care. Published online August 12, 2105. Retrieved from http://www.ajmc.com/journals/evidence-based-oncology/2015/august-2015/the-need-to-eliminate-barriers-to-personalized-medicine

Barton-Burke, M., Smith, E., Frian, J., & Loggins, C. (2010). Advanced cancer in underserved populations. *Seminars in Oncology Nursing, 26*, 157-167. Doi: 10.1016/j.soncn.2010.05.003

Belum, V. R., Cercek, A., Sanz-Motilva, V., & Lacouture, M. E. (2013). Dermatologic adverse events to targeted therapies in lower GI cancers: Clinical presentations and management. *Current Treatment Options in Oncology, 14*, 389-404. doi: 10.1007/s11864-013-0254-4

Bickell, N. A., & Cohen, A. (2008). Understanding reasons for underuse: An approach to improve quality and reduce disparities in breast cancer treatment. *Mount Sinai Journal of Medicine, 75*, 23-30. doi: 10.1002/msj.20013

Binder, P. & Mutch, D. G. (2014). Update on prognostic markers for endometrial cancer. *Women's Health, 10*, 277-288. doi: 10.2217/whe.14.13

Biooncology. (2015a). HER2 dysregulation. Retrieved from http://www.biooncology.com/research-education/her/her2/dysregulation

Boland, E., Eiser, C., Ezaydi, Y., Greenfield, D. M., Ahmedzai, S. H., & Snowden, J. A. (2013). Living with advanced but stable multiple myeloma: A study of the symptom burden and cumulative effects of disease and intensive (hematopoietic stem cell transplant-based)

treatment on health-related quality of life. *Journal of Pain and Symptom Management, 46,* 671-680. Doi:10.1016/j.jpainsymman.2012.11.003

Booth, C. M. & Eisenhauer, E. A. (2012). Progression-free survival: Meaningful of simply measurable? *Journal of Clinical Oncology, 30*, 1030-1033. doi: 10.1200/JCO.2011.38.7571

Bordeanu, L., Frankel, P., Yu, W., Hendrix, G., Pal, S. Badr, L…Luu, T. (2012). Chemotherapy-induced nausea and vomiting in Asian women with breast cancer receiving anthracycline-based adjuvant chemotherapy. *Journal of Supportive Oncology, 10,* 149-154. Doi: 10.1016/j.suponc.2011.10.007

Bose, R., Molina, H., Patterson, A. S., Bitok, J. K., Periaswamy, B., Bader, J. S…Cole, P. A. (2006). Phosphoproteomic analysis of Her2/neu signaling and inhibition. *Proceedings of the National Academy of Sciences, 103*, 9773-9778. doi: 10.1073/pnas.0603948103.

Bottomley, A., Flechtner, H., Efficace, F., Vanvoorden, V., Coens, C., Therasse, P., Velikova, G., Blazeby, J., Greimel, E. (2005). Health related quality of life outcomes in cancer clinical trials. *European Journal of Cancer, 41*, 1697-1709. doi: 10.1016/j.ejca.2005.05.007

Bretscher, M., Rummans, T., Sloan, J., Kaur, J., Bartlett, A., Borkenhagen, L., & Loprinzi, C. (1999). Quality of life in hospice patients: A pilot study. *Psychosomatics, 40*(4), 309-313. doi:10.1016/S0033-3182(99)71224-7

Bullock, M. (2007). Editorial: Secondary analysis—extending the value of data. *Journal of Applied Developmental Psychology, 28*, 383. doi:10.1016/j.appdev.2007.07.002

Burkett, V. S. & Cleeland, C. S. (2007). Symptom burden in cancer survivorship. *Journal of Cancer Survivorship, 1,* 167-175. doi: 10.1007/s11764-007-0017-y.

Carpenter, R. L. & Lo, H. (2013). Regulation of apoptosis by HER2 in breast cancer. *Journal of Carcinogenesis & Mutagenesis*, S7:003. doi: 10.4172/2157-2518.S7-003

Castle, J (2003). Maximizing research opportunities: Secondary data analysis. *Journal of Neuroscience Nursing, 35(5)*, 287-290.

Cataldo, J. K., Paul, S. P., Skerman, H., Alexander, K., Aouizerat, B., Blackman, V., Merriman, J…Miaskowski, C. (2013). Differences in the symptom experience of older versus younger oncology outpatients: A cross-sectional study. *BMC Cancer, 13(6*), 1-16. doi: 10.1186/1471-2407-13-6

Chandramouly, G., Willis, N. A., & Scully, R. (2011). A protective role for BRCA2 at stalled replication forks. *Breast Cancer Research, 13*(5), 314. doi:10.1186/bcr2918

Chen, M. L. & Lin, C. C. (2007). Cancer symptom clusters: A validation study. *Journal of Pain and Symptom Management, 44*, 590-599. doi: 10.1016/j.jpainsymman.2007.01.008

Chen, M.L., & Tseng, H.C. (2006). Symptom clusters in cancer patients. *Supportive Care in Cancer, 14,* 825-830. doi: 10.1007/s00520-006-0019-8

Chirico, A., Serpentini, S., Merluzzi, T., Mallia, L. Del Bianco, P., Martino, R…Giordano, A. (2017). Self-efficacy for coping moderates the effects of distress on quality of life in palliative cancer care. *Anticancer Research, 37*, 1609-1615. doi: 10.21873/anticanres.11491

Chunlestskul, K., Carlson, L. E., Koopmans, J. P., & Angen, M. (2008). Lived experiences of Canadian women with metastatic breast cancer in preparation for their death: A qualitative study. Part I – Preparations and consequences. *Journal of Palliative Care, 24*(1), 5-15.

Church, D., Kerr, R., Domingo, E., Rosmarin, D., Palles, C., Maskell, K…Kerr, D. (2014). Toxgnostics: An unmet need in cancer medicine. *Nature Reviews Cancer, 14*, 440-445. doi:10.1038/nrc3729

Cleeland, C. S. (2000). Cancer-related symptoms. *Seminars in Radiation Oncology, 10*(3), 175-190.

Cohen, J. (1992). A power primer. *Psychological Bulletin, 112*, 155-159. doi: 10.1037/0033-2909.112.1.155

Collins, F. S., & Varmus, H. (2015). A new initiative on precision medicine. *The New England Journal of Medicine, 372*, 793-795. doi: 10.1056/NEJMp1500523

Comorbidity. (2009) *Mosby's Medical Dictionary, 8th edition*. Retrieved from http://medical-dictionary.thefreedictionary.com/comorbidity

DeBoer, A. G., Genovesi, P. L., Sprangers, M. A., VanSandick, J. W., Obertopm H., & VanLanschot, J. J. (2000). Quality of life in long-term survivors after curative transhiatal oesophagectomy for oesophageal carcinoma. *British Journal of Surgery, 87*, 1716-1721.

de Moor, J. S., Mariotto, A. B., Parry, C., Alfano, C. M., Padgett, L., Kent, E. E.…Rowland, J. H. (2013). Cancer survivors in the United States: Prevalence across the survivorship trajectory and implications for care. *Cancer Epidemiology, Biomarkers & Prevention, 22*, 561-570. doi: 10.1158/1055-9965.EPI-12-1356

Devita, V. T., Eggermont, A. M., Hellman, S., & Kerr, D. J. (2014). Clinical cancer research: The past, present and the future. *Nature Reviews Clinical Oncology, 11*, 663-669. doi: 10.1038/nrclinonc.2014.153

DeVita, V. T., Lawrence, T. S., & Roseberg, S. A. (2011). *Cancer: Principles & practice of oncology*, 9th edition. Philadelphia, PA : Lippincott Williams & Wilkins

Di Maio, M., Gallo, C., Leighl, N. B., Piccirillo, M. C., Daniele, G., Nuzzo, F…Perrone, F. (2015). Symptomatic toxicities experienced during anticancer treatment: Agreement between patient and physician reporting in three randomized trials. *Journal of Clinical Oncology, 33*, 910-915. doi: 10.1200/JCO.2014.57.9334

Dodd, M., Janson, S., Facione, N., Faucett, J., Froelicher, E. S., Humphreys, J…Taylor, D. (2001). Advancing the science of symptom management. *Journal of Advanced Nursing, 33*, 668-676. doi: 10.1046/j.1365-2648.2001.01697.x

Donovan, K. A., Donovan, H. S., Cella, D., Gaines, M. E., Penson, R. T., Plaxe, S. C…Wenzel, L. (2014). Recommended patient-reported core set of symptoms and quality-of-life domains to measure in ovarian cancer treatment trials. *Journal of the National Cancer Institute, 106*(7), 1-4. doi: 10.1093/jnci/dju128

Dujit, S. F., Faber, M. M., Oldenburg, H. S., van Beurden, M., & Aaronson, N. K. (2011). Effectiveness of behavioral techniques and physical exercise on psychosocial functioning and health-related quality of life in breast cancer patients and survivors-a meta-analysis. *Psychooncology, 20*, 115-126. doi: 10.1002/pon.1728

Dy, G. K., & Adjei, A. A. (2013). Understanding, recognizing, and managing toxicities of targeted anticancer therapies. *Cancer, 63*, 249-279. Doi:10.1002/caac.21184

EORTC Quality of Life. (n.d.). EORTC QLQ-C30. Retrieved from http://groups.eortc.be/qol/eortc-qlq-c30

Escudier, B., Porta, C., Bono, P., Powles, T., Eisen, T., Sternberg, C. N…Cella, D. (2014). Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES study. *Journal of Clinical Oncology, 32*, 1412-1418. doi: 10.1200/JCO.2013.50.8267

Eversley, R., Estrin, D., Dibble, S., Wardlaw, L., Pedrosa, M., & Favila-Penney, W. (2005). Post-treatment symptoms among ethnic minority breast cancer survivors. *Oncology Nursing Forum, 32,* 250-258. doi: 10.1188/05.ONF.250-256

FACIT.org. (2010). Questionnaires. Retrieved from http://www.facit.org/FACITOrg/Questionnaires

Fadare, O., & Khabele, D. (2015). Molecular profiling of epithelial ovarian cancer. *My Genome*. Retrieved from http://www.mycancergenome.org/content/disease/ovarian-cancer/

Fan, G., Filipczack, L., & Chow, E. (2007). Symptom clusters in cancer patients: A review of the literature. *Current Oncology, 14*, 173-179

Ferketich, S. (1990). Focus on psychometrics, Internal consistency estimates of reliability. *Research in Nursing & Health*, *13*, 437-440.

Ferketich, S., & Verran, J. (1994). Focus on psychometrics. An overview of data transformation. *Research in Nursing & Health, 17*, 393-396. Doi: 10.1002/nur.4770170510

Ferrans, C. E. (1990). Development of a quality of life index for patients with cancer. *Oncology Nursing Forum, 17*, 15-19

Ferrans, C. E., Zerwic, J. J, Wilbur, J. E., & Larson, J. L. (2005). Conceptual model of health-related quality of life. *Journal of Nursing Scholarship, 37*, 336-342. doi: 10.1111/j.1547-5069.2005.00058.x

Ferreira, K., Kimura, M., Teixeira, J., Mendoza, T. R., da Nobrega, C., Graziani, S. R., & Takagaki, T. Y. (2008). Impact of cancer-related symptom synergism on health-related qualify of life and performance status. *Journal of Pain and Symptom Management, 35*, 604-616. doi: 10.1016/j.jpainsymman.2007.07.010

Field, A. (2013). Discovering statistics using SPSS. London: SAGE. Retrieved from https://books.google.com/books?id=c0Wk9IuBmAoC&printsec=frontcover&dq=inauthor:%22Andy+Field%22&hl=en&sa=X&ved=0ahUKEwinroDpz-LRAhVH2IMKHbuPB9YQ6AEIJTAA#v=onepage&q&f=false

Filazoglu, G., & Griva, K. (2008). Coping and social support and health related quality of life in women with breast cancer in Turkey. Psychology, Health & Medicine, 13, 559-573. doi: 10.1080/13548500701767353

FoundationOne. (2014). Technical information and test overview. Retrieved from http://foundationone.com/docs/FoundationOne/100316%20-%20F1%20Tech%20Specs%20(1).pdf?__hstc=197910000.f4823a40614c9b44882d24964bb139bf.1475497940453.1478795333311.1481140065350.20&__hssc=197910000.2.1481140065350&__hsfp=3109191104

Frampton, G. M., Fichtenholtz, A., Otto, G. A., Wang, K., Downing, S. R., He, J…Yelensky, R. (2013). Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. *Nature Biotechnology, 31,* 1023-1033. doi: 10.1038/nbt.2696

Ganz, P. A., Kwan, L., Stanton, A. L., Krunpick, J. L., Rowland, J. H., & Meyerowitz, B. E. (2004). Quality of life at the end of primary treatment of breast cancer: First results from the moving beyond cancer randomized trial. *Journal of the National Cancer Institute, 96*, 376-387.

Ganz, P. A., Land, S. R., Geyer, C. E., Cecchini, R. S., Costantino, J. P., Pajon, E. R…Swain, S.M. (2011). Menstrual history and quality-of-life outcomes in women with node-positive breast cancer treated with adjuvant therapy on the NSABP B-30 Trial. *Journal of Clinical Oncology, 29*, 1110-1116. doi:10.1200/JCO.2010.29.7689

Garrison, C. M., Overcash, J., & McMillan, S. C. (2011). Predictors of quality of life in elderly hospice patients with cancer. *Journal of Hospice and Palliative Nursing, 13*, 288-297. doi: 10.1097/NJH.0b013e1821adb2d

Genetics Home Reference. (2017). What is a gene mutation and how do mutations occur? Retrieved from https://ghr.nlm.nih.gov/primer/mutationsanddisorders/genemutation

Gerber, D. E. (2008). Targeted therapies: A new generation of cancer treatments. *American Family Physician, 77*, 311-319. Retrieved from http://www.aafp.org/afp/2008/0201/p311.html

Gilbertson-White, S., Aouizerat, B. E., Jahan, T., & Miaskowski, C. (2011). A review of the literature on multiple symptoms, their predictors, and associated outcomes in patients with advanced cancer. *Palliative Supportive Care, 9*, 81-102. doi: https://doi.org/10.1017/S147895151000057X

Gladwell, M. (2015). Tough medicine. The New Yorker. Retrieved from http://www.newyorker.com/magazine/2015/12/14/tough-medicine

Given, B., Given, C. W., McCorkle, R., Kozachik, S., Cimprich, B., Rahbar, M. H… Wojcik, C. (2002). Pain and fatigue management: Results of a nursing randomized clinical trial. *Oncology Nursing Forum, 29,* 949-56. doi:10.1188/02.ONF.949-956

Go, R. S., Frisby, K. A., Lee, J. A., Mathiason, M. A., Meyer, C. M., Ostern, J. L…Umberger, K. E. (2006). Clinical trial accrual among new cancer patients at a community-based cancer center. *Cancer, 106*, 426-433. doi: 10.1002/cncr.21597

Gonzalez, V. Williams, P. D., Tirado, M., & Williams, D. D. (2011, March). *Patient-reported symptoms, alleviation and self-care methods, daily activities, and health-related quality of life during outpatient cancer treatments in Puerto Rico*. Poster session presented at the Midwest Nursing Research Society Conference, Columbus, OH.

Gotze, H., Ernst, J., Brahler, W., Romer, G., & von Klizting. (2015). Predictors of quality of life of cancer patients, their children, and partners. *Psycho-Oncology, 24*, 787-795. doi: 10.1002/pon.3725

Gradishar, W. & Salerno, K.E. (2016). NCCN guidelines update: Breast cancer. *Journal of the National Comprehensive Cancer Network, 14*, 641-644.

Grady, P. A. & Gough, L. L. (2015). Nursing science: Claiming the future. *Journal of Nursing Scholarship, 47*, 512-521. doi: 10.1111/jnu.12170.

Green, S.B. (1991). How many subjects does it take to do a regression analysis? *Multivariate Behavioral Research, 26* (3), 499-510.

Grunberg, S. M., Groshen, S., Steingass, S., Zaretsky, S., & Meyerowicz, B. (1996). Comparison of conditional quality of life terminology and visual analogue scale measurements. *Quality of Life Research, 5*(1), 65-72. doi: 10.1007/BF00435970

Gudex, C., Dolan, P., Kind, P., & Williams, A. (1996). Health state valuations from the public using the visual analogue scale. *Quality of Life Research, 5*(6), 521-531. doi: 10.1007/BF00439226

Hamaker, M. E., Seynaeve, C., Wymenga, A. N., van Tinteren, H., Nortier, J. W., Maartense, E…Smorenburg, C. H. (2014). Baseline comprehensive geriatric assessment is associated with toxicity and survival in elderly metastatic breast cancer patients receiving single-agent chemotherapy: Results from the OMEGA study of the Dutch breast cancer trialists' group. *Breast, 23*, 81-87. doi:10.1016/j.breast.2013.11.004

Hammerlid, E. & Taft, C. (2001). Health-related quality of life in long-term head and neck cancer survivors: A comparison with general population norms. *British Journal of Cancer, 84,* 149-156. doi:10.1054/bjoc.2000.1576

Hamilton, R. (2009). Nursing advocacy in a post-genomic age. *Nursing Clinics of North America, 44,* 435-446. doi:10.1016/j.cnur.2009.07.007

Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. *Cell, 144*, 646-675. doi: 10.1016/j.cell.2011.02.013

Healthy People 2020. (2015). 2020 topics and objectives, cancer. Retrieved from http://www.healthypeople.gov/2020/topics-objectives/topic/cancer/objectives

Heinze, S. (2012). *Relationships among symptoms, brain-derived neurotrophic factor (BDNF), daily activities, self-care, and quality of life in breast cancer survivors.* (Doctoral dissertation). Retrieved from http://kuscholarworks.ku.edu/dspace/handle/1808/11445

Heinze, S., Williams, P. D., Pierce, J., Diaz, F. J., & Ferris-Kirschner, K. (2015). Brain-derived neurotrophic factor (BDNF) VALMET polymorphism and symptoms in breast cancer survivors. *Jacobs Journal of Cancer Science and Research, 1*(1), 1-9.

Herndon, J. E., Kornblith, A. B., Holland, J. C., & Paskett, E. D. (2008). Patient education level as a predictor of survival in lung cancer clinical trials. *Journal of Clinical Oncology, 26*, 4116-4123. doi: 10.1200/JCO.2008.16.7460

Hess, L., & Stehman, F. B. (2012). State of the science in ovarian cancer quality of life research: A systematic review. *International Journal of Gynecological Cancer, 22*, 1273-1280. doi: 10.1097/IGC.0b013e318263f02e

Howlander, N., Noone, A. M., Krapcho, M., Miller, D., Bishop, K., Altekruse, S. F…Cronin, K.A. (eds.). (2016). SEER cancer statistics review, 1975 – 2013. Retrieved from https://seer.cancer.gov/csr/1975_2013/

Huang, S. M., Tai, C. J., Lin, K. C., Tai, C. J., Tseng, L. M., & Chien, L. Y. (2013). A comparative study of symptoms and quality of life among patients with breast cancer

receiving target, chemotherapy, or combined therapy. *Cancer Nursing, 36,* 317-325. doi: 10.1097/NCC.0b013e318268f86d

Humphreys, J., Janson, S., Donesky, D., Dracup, K., Lee, K. A., Puntillo, K…Kennedy, C. (2008). Theory of symptom management. In M.J. Smith & P.R. Liehr (Eds.), *Middle Range Theory for Nursing* (pp. 145-158). New York, NY: Springer.

Hyland, M. E., & Sodergren, S. C. (1996). Development of a new type of global quality of life scale, and comparison of performance and preference for 12 global scales. *Quality of Life Research, 5,* 469-480. doi: 10.1007/BF00540019

ICD-10-CM official guidelines for coding and reporting (2016). Retrieved from http://www.cdc.gov/nchs/data/icd/10cmguidelines_2016_final.pdf

Institution for Digital Research and Education. (2017). Choosing the correct statistical test in SAS, STATA, SPSS, and R. Retrieved from http://stats.idre.ucla.edu/other/mult-pkg/whatstat/

Intron. (n.d.). Dictionary.com Unabridged. Retrieved from http://dictionary.reference.com/browse/intron

Janz, N. K., Mujahid, M., Chung, L. K., Lantz, P. M., Hawley, S. T., Morrow, M… Katz, S. J. (2007). Symptom experience and quality of life of women following breast cancer treatment. *Journal of Women's Health, 16*, 1348-1361. Doi:10/1089/jwh.2006.0255

Jeffe, D. B., Perez, M., Cole, E. F., Liu, Y., & Schootman, M. (2016). The effects of surgery type and chemotherapy on early-stage breast cancer patients'quality of life over 2-year follow-up. *Annals of Surgical Oncology, 23*, 735-743. doi: 10.1245/s10434-015-4926-0

Johnson, D. E. (1998). Prediction models and multivariate regression. In *Applied multivariate methods for data analysts* (pp. 489-522). Pacific Grove, CA: Duxbury Press

Jones, D., Vichaya, E. G., Wang, X. S., Williams, L. A., Shah, N. D., Thomas, S. K…Mendoza, T. R. (2013). Validation of the M.D. Anderson Symptom Inventory multiple myeloma module. *Journal of Hematology & Oncology, 6,* 1-9. Retrieved from: http://www.jhoonline.org/content/6/1/13

Kaufman, P. A., Awada, A., Twelves, C., Yelle, L., Perez, E. A., Velikova, G…Cortes, J. (2015). Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. *Journal of Clinical Oncology, 33*, 594-601. doi: 10.1200/JCO.2013.52.4892

Kenne-Sarenmalm, E., Ohlen, J., Jonsson, T., & Gaston-Johansson, F. (2007). Coping with recurrent breast cancer: Predictors of distressing symptoms and health-related quality of life. *Journal of Pain and Symptom Management, 36*, 468-479. Doi:10.1016/j.jpainsymman.2007.11.011

Kim, J. E., Dodd, M. J., Aouizerat, B. E., Jahan, T., & Miaskowski, C. (2009). A review of the prevalence and impact of multiple symptoms in oncology patients. *Journal of Pain and Symptom Management, 37*, 715-736. doi: http://dx.doi.org/10.1016/j.jpainsymman.2008.04.018

Kirkova, J., Davis, M. P., Walsh, D., Tiernan, E., O'Leary, N., LeGrande, S. B…Russell, K. M. (2006). Cancer symptom assessment instruments: A systematic review. *Journal of Clinical Oncology, 24*, 1459-1473. doi: 10.1200/JCO.2005.02.8332

Kirkova, J., Rybicki, L., Walsh, D., Aktas, A., Davis, M. P., & Karafa, M. (2011). Cancer symptom clusters: Clinical and research methodology. *Journal of Palliative Medicine, 14,* 1149-1166. doi: 10.1089/jpm/2010.0507

Kirkova, J., Rybicki, L., Walsh, D., & Aktas, A. (2012). Symptom prevalence in advanced cancer: Age, gender and performance status interactions. *American Journal of Hospice and Palliative Medicine, 29*(2), 139-145. doi: 10.1177/1049909111410965

Kirkova, J., Walsh, D., Rybicki, L., Davis, M. P., Aktas, A., Tao, J., Homsi, J. (2010). Symptom severity and distress in advanced cancer. *Palliative Medicine, 24*, 330- 339. doi: 10.1177/0269216309356380

Kluetz, P. G., Chingos, D. T., Basch, E. M., & Mitchell, S. A. (2016). Patient reported outcomes in cancer clinical trials: Measuring symptomatic adverse events with the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *American Society of Clinical Oncology Educational Book, 35*, 67-73. doi: 10.14694/EDBK_159514

Komurcu, S., Nelson, K. A., Walsh, D., Donnely, S. M., Homsi, J., Abdullah, O. (2000). Common symptoms in advanced cancer. *Seminars in Oncology, 27*(1), 24-33

Kos, Z. & Dabbs, D. J. (2016). Biomarker assessment and molecular testing for prognostication in breast cancer. *Histopathology, 68*, 70-85. doi:10.111/his.12795.

Land, L. H., Dalton, S. O., Jorgensen, T. L., & Ewertz, M. (2012). Comorbidity and survival after early breast cancer: A review. *Critical Reveiws in Oncology and Hematology, 81*, 196-205. doi: http://dx.doi.org/10.1016/j.critrevonc.2011.03.001

Larsen, M. J., Kruse, T. A., Tan, Q., Laenkholm, A. V., Bak, M., Lykkesfeldt, A. E…Thomassen, M. (2013). Classifications within molecular subtypes enables identification of BRCA1/BRCA2 mutation carriers by RNA tumor profiling. *PLoS ONE, 8*, e64268. doi:10.1371/journal.pone.0064268

Leung, J., Pachana, N. A., & McLaughin, D. (2014). Social support and health-related quality of life in women with breast cancer: A longitudinal study. *Psycho-Onoclogy, 23*, 1014-1020. doi:10.1002/pon.3523

Lewis, M. A., Zhao, F., Jones, D., Loprinzi, C. L., Brell, J., Weiss, M., & Fisch, M. J. (2015). Neuropathic symptoms and their risk factors in medical oncology outpatients with colorectal vs. breast, lung, or prostate cancer: Results from a prospective multicenter study. *Journal of Pain and Symptom Management, 49*, 1016-1024. Doi: 10.1016/j.jpainsymman.2014.11.300

Leyland-Jones, B. (2002). Trastuzumab: Hopes and realities. *Lancet Oncology, 3*(3), 137-144.

Leyland-Jones, B. & Smith, B. R. (2011). Serum HER2 testing in patients with HER2 positive breast cancer: The death knell tolls. *The Lancet Oncology, 12*, 286-295. doi: 10.1016/S1470-2045(10)70297-7

Lichwala, R. (2014). Fostering hope in the patient with cancer. *Clinical Journal of Oncology Nursing, 18*, 267-269. doi: 10.1188/14.CJON.267-269

Linder, L. (2010). Analysis of the UCSF symptom management theory: Implications for pediatric oncology nursing. *Journal of Pediatric Oncology Nursing, 27*, 316-324. doi: 10.1117/104345210368532

Liu, S., & Kurzock, R. (2014). Toxicity of targeted therapy: Implications for response and impact of genetic polymorphisms. *Cancer Treatment Reviews, 40*, 883-891. http://dx.doi.org/10.1016/j.ctrv.2014.05.003

Locke, D. E., Decker, P. A., Sloan, J., Brown, P. D., Malec, J. F., Clark, M. M…Buckner, J. C. (2007). Validation of single-item linear analog scale assessment of quality of life in neuro-oncology patients. *Journal of Pain and Symptom Management, 34*, 628-638. doi: http://dx.doi.org/10.1016%2Fj.jpainsymman.2007.01.016

Lopez, V., Williams, P. D., & Larkin, D. (2015). Treatment-related symptom severity and occurrences among adults in Australia. *Asia-Pacific Journal of Oncology Nursing, 2*, 144-151. doi: 10.4103/2347-5625.160973

Luoma, M. L., & Hakamies-Blomqvist, L. (2004). The meaning of quality of life in patients being treated for advanced breast cancer: A qualitative study. Psycho-Oncology, 13, 729-739. doi**:** 10.1002/pon.788

Ma, B., Yeo, W., Hui, P., Wing, M. H., & Johnson, P. J. (2002). Acute toxicity of adjuvant doxorubicin and cyclophosphamide for early breast cancer – a retrospective review of Chinese patients and comparison with an historic Western series. *Radiotherapy and Oncology, 62*, 185-189. Doi: 10.1016/S0167-8140(02)00003-8

Majithia, N., Loprinzi, C. L., & Smith, T. J. (2016). New practical approaches to chemotherapy-induced neuropathic pain: Prevention, assessment, and treatment. *Oncology, 30* (11), 1020-1029.

Manning, G. (2016). The human protein kinases. Retrieved from http://www.cellsignal.com/common/content/content.jsp?id=kinases

McCluggage, W. G. (2011). Morphological subtypes of ovarian carcinoma: A review with emphasis on new developments and pathogenesis. *Pathology, 43*, 420-432. doi: 10.1097/PAT.0b013e328348a6e7

McDermott, U., Downing, J., & Stratton, M. R. (2011). Genomics and the continuum of cancer care. *New England Journal of Medicine, 364*, 340-350. Doi:10.1056/NEJMra0907178

MedicineNet.com. (2016). Medical definition of surgery. Retrieved from http://www.medicinenet.com/script/main/art.asp?articlekey=5603

McFarland, D. (2014). Call for QOL experiences with targeted therapies. Retrieved from http://www.oncotherapynetwork.com/skin-cancer-melanoma-targets/call-qol-experiences-targeted-therapies

Meisel, J. L., Domchek, S. M., Vonderheide, R. H., Giobbie-Hurder, A., Lin, N., Winer, E. P…Partridge, A. H. (2012). Quality of life in long-term survivors of metastatic breast cancer. *Clinical Breast Cancer, 12*, 119-126. doi: http://dx.doi.org/10.1016/j.clbc.2012.01.010

Mendenhall, W., & Sincich, T. (2012). Some regression pitfalls. In *A second course in statistics: Regression analysis* (pp 355-382). Boston: Prentice Hall

Merriam-Webster Dictionary. (2015). Definition of kinase. Retrieved from http://www.merriam-webster.com/dictionary/kinase

Meyer, L. A., Anderson, M. E., Lacour, R. A., Suri, A., Daniels, M. S., Urbauer, D. L…Lu, K. H. (2010). Evaluating women with ovarian cancer for BRCA1 and BRCA2 mutations: Missed opportunities. *Obstetrics and Gynecology, 115*, 945-952. Doi: 10.1097/AOG.0b013e3181da08d7.

Miaskowski, C., Cooper, B. A., Paul, S. M., Dodd, M., Lee, K., Aouizerat, B. E…Bank, A. (2006). Subgroups of patients with cancer with different symptom experiences and quality-of-life outcomes: A cluster analysis. *Oncology Nursing Forum, 33*(5), E79-E89. doi: 10.1188/06.ONF.E79-E89

Miller-Reilly, C., Watkins-Brumer, D., Mitchell, S. A., Minasian, L., Basch, E., Dueck, A. C…Reeve, B. B. (2013). A literature synthesis of symptom prevalence and severity in persons receiving active cancer treatment. *Supportive Care Cancer, 21*, 1525-1550. doi: 10.1007/s00520-012-1688-0

Mische-Lawson L., Williams P. D., Glennon, C., Carithers, K., Schnabel, E., Andrejack, A., & Wright, N. (2012). Effect of art making on cancer therapy-related symptoms of blood & bone marrow transplant recipients. *Oncology Nursing Forum 39(4), E354-359*

Mkanta, W. N., Chumbler, N. R., Richardson, L. C., & Kobb, R. F. (2007). Age-related differences in quality of life in cancer patients. *Cancer Nursing, 30*, 434 – 440. doi: 10.1097/01.NCC.0000300167.80466.91

Montazeri, A. (2008). Health-related quality of life in breast cancer patients: A bibliographic review of the literature from 1974 to 2007. *Journal of Experimental and Clinical Cancer Research, 27*(1), 32. doi:10.1186/1756-9966-27-32

Morice, P., Leary, A., Creutzberg, C., Abu-Rustum, N., & Daria, E. (2016). Endometrial cancer. *The Lancet, 387*, 1094-1108. doi:10.1016/S0140-6736(15)00130-0

Mukherjee, S. (2016). The improvisational oncologist. New York Times. Retrieved from https://www.nytimes.com/2016/05/15/magazine/oncologist-improvisation.html?_r=0

Murff, H. J., Byrne, D., & Syngal, S. (2004). Cancer risk assessment: Quality and impact of the family history interview. *American Journal of Preventative Medicine, 27*, 239-245. doi:10.1016/j.amepre.2004.05.003

National Cancer Institute. (2015a). BRCA1 and BRCA2: Cancer risk and genetic testing. Retrieved from https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet

National Cancer Institute. (2015b). Cancer classification. Retrieved from http://training.seer.cancer.gov/disease/categories/classification.html

National Cancer Institute. (2016a). Cancer moonshot. Retrieved from https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative

National Cancer Institute. (n.d.a). NCI dictionary of cancer terms. Retrieved from http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=561720

National Cancer Institute. (n.d.b). NCI drug dictionary. Retrieved from http://www.cancer.gov/publications/dictionaries/cancer-drug?CdrID=372905

National Cancer Institute. (2016b). Phases of clinical research. Retrieved from https://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials/phases

National Cancer Institute. (2010). Radiation therapy for cancer. Retrieved from https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy/radiation-fact-sheet

National Cancer Institute. (2015c). SEER stat fact sheet: Vulvar cancer. Retrieved from http://seer.cancer.gov/statfacts/html/vulva.html

National Cancer Institute. (2015d). Surgery. Retrieved from http://www.cancer.gov/about-cancer/treatment/types/surgery

National Cancer Institute. (2014). Targeted Cancer Therapies. Retrieved from https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet

National Cancer Institute. (2015e). The genetics of cancer. Retrieved from https://www.cancer.gov/about-cancer/causes-prevention/genetics

National Cancer Institute. (2013). Tumor grade. Retrieved from http://www.cancer.gov/about-cancer/diagnosis-staging/prognosis/tumor-grade-fact-sheet

National Cancer Institute. (2015f). What is cancer? Retrieved from http://www.cancer.gov/about-cancer/what-is-cancer#types-of-cancer

National Comprehensive Cancer Network. (2017). Breast Cancer. Retieved from https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

National Comprehensive Cancer Network. (2015). NCCN history. Retrieved from http://www.nccn.org/about/history.aspx

National Comprehensive Cancer Network. (2016). Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Retrieved fom https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

National Genetics and Genomics Education Centre. (n.d.). Next generation sequencing. Retrieved from http://www.geneticseducation.nhs.uk/laboratory-process-and-testing-techniques/next-generation-sequencing-ngs

National Institutes of Health. (n.d.a). Precision Medicine Initiative Cohort Program. Retrieved from https://www.nih.gov/research-training/allofus-research-program

National Institutes of Health. (n.d.b.). What is cancer genomics? Retrieved from http://cancergenome.nih.gov/cancergenomics/whatisgenomics/whatis

National Institute of Nursing Research. (n.d.). Implementing NINR's strategic plan: Key themes. Retrieved from: http://www.ninr.nih.gov/aboutninr/keythemes#.VrZROkthmIw

National Institute of Nursing Research (2016). The NINR strategic plan: Advancing science, improving lives. Retrieved from: https://www.ninr.nih.gov/sites/www.ninr.nih.gov/files/NINR_StratPlan2016_reduced.pdf

Natrajan, R. C. (2015). Breast cancer heterogeneity: Parallel evolution or conscious uncoupling? *Journal of Pathology, 237*, 1-3. doi: 10.1002/path.4557

Nature.com. (2015). Next-generation sequencing. Retrieved from http://www.nature.com/subjects/next-generation-sequencing

Niraula, S., Seruga, B., Ocana, A., Shao, T., Goldstein, R., Tannock, I. F., & Amir, E. (2012). The price we pay for progress: A meta-analysis of harms of newly approved anticancer drugs. *Journal of Clinical Oncology, 30*, 3012-3019. Doi: 10.1200/JCO.2011.40.3842

Oh, S., Heflin, L., Meyerowitz, B. E., Desmond, K. A., Rowland, J. H., & Ganz, P. A. (2004). Quality of life of breast cancer survivors after a recurrence: A follow-up study. *Breast Cancer Research and Treatment, 87*, 45-57. doi: 10.1023/B:BREA.0000041580.55817.5a

Oncology Nursing Society. (2013). Oncology nursing: The application of cancer genetics and genomics throughout the oncology care continuum. *Oncology Nursing Forum, 40*(1), 10-13. Doi: 10.1188/13.ONF.10-11

Osaba, D. (2011). Health-related quality of life and cancer clinical trials. *Therapeutic Advances in Medical Oncology, 3,* 57-71. doi: 10.1177/1758834010395342

Osaba, D., Slamon, D. J., Burchmore, M., Murphy, M. (2002). Effects on quality of life of combined trastuzumab and chemotherapy in women with metastatic breast cancer. *Journal of Clinical Oncology, 20*(14), 3106-3113. doi: 10.1200/JCO.2002.03.090

Osborne, C. K. & Schiff, R. (2011). Mechanisms of endocrine resistance. *Annual Reviews of Medicine, 62*, 233-247. doi: 10.1146/annurev-med-070909-182917

Ozols, R. F. (2006). Challenges for chemotherapy in ovarian cancer. *Annals of Oncology, 17*, 181-187. doi:10.1093/annonc/mdj978

Padilla, G. V., Presant, C., Grant, M. M., Metter, G., Lipsett, J., & Heide, F. (1983). Quality of life index for patients with cancer. *Research in Nursing & Health, 6*(3), 117-126

Palmieri, C., Macpherson, I. R., Yan, K., Ades, F., Riddle, P., Ahmed, R…Howell, S. J. (2015). Neoadjuvant chemotherapy and trastuzumab versus neoadjuvant chemotherapy followed by postoperative trastuzumab for patients with HER2-positive breast cancer. *Oncotarget,* 7, 13209-13220. doi: 10.18632/oncotarget.4801

Park, J. H., Bae, S. H., Jung, Y. S., & Kim, K. S. (2012). Quality of life and symptom experience in breast cancer survivors after participating in a psychoeducational support program: A pilot study. *Cancer Nursing, 35*, E34-E41. doi:10.1097/NCC.0b013e318218266a

Patnaik, J. L., Byers, T., DiGuiseppi, C., Denberg, T. D., & Dabelea, D. (2011). The influence of comorbidities on overall survival among older women diagnosed with breast cancer. *Journal of National Cancer Institute, 103*, 1101-1111. doi: 10.1093/jnci/djr188

Payne, S. & Miles, D. (2008) Mechanisms of Anticancer Drugs. In CRC Press, 34-46. Retrieved from http://www.crcnetbase.com/doi/abs/10.1201/b15118-6

Peterson, S. J. & Bredow, T. S. (2013). *Middle Range Theories: Application to Nursing Research. Philadelphia*, PA: Lippincott Williams & Wilkins

Petrelli, F., & Barni, S. (2012). Meta-analysis of concomitant compared to sequential adjuvant trastuzumab in breast cancer: The sooner the better. *Medical Oncology, 29*, 503-510. Doi: 10.1007/s12032-011-9897-9

Piamjarijakul, U., Williams, P., Prapakorn, S., Park, L., Rojjanansrirat, W., & Williams, A. (2010). Cancer treatment, symptom monitoring, and self-care in Thai adults. *European Journal of Oncology Nursing*, 1-8

Pignata, S., Scambia, G., Katsaros, D., Pujade-Lauraine, E., De Placido, S., Bologna, A., Weber, B….Perrone, F. (2014). Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): A randomized multicenter, open-label, phase 3 trial. *Lancet Oncology, 15*, 396-405. doi: 10.1016/S1470-2045(14)70049-X

Polit, D. & Beck, C. (2008). *Nursing research: Generating and assessing evidence for nursing practice* (8th ed.). Philadelphia, PA: Lippincott, Williams, and Wilkins

Popovic, M., Lao, N., Zeng, L., Zhang, L., Cella, D. Beaumont, J…Chow, E. (2013). The impact of clinical and sociodemographic features on quality of life in patients with early stage cancers using the Functional Assessment of Cancer Therapy – General assessment tool. *Supportive Care in Cancer, 21*, 2267-2277. doi: 10.1007/s00520-013-1789-4

Portenoy, R. K., Thaler, H. T., Kornblith, A. B. Lepore, J. M., Friedlander-Klar, H., Sobel, K…Norton, L. (1994). The Memorial Symptom Assessment Scale: An instrument for the evaluation of symptom prevalence, characteristics and distress. *European Journal of Cancer, 30*(9), 1326-1336

Raja, F. A., Chopra, N., & Ledermann, J. A. (2012). Optimal first-line treatment in ovarian cancer. *Annals of Oncology, 23*, 118-127. doi: 10.1093/annonc/mds315

Reeve, B. B., Mitchell, S. A., Dueck, A. C., Basch, E., Cella, D., Reilly, C. M., M…Bruner, D. W. (2014). Recommended patient-reported core set of symptoms to measure in adult cancer treatment trials. *Journal of the National Cancer Institute, 106*(7), 1-8. doi:10.1093/jnci/dju129

Rubin, R. (2015). Expert critical of America's right-to-try drug laws. *The Lancet, 386*, 1325-1326. Retrieved from http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00393-1/fulltext?rss%3Dyes

Rudberg, L., Carlsson, M., Milsson, S., & Wikblad, K. (2002). Self-perceived physical, psychologic, and general symptoms in survivors of testicular cancer 3 to 13 years after treatment. *Cancer Nursing, 25*, 187-195

Rugo, H., Brammer, M., Zhang, F., & Lalla, D. (2010). Effect of trastuzumab on health-related quality of life in patients with HER2-positive metastatic breast cancer: Data from three clinical trials. *Clinical Breast Cancer, 10*, 288-293. doi:10.3816/CBC.2010.n.037

Sarenmalm, E. K., Thoren-Jonsson, A.L., Gaston-Johansson, F., & Ohlen, J. (2009). Making sense of living under the shadow of death: Adjusting to a recurrent breast cancer illness. *Qualitative Health Research, 19*, 1116-1130. doi: 10.1177/1049732309341728

Sateren, W. B., Trimble, E. L., Abrams, J., Brawley O., Breen, N., Ford, L…Christian, M. C. (2002). How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. *Journal of Clinical Oncology, 15,* 2109-17. doi: 10.1200/JCO.2002.08.056

Schnitt, S. J. (2015). Classification and prognosis of invasive breast cancer: From morphology to molecular taxonomy. *Modern Pathology*. Retrieved from http://www.nature.com/modpathol/journal/v23/n2s/fig_tab/modpathol201033t1.html

Schwaederle, M., Daniels, G. A., Piccioni, D. E., Kesari, S., Fanta, P. T., Schwab, R.B …Kuzrock, R. (2015). Next generation sequencing demonstrates association between tumor suppressor gene aberrations and poor outcome in patients with cancer. *Cell Cycle, 14*, 1730-1737. Retrieved from http://dx.doi.org/10.1080/15384101.2015.1033596

Servaes, P., Verhagen, C., & Bleijenberg, G. (2002). Fatigue in cancer patients during and after treatment: Prevalence, correlates and interventions. *European Journal of Cancer, 38(1)*, 27-43

Shadish, W. R., Cook, T. D., & Campbell, D. T. (2002). *Experimental and quasi-experimental designs for generalized causal inference.* New York: Houghton Mifflin Company

Shah, M. M., Erickson, B. K., Matin, T., McGwin, G., Martin, J. Y., Daily, L. B…Leath, C. A. (2014). Diabetes mellitus and ovarian cancer: More complex than just increasing risk. *Gynecology Oncology, 135*, 273-277. Doi: 10.1016/j.ygyno.2014.09.004

Shayne, M., Crawford, J., Dale, D. C., Culakova, E., Lyman, G. H., & ANC Study Group. (2006). Predictors of reduced dose intensity in patients with early-stage breast cancer receiving adjuvant chemotherapy. *Breast Cancer Research and Treatment, 100*, 255-263. doi: 10.1007/s10549-006-9254-4

Siegel, R. L., Miller, K. D., & Jemal, A. (2015). Cancer statistics 2015. *CA: A Cancer Journal for Clinicians, 65*(1), 5-29. doi: 10.3322/caac.21254

Siegelmann-Danieli, N., Khandelwal, V., Wood, G. C., Mainali, R., Prichard, J., Murphy, T. J…Bernath, A. M. (2006). Breast cancer in elderly women: Outcomes as affected by age, tumor features, comorbidities, and treatment approach. *Clinical Breast Cancer, 7*, 59-66. doi: http://dx.doi.org/10.3816/CBC.2006.n.014

Slamon, D. J., Leyland-Jones, B., Shak, S., Fuchs, H., Paton, V., Bajamonde, A…Norton, L. (2001). Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *The New England Journal of Medicine, 344*, 783-792. doi: 10.1056/NEJM200103153441101

Sloan, J. A., Cella, D., Forst, M., Guyatt, G. H., Sprangers, M., & Symonds, T. Clinical Significance Consensus Group. (2002). Assessing clinical significance in measuring oncology patient quality of life: Introduction to the symposium, content overview, and definition of terms. *Mayo Clinic Proceedings, 77*(4), 367-370. doi: 10.4065/77.4.367

Sloan J. A., Cella, D., & Hays, R. D. (2005). Clinical significance of patient-reported questionnaire data: Another step toward consensus. *Journal of Clinical Epidemiology, 58*, 1217-1219. doi: 10.1016/j.jclinepi.2005.07.009

Smith, A. W., Bellizzi, K. M., Keegan, T., Zebrack, B., Chen, V. W., Neale, A. V…Lynch, C. (2013). Health-related quality of life of adolescent and young adult patients with cancer in the United States: The adolescent and young adult health outcomes and patient experience study. *Journal of Clinical Oncology, 31*, 2136-2145. doi: 10.1200/JCO.2012.47.3173

Smith, S. K., Dixon, A., Trevena, L., Nutbeam, & McCaffery, K. J. (2009). Exploring patient involvement in healthcare decision making across different education and functional health literacy groups. *Social Science & Medicine, 69*, 1805-1812. doi: http://dx.doi.org/10.1016/j.socscimed.2009.09.056

So, W. K., Leung, D. Y., Ho, S. S., Lai, E. T., Sit, J. W., & Chan, C. W. (2012). Associations between social support, prevalent symptoms and health-related quality of life in Chinese women undergoing treatment for breast cancer: A cross-sectional study using structural equation modelling. *European Journal of Oncology Nursing, 4*, 442-448. doi: http://dx.doi.org/10.1016/j.ejon.2012.11.001

Sorror, M. L., Martin, P. J., Storb, R. F., Bhatia, S., Maziarz, R. T., Pulsipher, M. A…Gooley, T. A. (2014). Pretransplant comorbidities predict severity of acute graft-versus-host disease and subsequent mortality. *Blood, 10*, 287-295. doi: 10.1182/blood-2014-01-550566

Sousa, V. (2015). Multiple linear regression [class handout]. University of Kansas, Kansas City, KS.

Spichiger, E., Muller-Frohlich, C., Denhaerynch, K., Stoll, H., Hantikainen, V., & Dodd, M. (2011). Prevalence of symptoms, with a focus on fatigue and changes of symptoms over three months in outpatients receiving chemotherapy. *Swiss Medical Weekly, 141*, 1-11. doi: 10.4414/smw.2011.13303

Sreedhar, J. S. (2016). Symptom occurrence, severity and quality of life as predicted by variables related to the cancer condition and selected demographic variables. Retrieved from https://kuscholarworks.ku.edu/bitstream/handle/1808/22498/Sreedhar_ku_0099D_14577_DATA_1.pdf?sequence=1&isAllowed=y

Stanton, A. L., Danoff-Burg, S., & Huggins, M. E. (2002). The first year after breast cancer diagnosis: Hope and coping strategies as predictors of adjustment. *Psycho-Oncology, 11*, 93-102. doi:10.1002/pon.574

Sun, W., Lu, J., Wu, S., Bi, Y., Mu, Y., Zhao, J…Wang, W. (2016). Association of insulin resistance with breast, ovarian, endometrial and cervical cancers in non-diabetic women. *American Journal of Cancer Research, 6*(10), 2334-2344

Svensson, H., Brandberg, Y., Einbeigi, Z., Hatschek, T., & Ahlberg, K. (2009). Psychological reactions to progression of metastatic breast cancer – An interview study. *Cancer Nursing, 32*, 55-63. doi: 10.1097/01.NCC.0000343374.09270.ff

Taira, N., Shimozuma, K., Shiroiwa, T., Ohsumi, S., Kuroi, K., Sji, S…Katsumata, N. (2011). Associations among baseline variables, treatment-related factors and health-related quality of life 2 years after breast cancer surgery. *Breast Cancer Research and Treatment, 128*, 735-747. doi:10.1007/s10549-011-1631-y

Tannir, N. M., Cohen, L., Wang, X., Thall, P., Matthew, P. F., Jonasch, E…Logothetis, C. (2006). Improved tolerability and quality of life with maintained efficacy using twice-daily low-dose interferon-α-2b. *Cancer, 107*, 2254-2261. doi: 10.1002/cncr.22253

Tsimberidou, A. M., Iskander, N. G., Hong, D. S., Wheler, J. J., Falchook, G. S., Fu, S…Kurzrock, R. (2012). Personalized medicine in a phase I clinical trials program: The MD Anderson Cancer Center initiative. *Clinical Cancer Research, 18*, 6373-6383. doi: 10.1158/1078- 0432.CCR-12-1627

Tsimberidou, A. M., Wen, S., Hong, D. S., Wheler, J. J., Falchook, G. S., Fu, S…Berry, D. (2014). Personalized medicine for patients with advanced cancer in the phase I program at MD Anderson: Validation and landmark analyses. *Clinical Cancer Research, 20*, 4827-4836. doi: 10.1158/1078-0432.CCR-14-0603

United States Census Bureau. (2015). Quick facts South Dakota. Retrieved from http://www.census.gov/quickfacts/table/PST045215/46

Untch, M., Gelber, R. D., Jackisch, C., Procter, M., Baselga, J., Bell, R…Goldhirsch, A. (2008). Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. *Annals of Oncology, 19*, 1090-1096. doi: 10.1093/annonc/mdn005

Urban, R. R., He, H., Alfonso, R., Hardesty, M. M., Gray, H. J., & Goff, B. A. (2016). Ovarian cancer outcomes: Predictors of early death. *Gynecology Oncology, 140*, 474-480. doi: 10.1016/j.ygyno.2015.12.021

Van Cleave, J. H., Egleston, B. L., Ercolano, E., & McCorkle, R. (2013). Symptom distress in older adults following cancer surgery. *Cancer Nursing, 36*, 292-300. doi: 10.1097/NCC.0b013e31826dd517

Vance, D. E. (2012). Troubles and triumphs of secondary data analysis: General guidelines. *Research Practitioner*, 13(4), 128-135

Visser, M. R., Smets, E. M., Sprangers, M. A., & de Haes, H. J. (2000). How response shift may affect the measurement of change in fatigue. *Journal of Pain and Symptom Management, 20*, 12-18. doi:10.1016/S0885-3924(00)00148-2

Valeberg, B. T. & Grov, E. K. (2013). Symptoms in the cancer patient: Of importance for their caregivers' quality of life and mental health? *European Journal of Oncology Nursing, 17,* 46-51. doi: 10.1016/j.ejon.2012.01.009

Vo, J. B., Nolan, T. S., Vance, D. E., Patrician, P. A., & Meneses, K. (2017). Cardiovascular disease risk among breast cancer survivors: An evolutionary concept analysis. Nursing: Research and Reviews, 7, 9-16. doi: https://doi.org/10.2147/NRR.S122852

Vona-Davis, L., & Rose, D. P. (2009). The influence of socioeconomic status on breast cancer tumor biology and prognosis: A review. *Journal of Women's Health, 18*, 883-896. Doi: 10.1089/jwh.2008.1127

Vrachnis, N., Iavazzo, C., Iliodromiti, Z., Sifakis, S., Alexandrou, A., Siristatidis, C., Grigoriadis, C., Botsis, D., & Creatsas, G. (2016). Diabetes mellitus and gynecologic cancer: Molecular mechanisms, epidemiological, clinical and prognostic perspectives. Archives of Gynecology and Obstetrics, 293, 239-246. doi: 10.1007/s00404-015-3858-z

Walsh, D., Donnelly, S., & Rybicki, L. (2000). The symptoms of advanced cancer: Relationship to age, gender, and performance status in 1,000 patients. *Supportive Care in Cancer, 8*, 175-179. doi: 10.1007/s005209900128

Weigelt, B., & Reis-Filho, J. (2009). Histological and molecular types of breast cancer: Is there a unifying taxonomy? *Nature Reviews Clinical Oncology, 6*, 718-730. doi: 10.1038/nrclinonc.2009.166

Wieduwilt, M. J., & Moasser, M. M. (2008). The epidermal growth factor receptor family: Biology driving targeted therapeutics. *Cell Molecular Life Science, 65*, 1566-1584. doi: 10.1007/s00018-008-7440-8

Wikipedia. (2017). Cancer genome sequencing. Retrieved from https://en.wikipedia.org/wiki/Cancer_genome_sequencing

Winer, E., Gralow, J., Diller, L., Karlan, B., Loehrer, P., Pierce, L…Schilsky, R. L. (2009). Clinical cancer advances 2008; Major research advances in cancer treatment, prevention, and screening: A report from the American Society of Clinical Oncology. *Journal of Clinical Oncology, 27*, 812-826

Williams, P., Balabagno, A., Manahan, L., Piamjariuakul, U., Ranallo, L., & Laurente, C…Williams, A. (2010a). Symptom monitoring and self-care practices among Filipino cancer patients. *Cancer Nursing*, *33*(1), 37-46

Williams, P., Ducey, K., Sears, A., Williams, A., Tobin-Rumelhart, S., & Bunde, P. (2001). Treatment type and symptom severity among oncology patients by self-report. *International Journal of Nursing Studies*, *38*, 359-367

Williams, P. D., Graham, K. M., Storlie, D. L., Pedace, T. M., Haeflinger, K. V., Williams, D. D…Williams, A. R. (2013). Therapy-related symptom checklist use during treatments at a cancer center. *Cancer Nursing, 36*, 245-254. Doi: 10.1097/NCC.0b013e3182595406

Williams, P. D., Lopez, V., Sek Ying, C., Piamjariyakul, U., Wenru, W., Hung, G., ... Williams, A. (2010b). Symptom monitoring and self-care practices among oncology adults in China. *Cancer Nursing*, *33*(3), 185-193.

Williams, A., Mowlazadeh, B., Sisler, L., and Williams, P. D. (2015a). Self-reported assessment of symptoms and self-care within a cohort of U.S. Veterans during outpatient care for cancer. *Clinical Journal of Oncology Nursing, 19*, 595-602. doi: 10.1188/15.CJON.595-602

Williams, P. D., Piamjariyakul, U., Ducey, K., Badura, J., Boltz, K., Olberding, K., ... Williams, A. (2006a). Cancer treatment, symptom monitoring, and self-care in adults. *Cancer Nursing*, *29*(5), 347-355.

Williams, A. R., Williams, P. D., & Doolittle, G. C. (2006b, October). *Use of a Therapy-Related Symptom Checklist (TRSC) in a rural telemedicine hematology/oncology practice in the United States*. Poster session presented at the IPOS, International Psycho-Oncology Society Congress, Venice, Italy.

Williams, P. D., Williams, A. R., Ducey, K., Sears, A., & Tobin, S. (1997). Therapy-Related Symptom Checklist (TRSC) for Oncology Patients. *Oncology Nursing Forum*, 24(2), 301

Williams, P. D., Williams, A. R., Kelly, K. P., Dobos, C., Gieseking, A., Connor, R…Favero, D. (2012). A symptom checklist for children with cancer: The Therapy-Related Symptom Checklist-Children. *Cancer Nursing, 35*, 89-98. doi: 10.1097/NCC.0b013e31821a51f6

Williams, P. D., Williams, K., LaFaver-Roling, S., Johnson, R., & Williams, A. R. (2011). An intervention to manage patient-reported symptoms during cancer treatment. *Clinical Journal of Oncology Nursing, 15,* 253-258. doi:10.1188/11.CJON.253-258

Williams, A. R., Williams, D. D., & Williams, P. D. (2014). The development and application of an oncology Therapy-Related Symptom Checklist for adults (TRSC), and for children (TRSC-C). In *Proceedings IWBBIO 2014 International Work-Conference on Bioinformatics and Biomedical Engineering* (vol. 1, pp. 298-307); Granada, Spain.

Williams, A. R., Williams, D. D., Williams, P. D., Alemi, F., Hesham, H., Donley, B, & Kheirbek, R. E. (2015b). The development and application of an oncology Therapy-Related Symptom Checklist for adults (TRSC) and children (TRSC-C) and e-health applications. *Biomedical Engineering Online, 14*(Suppl 2); S1. doi:10.1186/1475-925X-14-S2-S1

Willis, K., Lewis, S., Ng, F., & Wilson, L. (2015). The experience of living with metastatic breast cancer – A review of the literature. *Health Care for Women International, 3*6, 514-542. doi: 10.1080/07399332.2014.896364

Wood, M. E., Kadlubek, P., Pham, T. H., Wollins, D., Lu, K. H., Weitzel…Hughes, K. (2014). Quality of cancer family history and referral for genetic counseling and testing among oncology practices: A pilot test of quality measures as part of the American Society of Clinical Oncology Quality Oncology Practice Initiative. *Journal of Clinical Oncology, 32*, 824-829. doi: 10.1200/JCO.2013.51.4661

World Health Organization. (2015). Human genetics programme. Retrieved from http://www.who.int/genomics/geneticsVSgenomics/en/

Wright, A.A., Bohlke, K., Armstrong, D.K., Bookman, M.A., Cliby, W.A., Coleman, R.L…Eldeson, M.I. (2016). Chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology clinical practice guideline. *Journal of Clinical Oncology, 34*, 3460-3473. doi: 10.1200/JCO.2016.68.6907

Wu, H. S., & Harden, J. K. (2015). Symptom burden and quality of life in survivorship: A review of the literature. *Cancer Nursing, 38*, E29-54. doi: 10.1097/NCC.0000000000000135

Yabroff, K. R., Lund, J., Kepka, D., & Marrioto, A. (2011). Economic burden of cancer in the US: Estimates, projections, and future research. *Cancer Epidemiology and Biomarkers, 20*, 2006-2014. doi: 10.1158/1055-9965.EPI-11-0650

Yabroff, K. R., McNeel, T. S., Waldron, W. R., Davis, W. W., Brown, M. L., Clauser, S., & Lawrence, W. F. (2007). Health limitations and quality of life associated with cancer and other chronic disease by phase of care. *Medical Care, 45*, 629-637. doi: 10.1097/MLR.0b013e318045576a

Yap, T. A., Omlin, A., & de Bono, J. S. (2013). Development of therapeutic combinations targeting major cancer signaling pathways. *Journal of Clinical Oncology, 31*, 1592-1605. doi: 10.1200/JCO.2011.37.6418

Youngblood, M., Williams, P. D**.,** Eyles, H., Waring, J., & Runyon, S. (1994). A comparison of two methods of assessing cancer therapy-related symptoms. *Cancer Nursing*, 17(1), 37-44

Zafar, S. Y. (2016). Financial toxicity of cancer care: It's time to intervene. *Journal of the National Cancer Institute, 108*, 1-4. doi:10.1093/jnci/djv3

Appendix A

THERAPY-RELATED SYMPTOMS CHECKLIST (TRSC)

Name: _____ Hospital #_____ Date:_____

PLEASE **CHECK** THE PROBLEMS YOU HAVE HAD IMMEDIATELY AFTER AND SINCE YOUR LAST TREATMENT. PLEASE CIRCLE HOW SEVERE THE PROBLEM WAS ACCORDING TO THE FOLLOWING SCALE:

0 = NONE 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE

CHECK ☒	EXAMPLE Pain	Degree of Severity **(CIRCLE)** 0	1	2	3	4
☐	Taste Change	0	1	2	3	4
☐	Loss of appetite	0	1	2	3	4
☐	Nausea	0	1	2	3	4
☐	Vomiting	0	1	2	3	4
☐	Weight loss	0	1	2	3	4
☐	Sore mouth	0	1	2	3	4
☐	Cough	0	1	2	3	4
☐	Sore throat	0	1	2	3	4
☐	Difficulty swallowing	0	1	2	3	4
☐	Jaw pain	0	1	2	3	4
☐	Shortness of breath	0	1	2	3	4
☐	Numbness in fingers and/or toes	0	1	2	3	4
☐	Feeling sluggish	0	1	2	3	4
☐	Depression	0	1	2	3	4
☐	Difficulty concentrating	0	1	2	3	4
☐	Fever	0	1	2	3	4
☐	Bruising	0	1	2	3	4
☐	Bleeding	0	1	2	3	4
☐	Hair loss	0	1	2	3	4
☐	Skin changes	0	1	2	3	4
☐	Soreness in vein where chemotherapy was given	0	1	2	3	4
☐	Difficulty sleeping	0	1	2	3	4
☐	Pain	0	1	2	3	4
☐	Decreased interest in sexual activity	0	1	2	3	4
☐	Constipation	0	1	2	3	4
	Other problems (please list below)					
☐	_____	0	1	2	3	4
☐	_____	0	1	2	3	4
☐	_____	0	1	2	3	4
☐	_____	0	1	2	3	4

Appendix B

Health-Related Quality of Life (HRQOL), Linear Analogue Self Assessment (LASA)

ID #: _____ Date: _____

Directions: Please **circle the number (0-10)** best reflecting your response to the following that describes your feelings **during the last week, including today.**

A. How would you describe :

1. your overall Quality of Life ?

0 1 2 3 4 5 6 7 8 9 10

As bad as it can be As good as it can be

2. your overall mental (intellectual) well-being?

0 1 2 3 4 5 6 7 8 9 10

As bad as it can be As good as it can be

3. your overall physical well-being?

0 1 2 3 4 5 6 7 8 9 10

As bad as it can be As good as it can be

4. your overall emotional well-being?

0 1 2 3 4 5 6 7 8 9 10

As bad as it can be As good as it can be

5. your level of social activity?

0 1 2 3 4 5 6 7 8 9 10

As bad as it can be As good as it can be

6. your overall spiritual well-being?

0 1 2 3 4 5 6 7 8 9 10

As bad as it can be As good as it can be