

**Functional Status, Quality of Life, and Long-Term Survival  
in a Cohort of Women with Breast Cancer and Heart Failure:  
Results from the Medicare Health Outcomes Survey**

by

**Jordan M. Harrison**

**A dissertation submitted in partial fulfillment  
of the requirements for the degree of  
Doctor of Philosophy  
(Nursing)  
in the University of Michigan  
2017**

**Doctoral Committee:**

**Professor Christopher R. Friese, Co-Chair  
Assistant Professor Matthew A. Davis, Co-Chair  
Professor Debra L. Barton  
Professor Nancy K. Janz  
Professor Susan J. Pressler, Indiana University**

Jordan M. Harrison

joharr@umich.edu

ORCID iD: 0000-0002-4932-8504

© Jordan M. Harrison 2017

## Table of Contents

List of Tables .....	iv
List of Figures .....	v
ABSTRACT .....	vi
<b>Chapter 1. Introduction.....</b>	<b>1</b>
Statement of the Problem.....	3
Purpose.....	4
Research Questions .....	6
Review of the Literature .....	7
Theoretical Framework.....	31
References.....	35
<b>Chapter 2. Cardiotoxic Heart Failure in Breast Cancer Survivors: A Concept Analysis ...</b>	<b>53</b>
Abstract.....	53
Introduction.....	55
Background.....	56
Data Sources .....	58
Results.....	59
Discussion.....	70
Conclusions.....	71
References.....	73

<b>Chapter 3. Functional Status and Quality of Life Among Breast Cancer Survivors with Heart Failure: Results from the Medicare Health Outcomes Survey .....</b>	<b>81</b>
Abstract .....	81
Introduction.....	83
Methods.....	84
Results.....	89
Discussion.....	91
References.....	101
 <b>Chapter 4. Heart Failure and Long-Term Survival Among Older Women with Breast Cancer .....</b>	 <b>108</b>
Introduction.....	108
Methods.....	109
Results.....	111
Discussion.....	112
References.....	119
 <b>Chapter 5. Synthesis and Conclusions .....</b>	 <b>122</b>
Summary of Major Research Findings .....	122
Significance.....	125
Strengths and Limitations .....	127
Directions for Future Research .....	129
Conclusions.....	134
References.....	136
 <b>Appendix.....</b>	 <b>144</b>

## List of Tables

<b>Table 1.1</b>	Measures.....	33
<b>Table 2.1</b>	Literature Search Terms.....	59
<b>Table 3.1</b>	Characteristics of Study Participants According to Heart Failure Status.....	95
<b>Table 4.1</b>	Characteristics of Study Participants According to Heart Failure Status.....	116
<b>Table 4.2</b>	Five- and Ten-Year Survival Rates Among Breast Cancer Patients According to Heart Failure Status .....	117

## List of Figures

<b>Figure 1.1</b>	Wilson and Cleary Model of Health-Related Quality of Life (1995).....	22
<b>Figure 1.2</b>	Conceptual Model Informed by the Wilson and Cleary Model for Health-Related Quality of Life .....	32
<b>Figure 3.1</b>	Selection of Breast Cancer Sample from SEER-MHOS Database.....	97
<b>Figure 3.2</b>	Mean Difference (95% Confidence Intervals) in SF-36 Health-Related Quality of Life Scores Among Breast Cancer Survivors According to Heart Failure Status	98
<b>Figure 3.3</b>	Activities of Daily Living Impairment Among Breast Cancer Survivors with Heart Failure Compared with Matched Controls.....	99
<b>Figure 3.4</b>	Adjusted Odds Ratios (95% Confidence Intervals) for the Association Between Heart Failure and Activities of Daily Living Impairment Among Breast Cancer Survivors.....	100
<b>Figure 4.1</b>	Selection of Breast Cancer Sample from SEER-MHOS Database.....	115
<b>Figure 4.2</b>	Survival Curves Overall and by Heart Failure Status Among Older Women with Breast Cancer.....	118

## **ABSTRACT**

The aging population and marked growth of chronic non-communicable disease pose new challenges for the United States healthcare system. Breast cancer survivors with complex chronic conditions are a growing population. Of particular interest are women with chronic heart failure, a progressive, life-limiting condition that affects approximately one third of breast cancer survivors aged 65 and older. Despite the high prevalence of heart failure in this population, little is known about the implications of chronic heart failure for patient outcomes in breast cancer survivors. The purpose of this dissertation research is to examine health-related quality of life (HRQOL), functional status, and survival in a cohort of older women with two complex chronic conditions: breast cancer and heart failure. This dissertation consists of three parts: 1) a concept analysis to examine the concept of cardiotoxic heart failure in breast cancer survivors; 2) a cross-sectional, population-based study to evaluate the relationship between heart failure diagnosis and patient-reported functional status and HRQOL among breast cancer survivors; and 3) a retrospective cohort study to examine the association between heart failure diagnosis and long-term survival among older women with breast cancer. These results will establish the foundation for future prospective research by identifying clinical subgroups of breast cancer survivors at greatest risk for adverse sequelae associated with heart failure, as well as identifying deficits in HRQOL or functional status to target for future intervention. This dissertation provides crucial data to inform a research program focused on management of complex chronic conditions in women, specifically the notable number of breast cancer survivors who also live with chronic heart failure.

## **Chapter 1**

### **Introduction**

The aging population and marked growth of chronic non-communicable disease pose new challenges for the US healthcare system (DeSantis et al., 2014; Vogeli et al., 2007). Multimorbidity in older adults results in greater healthcare service use, challenges to coordination of care, and increased complexity of disease self-management (Vogeli et al., 2007). The majority of Americans aged 65 and older have multiple chronic conditions, and nearly one in five have a history of cancer (Vogeli et al., 2007). Clinicians need better resources to preserve health-related quality of life (HRQOL) and reduce disability in aging cancer survivors with multiple chronic conditions. Breast cancer survivors with complex chronic conditions are a growing population. Over 70% of breast cancer survivors in the US are aged 60 and older, and many have comorbid conditions that impact their long-term function, quality of life, and survival (DeSantis et al., 2014; Hung, Ross, Boockvar, & Siu, 2011). Of particular interest are women with chronic heart failure, a progressive, life-limiting condition that disproportionately affects breast cancer survivors (Mozaffarian et al., 2015; Pinder, Duan, Goodwin, Hortobagyi, & Giordano, 2007).

Breast cancer survivors experience alarmingly high rates of chronic heart failure, and increasing clinician concerns for patients with diagnoses of cancer and heart disease has catalyzed an emerging cross-disciplinary field of cardio-oncology (Barac et al., 2015; Moslehi, 2013, 2016; Shelburne et al., 2014). Among women diagnosed with breast cancer between ages 66 to 70, ten-year prevalence of heart failure is 38% for women who receive anthracycline-based



chemotherapy (an agent known to cause cumulative, dose-dependent cardiomyocyte death), 33% for women who receive non-anthracycline chemotherapy, and 29% for women who receive no chemotherapy (Pinder et al., 2007; Volkova & Russell, 2011). Comparatively, overall prevalence of heart failure in American women aged 60 to 79 is 5% (Mozaffarian et al., 2015).

Multiple factors account for the high prevalence of heart failure in older women with breast cancer. Cardiovascular disease and breast cancer share many risk factors, including advanced age, obesity, physical inactivity, and smoking. At the time of breast cancer diagnosis, many older women have preexisting comorbidities such as coronary artery disease, hypertension, and diabetes. Furthermore, many breast cancer therapies are cardiotoxic and interact synergistically with existing cardiovascular risk factors to increase the risk of heart failure. Breast cancer treatments, including anthracycline chemotherapy, mediastinal radiation, and biological therapies such as trastuzumab, increase women's risk for developing chronic heart failure (Lindenfeld & Kelly, 2010; Schmitz, Prosnitz, Schwartz, & Carver, 2012).

Heart failure and breast cancer share many overlapping symptoms and associated deficits in HRQOL and functional status. Fatigue, sleep disturbance, neurocognitive issues, edema, chronic pain, depression, and functional decline are common in patients with heart failure as well as women who survive breast cancer. In a review of the literature, no studies were found that assessed HRQOL or functional status among breast cancer survivors who were also diagnosed with chronic heart failure, who likely experience severe and prolonged deficits in function and quality of life. The first step to improving breast cancer survivorship care for women with chronic heart failure is to gain a better understanding of how heart failure impacts these patient-centered outcomes.

## Statement of the Problem

The consequences of cardiovascular comorbidity in older women with breast cancer are understudied. Despite the high prevalence of heart failure in this population, little is known about the impact of chronic heart failure on HRQOL, functional status, and long-term survival in breast cancer survivors aged 65 and older.

Heart failure is associated with known deficits in HRQOL and functional status, but due to a dearth of focused research, the extent of these deficits for breast cancer survivors is unknown (Harrison, Pressler, & Friese, 2016; Heo, Doering, Widener, & Moser, 2008; Juenger et al., 2002). Our extant understanding of HRQOL in heart failure originated from clinical trials in which women were consistently underrepresented and patients with cancer were systematically excluded (Harris & Douglas, 2000; Heiat, Gross, & Krumholz, 2002; Wenger, 2002). Interventions to preserve HRQOL in breast cancer survivors were not designed for the subset of women with chronic heart failure, and sparse data exist to inform development of interventions targeted towards this population.

In addition, chronic heart failure is a competing risk factor for mortality in older women with breast cancer (Schmitz et al., 2012). However, patients with comorbidities such as heart failure are typically excluded from oncology clinical trials (Lewis, 2003), and clinical studies with limited follow-up time underestimate the long-term survival impact of heart failure in patients with breast cancer (Pinder et al., 2007). Thus, little is known about the association between heart failure and long-term survival among older women with breast cancer. Furthermore, it is unclear how the relative contribution of heart failure to mortality risk varies by breast cancer stage – an important consideration, as the competing mortality risk of heart failure must be weighed against the benefits of cancer treatment for each individual.

## **Purpose**

The purpose of this dissertation research is to examine HRQOL, functional status, and survival in a cohort of women with two complex chronic conditions: breast cancer and heart failure. These analyses were conducted using national data from the Surveillance, Epidemiology, and End Results-Medicare Health Outcomes linked database (SEER-MHOS), which integrates robust clinical data from SEER cancer registries with annual Medicare Health Outcomes Surveys.

This dissertation is divided into three parts:

### **Part 1: Cardiotoxic Heart Failure in Breast Cancer Survivors: A Concept Analysis**

A concept analysis involves using a structured framework to create a precise operational definition of a concept for use in research or practice (Walker & Avant, 2011). The purpose of this concept analysis was to establish the context of this dissertation research by examining the concept of “cardiotoxic heart failure” in breast cancer survivors. Despite numerous studies reporting cardiotoxic effects of breast cancer therapies, the literature lacks consistent terminology to describe cancer treatment-induced heart failure, defined in this concept analysis as “cardiotoxic heart failure.” Although heart failure in breast cancer survivors is not always cardiotoxic in origin, this concept analysis demonstrates the potential for interaction between cardiotoxic breast cancer therapies and an individual’s preexisting cardiovascular risk factors, resulting in elevated risk for heart failure. Using the methods of Walker and Avant (2011), previous research findings were synthesized in an integrative review of etiologies and risk factors for cardiotoxic heart failure in breast cancer survivors. The concept of cardiotoxic heart failure was defined, and a series of four case studies demonstrated its defining attributes in breast cancer survivors, in addition to antecedents, consequences, and empirical referents.

## **Part 2: Functional Status and Quality of Life among Breast Cancer Survivors with Heart Failure: Results of the Medicare Health Outcomes Survey**

The purpose of this cross-sectional, population-based study was to evaluate the relationship between heart failure diagnosis and patient-reported functional status and HRQOL among breast cancer survivors aged 65 and older (n = 924). To do so we used national data from the Medicare Health Outcomes Survey linked to SEER cancer registries. Findings from these analyses will help inform development of evidence-based interventions to prevent deterioration of HRQOL and functional status among breast cancer survivors with chronic heart failure.

## **Part 3: Heart Failure and Long-Term Survival among Older Women with Breast Cancer**

The purpose of this retrospective cohort study was to examine the association between heart failure diagnosis and long-term survival (survival up to ten years after cancer diagnosis) among older women with breast cancer (n = 3,689) using data from SEER cancer registries linked to the Medicare Enrollment Database. To our knowledge, no prior study has examined the association between comorbid heart failure and overall survival at ten years across cancer stages among a diverse sample of women with breast cancer. Given the high prevalence of heart failure in this population, understanding any differences in survival associated with heart failure diagnosis is important to inform breast cancer treatment decisions and survivorship care.

In summary, results from these analyses will establish the foundation for future prospective research by identifying clinical subgroups of breast cancer survivors at greatest risk for adverse sequelae associated with heart failure, as well as identifying deficits in HRQOL or functional status to target for future intervention. This dissertation provides crucial data to inform a research program focused on management of complex chronic conditions in women,

specifically the notable number of breast cancer survivors who also live with chronic heart failure.

### **Research Questions**

The following research questions guided the analyses for this dissertation:

**Aim 1:** Among breast cancer survivors aged 65 and older, evaluate the relationship between heart failure diagnosis and eight domains of physical and mental HRQOL, for the entire study cohort and then for subgroups stratified by breast cancer stage. Clinically important deficits in HRQOL are defined as 3-point (3%) differences in each of the eight domain scores, or 2-point (2%) differences in the overall mental and physical component scores.

**RQ-1a.** Among breast cancer survivors aged 65 and older, do women with a heart failure diagnosis report clinically significant deficits in physical and/or mental domains of HRQOL, compared to those without heart failure? If so, which domains? (Physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health, overall physical and mental components).

**RQ-1b.** How do the associations between heart failure and physical and/or mental HRQOL deficits vary across clinical stage of breast cancer?

**Aim 2:** Among breast cancer survivors aged 65 and older, evaluate the relationship between heart failure and functional status, for the entire study cohort and then for subgroups stratified by breast cancer stage. Functional status is measured by self-reported impairment (yes/no) in performing six activities of daily living (ADLs).

**RQ-2a.** Among breast cancer survivors aged 65 and older, do women with heart failure report significantly greater odds of ADL impairment relative to those without heart failure? If so, which ADLs are impaired?

**RQ-2b.** How do the associations between heart failure and ADL impairment vary across breast cancer stage?

**Aim 3:** Among women with breast cancer aged 65 and older, examine the association between heart failure status and overall survival up to ten years after breast cancer diagnosis, for the entire study cohort and then for subgroups stratified by breast cancer stage.

**RQ-3a.** Among women with breast cancer aged 65 and older, is heart failure associated with overall survival at ten years?

**RQ-3b.** How does the association between heart failure and ten-year mortality vary by breast cancer stage?

### **Review of the Literature**

This review of the literature is organized into the following categories:

- 1) Multimorbidity in Cancer Survivors
- 2) Correlates of Overall Survival in Non-Metastatic Breast Cancer
- 3) Quality of Life Deficits and Functional Impairment: Women with Breast Cancer
- 4) Quality of Life Deficits and Functional Impairment: Women with Heart Failure
- 5) Survey Methodology for Measurement of Health-Related Quality of Life in Cancer Survivors
- 6) Activities of Daily Living Performance as a Measure of Functional Status in Older Adults with Chronic Illness
- 7) Utility of the Medicare Health Outcomes Survey to Measure Comorbidity in Older Adults
- 8) Summary and Remaining Gaps

## **Multimorbidity in Cancer Survivors**

Multimorbidity is a term used to describe the presence of multiple chronic conditions in one individual (Brettschneider et al., 2013). The prevalence of chronic non-communicable disease and multimorbidity among older adults in the US has increased significantly in recent years. Between 1998 and 2008, the percentage of Americans aged 65 and older reporting one or more chronic diseases increased from 86.9% to 92.2%, and the percentage reporting four or more chronic diseases increased from 11.7% to 17.4%. The prevalence of hypertension, diabetes, cancer, chronic lung disease, and arthritis in older adults increased significantly during this time period (Hung et al., 2011).

Cancer survivors, in particular, have high rates of multimorbidity and increasing multimorbidity in the years following cancer treatment (Kenzik, Kent, Martin, Bhatia, & Pisu, 2016; Leach et al., 2015). Multimorbidity is consistently associated with poor outcomes among cancer survivors, including increased mortality risk (Piccirillo, Tierney, Costas, Grove, & Spitznagel, 2004), impaired physical function (Deimling, Arendt, Kypriotakis, & Bowman, 2009; Kenzik et al., 2016; Leach, Bellizzi, Hurria, & Reeve, 2016), and deficits in health-related quality of life (Bellizzi et al., 2012; A. W. Smith et al., 2008; Weaver et al., 2012). Furthermore, oncology patients with multimorbidity are less likely to receive or complete guideline-recommended cancer treatment, and they have increased risk of post-surgical complications and mortality (Sogaard, Thomsen, Bossen, Sorensen, & Norgaard, 2013).

In cancer survivors aged 65 and older, comorbid conditions often occur in “multimorbidity clusters,” or distinct clusters of two or more conditions. One study examined prevalence of disease clusters roughly one year before cancer diagnosis and one year post-cancer diagnosis among patients with prostate, breast, colorectal, genitourinary, and lung cancer.

Distribution of clusters varied by cancer type, but overall the most common clusters identified pre- and post-cancer diagnosis were a metabolic cluster (defined as co-occurring hypertension and diabetes), musculoskeletal conditions, cardiovascular conditions, and a cluster comprised of depressive disorder risk, gastrointestinal conditions, and pulmonary conditions. Multimorbidity clusters increased significantly from pre- to post-cancer diagnosis and were associated with significant functional deficits (Kenzik et al., 2016).

Patients with multimorbidity, particularly older adults, are underrepresented in oncology research. Most oncology clinical trials are conducted with relatively healthy patients. Patients aged 65 and older comprise 61% of new cancer diagnoses but only 25% of participants in oncology clinical trials, primarily due to exclusion of patients with functional limitations or comorbid conditions such as cardiovascular disease or renal disease (Lewis, 2003). Due to exclusion from clinical studies, little is known about long-term outcomes in patients with cancer and comorbid chronic conditions.

**Measurement of multimorbidity in cancer survivors.** The Charlson Comorbidity Index (CCI) has been used in numerous studies to assess comorbidity burden in cancer survivors (Eley et al., 1994; Fu et al., 2015; Sehl, Lu, Silliman, & Ganz, 2013; Tammemagi, Nerenz, Neslund-Dudas, Feldkamp, & Nathanson, 2005). The CCI was derived from inpatient Medicare claims data as a measure of mortality risk from comorbid conditions (Charlson, Pompei, & Ales, 1987). The instrument evaluates the presence of 19 conditions, each assigned a weighted score based on one-year mortality risk. Total score on the CCI accounts for number and severity of comorbid conditions. However, the CCI may not accurately predict mortality risk from competing causes in cancer survivors because the risk associated with specific conditions differs by cancer site (Klabunde, Potosky, Legler, & Warren, 2000).



Several adaptations of the CCI have been developed for more accurate assessment of competing mortality risk from comorbid conditions in cancer populations. An example is the NCI Combined Index, a cancer site-specific comorbidity index that uses empirically-derived weights for each condition to predict two-year non-cancer mortality. Klabunde et al. used SEER-linked Medicare claims data to derive four versions of the index for patients with breast, prostate, colorectal, and lung cancer. Cancer site-specific indices such as these may be useful to inform cancer treatment choices, although the use of claims-based data is a potential limitation and the indices only estimate short-term mortality risk (Klabunde, Legler, Warren, Baldwin, & Schrag, 2007).

**Risk factors for multimorbidity in breast cancer survivors.** Compared to other cancer populations, multimorbidity may be more frequent and severe among breast cancer survivors. In a survey of 1,527 survivors of breast, prostate, lung, and colorectal cancer, patients reported an average of 5 comorbid conditions, with an average of 1.9 conditions diagnosed after cancer. Breast cancer survivors reported the greatest multimorbidity, with an average of 5.8 comorbid conditions and, on average, 2.9 conditions diagnosed after cancer. Comorbidities were most likely to occur after cancer diagnosis for breast cancer survivors who were obese, physically inactive, or greater than ten years post-cancer diagnosis (Leach et al., 2015).

Comorbid conditions may be present at the time of breast cancer diagnosis, or they may develop over time after cancer diagnosis and treatment. Clinical evaluation for patients with newly diagnosed breast cancer may uncover comorbidities that were previously undetected, such as EKG abnormalities or hyperglycemia. Various clinical and sociodemographic risk factors have been associated with multimorbidity among breast cancer survivors.

**Advanced age.** One of the most common risk factors for multimorbidity in breast cancer survivors is advanced age. Breast cancer occurs most frequently in women aged 55 to 64, and the median age at diagnosis is 62 years (National Cancer Institute, 2011). Of the 3.1 million breast cancer survivors in the US, approximately 72% are over the age of 60 (DeSantis et al., 2014). Many women in this age group have preexisting chronic conditions. In the 2008 Health and Retirement Survey, 71.8% of women aged 65 and older reported having two or more chronic conditions, including hypertension, heart disease, chronic lung disease, diabetes, stroke, cancer, and arthritis (Hung et al., 2011).

**Race and ethnicity.** Comorbidity burden among breast cancer survivors varies by race and ethnicity. In a study of black and Latina breast cancer survivors, 75% of women reported one or more comorbid conditions. Latinas were most likely to report diabetes, psychological problems, and greater than three comorbidities, while nearly half of black women reported hypertension and arthritis. Among all study participants, the most commonly reported comorbidities were arthritis (37%), hypertension (37%), psychological problems (29%), diabetes (19%), headache/migraine (17%), and osteoporosis (14%) (Ashing, Rosales, Lai, & Hurria, 2014).

Compared to white women, black women diagnosed with breast cancer have greater comorbidity burden and are more likely to die of competing causes. In a longitudinal cohort study of breast cancer survivors, black women had 3.20 times greater odds of having at least one adverse comorbidity, defined as a condition associated with significantly increased mortality risk, compared to white women (86.0% vs. 65.7%). Black women also had significantly higher rates of diabetes (26.4% vs. 9.5%) and hypertension (63.4% vs. 35.5%) than white women, and these conditions were the main drivers of disparity in survival rates (Tammemagi et al., 2005).

**Obesity.** Typically defined as a body mass index (BMI) greater than 30, obesity is a shared risk factor for breast cancer, cardiovascular disease, and pulmonary disease, among other chronic conditions (Klein et al., 2004; Schmitz et al., 2012). Adiposity is thought to increase the risk of hormone-driven cancers such as breast cancer through increased lifetime exposure to estrogen (Carmichael & Bates, 2004). Development of coronary heart disease is directly related to obesity-related risk factors such as insulin resistance and type 2 diabetes, dyslipidemia, and hypertension (Klein et al., 2004). Obesity prevalence is increasing among breast cancer survivors in the US, with an average increase of 3.0% per year between 1997 and 2014. In 2014, estimated obesity prevalence among breast cancer survivors was 33%, compared to 29.4% in women with no history of cancer (Greenlee, Shi, Sardo Molmenti, Rundle, & Tsai, 2016).

### **Correlates of Overall Survival in Non-Metastatic Breast Cancer**

Overall survival, otherwise known as all-cause survival, encompasses both breast cancer-specific and competing cause survival. In addition to cancer-related variables, other clinical and demographic factors influence breast cancer survival outcomes.

**Prognostic and predictive factors for non-metastatic breast cancer.** Breast cancer mortality risk, i.e., the risk of distant recurrence and death from breast cancer, can be estimated based on prognostic and predictive disease characteristics. Prognostic factors are associated with disease-free survival regardless of cancer treatment. Predictive factors are associated with response to anti-estrogen therapy. Some factors are both prognostic and predictive (Cianfrocca & Goldstein, 2004).

Breast cancer staging is based upon tumor size, lymph node status, and presence of metastases, all of which are prognostic factors. Larger tumor size, greater lymph node involvement, and presence of metastases are negative prognostic factors. Tumor type and grade,

i.e., histologic characteristics of the tumor, also influence prognosis (Cianfrocca & Goldstein, 2004).

Estrogen and progesterone receptor status refer to the presence of hormone receptors on the tumor, which indicate hormone sensitivity of the cancer. ER- and PR-positive status is predictive of response to anti-estrogen therapy with tamoxifen, aromatase inhibitors, or ovarian suppression. Tumors that overexpress the HER2 protein (human epidermal growth factor receptor-2) are associated with greater likelihood of recurrence (a negative prognostic factor) but positive predictive response to treatment with trastuzumab, a targeted therapy for treatment of HER2-positive breast cancer (Cianfrocca & Goldstein, 2004).

The potential survival benefit of treatment with systemic therapy (chemotherapy) for women with non-metastatic breast cancer depends upon the likelihood of disease recurrence (Cianfrocca & Goldstein, 2004). When the marginal benefit of systemic therapy is uncertain, genetic testing of the tumor can estimate the likelihood of disease recurrence. Since 2005, the Oncotype DX 21-gene assay has been available to inform treatment decisions regarding the use of systemic therapy for treatment of hormone receptor-positive breast cancer (Hassett et al., 2012). The test generates a recurrence score between 0 and 100 that correlates with the likelihood of cancer recurrence within 10 years of diagnosis. Use of genetic testing to inform treatment decision making has safely reduced the overall use of chemotherapy (Haas et al., 2011; Sparano et al., 2015).

In addition to cancer characteristics, certain demographic variables such as race/ethnicity and age at cancer diagnosis may be prognostic. Black and Latina women are more likely to be diagnosed with hormone receptor-negative breast cancer with higher stage at diagnosis. Younger

age at diagnosis (under 35) may be associated with worse prognosis (Cianfrocca & Goldstein, 2004).

*Age and comorbidity.* Women aged 65 and older have a 6-fold greater incidence of breast cancer, as well as an 8-fold greater breast cancer mortality rate compared to younger women (Alberg & Singh, 2001). The greater mortality rate in older women is not due to age alone but also the interaction of age-related risk factors such as comorbidity. It is difficult to separate the effects of age and comorbidity, as older women tend to have greater comorbidity burden. However, when accounting for the relative survival of age-matched women, the prognosis for older women with breast cancer is similar to that of younger women (Alberg & Singh, 2001; Howlader et al., 2016).

Comorbidity complicates treatment decision-making in patients with cancer and may limit treatment options. Cancer treatment modification due to comorbidity occurs in up to 50% of patients aged 65 and older (Extermann, 2012). Among postmenopausal women diagnosed with early-stage breast cancer, patients aged 65 and older have greater comorbidity and are less likely to receive guideline-recommended cancer therapy (Yancik et al., 2001). Breast cancer patients with comorbidity receive less extensive treatment and are less likely to receive radiotherapy or chemotherapy (Giordano, Duan, Kuo, Hortobagyi, & Goodwin, 2006; Louwman et al., 2005). However, comorbidity negatively affects prognosis independent of age, cancer stage, and treatment (Louwman et al., 2005).

Among women with breast cancer, total comorbidity burden predicts all-cause survival (Eley et al., 1994; Tammemagi et al., 2005). Increasing comorbidity burden, as measured by the Charlson Comorbidity Index, is associated with a dose-response effect on overall mortality risk, and diabetes and hypertension are significant drivers of non-cancer mortality risk (Tammemagi

et al., 2005). In a cohort study restricted to women with breast cancer aged 66 and older, preexisting comorbidities associated with significantly greater risk of all-cause mortality included cardiovascular disease, history of previous cancer, diabetes, and chronic obstructive pulmonary disease (Patnaik, Byers, DiGuseppi, Dabelea, & Denberg, 2011). The prevalence and relative impact of comorbid conditions on patient outcomes differs by cancer site (Klabunde et al., 2007). Additional cancer survivorship studies are needed to evaluate the impact of comorbid conditions on long-term survival outcomes.

***Obesity and lifestyle factors.*** Obesity is associated with greater mortality risk in women with breast cancer, although the mechanisms are unclear and there is no clear evidence that weight loss after cancer diagnosis improves survival. In a meta-analysis of 43 studies, obesity was associated with significantly worse overall mortality (HR 1.33; 95% CI: 1.21, 1.47) and worse breast cancer-specific mortality among women with breast cancer (HR 1.33; 95% CI: 1.19, 1.50) (Protani, Coory, & Martin, 2010). Adverse outcomes associated with obesity in breast cancer survivors may be mediated by comorbidity, and further research is needed to determine the mechanisms by which obesity influences survival (Protani et al., 2010).

In addition to obesity, lifestyle factors such as diet, physical activity, and smoking status have been associated with breast cancer-specific and overall survival outcomes, likely because these factors are also linked to cardiovascular disease and other comorbidities (Kushi, Kwan, Lee, & Ambrosone, 2007). Regular physical activity and smoking cessation are associated with improved cancer survival outcomes (Vijayvergia & Denlinger, 2015).

**Remaining gaps.** Most studies that have evaluated the impact of comorbidities on overall survival in women with breast cancer only examined survival up to five years post-cancer diagnosis (Eley et al., 1994; Patnaik, Byers, Diguseppi, Denberg, & Dabelea, 2011; Tammemagi

et al., 2005). Furthermore, most studies only evaluated preexisting comorbidities that were present at the time of cancer diagnosis. These studies likely underestimate the prevalence and long-term survival impact of comorbidities. It is also unclear how the relative contribution of comorbidities to mortality risk varies by breast cancer stage – a factor that may influence cancer treatment decisions. More research is needed to determine the long-term mortality risk associated with chronic conditions such as heart failure in women with breast cancer, including potential variation in mortality risk by cancer stage.

### **Quality of Life Deficits and Functional Impairment: Women with Breast Cancer**

With more effective diagnosis and treatment, including improved surgical techniques, targeted biological therapies, and genomic sequencing of tumor type, survival rates for breast cancer have increased substantially in the past 30 years (Fallowfield & Jenkins, 2015). After an initial lapse in HRQOL that typically occurs in the first six months following breast cancer diagnosis, many women's HRQOL improves over time (Stover et al., 2014). However, a subset of women who survive breast cancer experience chronic, unmanaged symptoms following treatment that impair HRQOL and functional status (Fallowfield & Jenkins, 2015).

Breast cancer survivors often experience clusters of co-occurring symptoms, both mental and physical (Dodd, Cho, Cooper, & Miaskowski, 2010; Roiland & Heidrich, 2011). Chronic symptoms may result from chemotherapy, radiotherapy, biological therapies, breast cancer surgery, and/or long-term hormone therapy. For many women, late effects of breast cancer treatment include persistent fatigue, depression, anxiety, sleep disturbance, hot flashes and other vasomotor symptoms, cognitive dysfunction, chronic pain, lymphedema, and sexual dysfunction (Accortt, Bower, Stanton, & Ganz, 2015; Blaney et al., 2015; Fallowfield & Jenkins, 2015; Schmidt et al., 2014; Von Ah & Tallman, 2015).

Fatigue is one of the most common post-treatment symptoms reported by breast cancer survivors, particularly women who received chemotherapy. The biological mechanism of cancer-related fatigue is thought to be related to activation of proinflammatory cytokines. Although fatigue often improves over time, approximately 30% of women experience chronic fatigue that may continue for years after treatment, often with co-occurring symptoms of depression, pain, and sleep disturbance. Fatigue in breast cancer survivors is associated with psychological morbidity, poor overall quality of life, and impairment in activities of daily living (Bower et al., 2000; Bower & Lamkin, 2013).

Up to 85% of breast cancer survivors report chronic pain, a major determinant of quality of life (Roiland & Heidrich, 2011). Pain is a common side effect of many breast cancer treatment modalities. Some women experience neuropathic pain resulting from breast cancer surgery, radiation, or chemotherapy-induced peripheral neuropathy (Reyes-Gibby, Morrow, Bennett, Jensen, & Shete, 2010). Lymphedema resulting from breast cancer surgery may cause pain, loss of sensation, and limited mobility (DiSipio, Rye, Newman, & Hayes, 2013). Many women taking aromatase inhibitors also report generalized musculoskeletal pain and arthralgias (Files, Ko, & Pruthi, 2010; Roiland & Heidrich, 2011).

Neurocognitive issues such as dizziness, loss of balance, and memory problems are common in breast cancer survivors (Roiland & Heidrich, 2011). Many women report persistent symptoms of cognitive dysfunction that impact their quality of life. Perceived cognitive dysfunction in breast cancer survivors is associated with symptoms of depression, fatigue, and anxiety. Chemotherapy and endocrine therapies may contribute to cognitive problems, but the mechanisms are unclear (Von Ah, Habermann, Carpenter, & Schneider, 2013; Von Ah & Tallman, 2015).



Women who receive systemic therapy for treatment of breast cancer report greater physical symptom burden and worse physical HRQOL (Ganz, 2002; Ganz, Kwan, Stanton, Bower, & Belin, 2011). In the first year post-treatment, women who received adjuvant chemotherapy report more severe and persistent physical symptoms, including musculoskeletal pain, weight problems, and nausea (Ganz et al., 2011). Among long-term, disease-free survivors (mean 6.3 years post-diagnosis), women who received systemic therapy with chemotherapy and/or tamoxifen report worse quality of life, including worse physical and social functioning, worse pain, and worse general health compared to women who did not receive systemic therapy. Of particular concern for women who receive systemic therapy are persistent and worsening deficits in physical function and overall physical health status five to ten years post-diagnosis (Ganz, 2002).

Functional impairment following breast cancer treatment can affect women of all ages and is independently associated with increased all-cause and competing-cause mortality (Braithwaite et al., 2010). Breast cancer survivors are more likely to report functional impairment if they are overweight or obese, aged 65 or older, or have comorbid conditions. Receipt of chemotherapy or radiotherapy is also associated with increased likelihood of functional impairment (Braithwaite et al., 2010). Women who report multiple symptoms or greater symptom-related distress have greater functional impairment and worse quality of life (Roiland & Heidrich, 2011).

In summary, chronic symptoms and HRQOL deficits have been well characterized among breast cancer survivors. However, in a review of the literature, no studies were found that examined these outcomes for breast cancer survivors also diagnosed with chronic heart failure.

## **Quality of Life Deficits and Functional Impairment: Women with Heart Failure**

Both mental and physical symptoms contribute to poor HRQOL in patients with heart failure. Two main symptom clusters are common in both men and women: a physical symptom cluster (dyspnea, fatigue, sleep disturbance) and an emotional symptom cluster (anxiety, depression, cognitive dysfunction) (Lee et al., 2010). When compared with men, women with heart failure have greater physical and emotional symptom burden and higher incidence of depression (Eastwood et al., 2012). Among women with heart failure, depressive symptoms are associated with anxiety, low perceived control, and higher body mass index (Eastwood et al., 2012). In a study of symptom clusters and level of distress in heart failure patients (35% women), women were more likely than men to be distressed by symptoms of depression, fatigue, and sleep disturbance (Lee et al., 2010). Heart failure patients with depression have lower adherence with therapy, more frequent hospitalizations, and higher mortality rates (Jiang et al., 2001).

Pain is a common and distressing symptom in patients with heart failure. In a multi-site study of 347 patients with advanced heart failure (36% women), 84% of patients reported pain, and 70% reported that pain interfered with daily activities. Forty percent of patients reported chest pain, and 76% reported pain at other sites. Commonly reported types of pain were lower back pain, arthritis pain, and angina pectoris with or without chest pain. Predictors of pain included degenerative joint disease, other arthritis, shortness of breath, and angina pectoris. Pain prevalence was similar among men and women (Goodlin et al., 2012).

Loss of balance is another heart failure symptom with significant implications for HRQOL and functional status, particularly in older women (Seo et al., 2008). Patients with heart failure are at increased risk for falls (Tymkew & Templin, 2011). Poor balance in heart failure

patients may result from long term activity intolerance and deconditioning (Seo et al., 2008), as well as changes in brain perfusion that result in damage to the cerebellum, which affects balance (Kumar et al., 2011).

Functional disability is common in heart failure patients and becomes more severe with advancing disease (Dunlay et al., 2015). Heart failure patients often experience symptoms of dyspnea, fatigue, activity intolerance, and loss of balance, resulting in deconditioning and loss of muscle strength over time (Seo et al., 2008). Cognitive dysfunction, another common symptom of heart failure, appears to mediate the effect of poor physical fitness on decreased functional status, although further research is needed to determine the mechanism (Alosco et al., 2015). In a longitudinal cohort study of heart failure patients (mean age 75 years; 49% women), difficulty performing ADLs was associated with increased risk of mortality and all-cause hospitalization, with the highest risk observed in patients who reported moderate to severe difficulty with ADLs (Dunlay et al., 2015).

Women are consistently underrepresented in heart failure clinical studies (Harris & Douglas, 2000; Heiat et al., 2002; Pressler, 2016), despite potential gender differences in heart failure symptoms, etiologies and response to drugs and other therapies (Harris & Douglas, 2000). Furthermore, patients with cancer are typically excluded from heart failure clinical trials (Wenger 2002). Consequently, very little is known about women with cancer and heart failure (Harrison et al., 2016).

### **Survey Methodology for Measurement of Health-Related Quality of Life Among Cancer Survivors**

Disease-free survival is no longer the only endpoint of cancer treatment success; achieving a high quality of life post-cancer treatment is the ultimate goal for many patients.

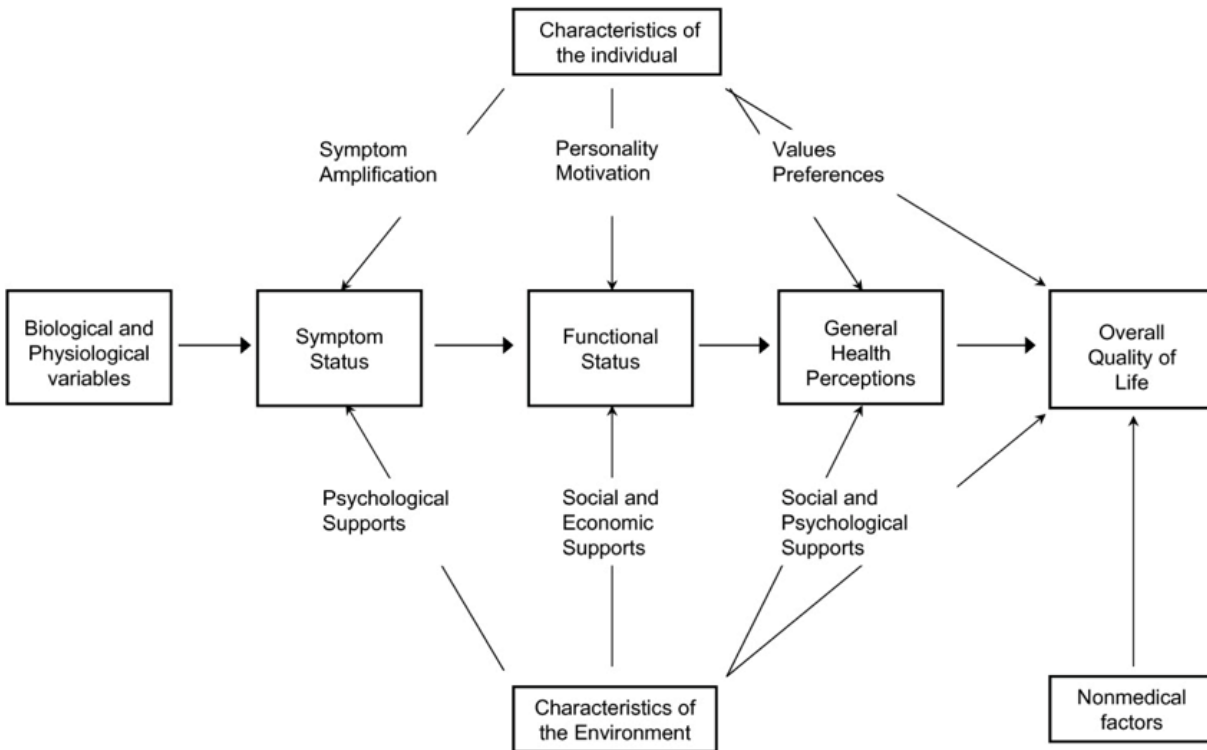
However, quality of life is a complex, multidimensional construct, and instruments designed to measure it vary widely in terms of what is actually measured. Because quality of life is multidimensional in nature, it may also be viewed as a “family” of related concepts. The ideal instrument to measure quality of life depends upon the population of interest, as well as the setting and aims of the study; therefore there is no gold standard instrument for measurement of quality of life (Ferrans, 2010).

Health-related quality of life (HRQOL) is defined as a multi-dimensional concept that encompasses the domains of physical, mental, emotional, and social functioning in the context of health and disease (Healthy People 2020 Foundation, 2010). Measurement of HRQOL is intended to capture the impact of health status on quality of life in each of these domains. The method in which HRQOL is operationalized depends upon the underlying conceptual model. HRQOL can be operationalized in multiple different ways, including patient-reported symptom burden, functional status, or overall “wellbeing” or life satisfaction (Healthy People 2020 Foundation, 2010).

The Wilson and Cleary Model of HRQOL (Figure 1.1) is a commonly used conceptual framework to study HRQOL. Wilson and Cleary define HRQOL as a multidimensional concept comprised of physical functioning, social functioning, role functioning, mental health, and general health perceptions. The authors describe the model as a classification scheme for different measures of health outcomes. The outcomes are divided into five levels: biological and physiological variables, symptoms, functional status, general health perceptions, and overall quality of life. From left to right, these five domains progress from the cellular level to the individual level to the interaction of the individual with society. Characteristics of the individual and his or her environment affect health outcomes at each level. A disease process such as heart

failure or breast cancer is considered a biological variable that will influence symptom status. A premise of the model is that symptoms predict HRQOL and can be alleviated through interventions (Wilson & Cleary, 1995).

**Figure 1.1** Wilson and Cleary Model for Health-Related Quality of Life (1995)



Measures of HRQOL derived from the Wilson and Cleary model vary substantially in the components of the model that are assessed. Biological and physiological variables are measured via laboratory and diagnostic tests and physical assessment. The other four components (symptom status, functional status, general health perceptions, and overall quality of life, i.e., overall satisfaction with life) are patient-reported outcomes, which by definition must be provided by the patient. Some HRQOL measures are disease-specific, while others such as the

Short Form-36 (SF-36) are generic measures that may be used in a variety of patient populations (Ferrans, 2010).

Most HRQOL measures are categorized by domain, including physical, mental, social, and emotional domains. These domains may be assessed in terms of symptoms, function, health perceptions, or overall wellbeing. Some measures focus predominantly on symptom status, while other focus predominantly on function in various domains or some combination of symptoms and function. In cancer clinical trials, the three most commonly used HRQOL measures are the FACT-G (Functional Assessment of Cancer Therapy-General), EORTC QLQ C-30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30), and the SF-36 (Cella et al., 1993; Fayers, Aaronson, & Bjordal, 2001; Turner-Bowker, 2002). The FACT-G and EORTC were both designed specifically for cancer clinical trials and include questions about cancer-specific symptoms, while the SF-36 is a generic measure not specific to cancer patients. Each of the three instruments measures different aspects of HRQOL; therefore selection of an appropriate measure depends upon the aims of the study (Ferrans, 2010).

The SF-36 has been used to measure HRQOL in numerous populations, including heart failure, cancer, and other chronic conditions (Turner-Bowker, 2002). A benefit of using this measure is the availability of age- and gender-adjusted SF-36 scores for the general US population. Non-specific instruments allow for comparisons with the general population, allowing researchers to quantify the average impact of the illness on quality of life (Ferrans, 2010). A potential drawback to broader HRQOL instruments is that they may not adequately measure symptoms or aspects of HRQOL specific to the condition of interest. For instance, common symptoms among breast cancer survivors include hot flashes, sleep disturbance, lymphedema, fatigue, depression, and anxiety (Fallowfield & Jenkins, 2015). These symptoms

are not directly measured by the SF-36. However, for the purposes of this study, a generic instrument such as the SF-36 is ideal for comparison of HRQOL between two groups with and without heart failure.

**Psychometric properties of the Short Form-36 and Veterans Rand-12 in breast cancer survivors.** The SF-36 has been validated extensively in breast cancer survivors. The following section describes reliability and validity of the SF-36 and its derivatives for breast cancer survivors, including convergent validity with cancer-specific quality of life measures and symptom-specific measures for lymphedema and fatigue. The Veterans Rand-12 (VR-12) is a derivative of the SF-36 that consists of the shortened SF-12 plus two additional questions to assess change over the past year in physical and emotional health.

In a systematic review to assess reliability and validity of the SF-36 and its derivatives for breast cancer survivors, seven papers were identified that assessed psychometric properties of the SF-36 (n=5), partial SF-36 (n=1), or the shortened SF-12 (n=1) in breast cancer survivors (Treanor & Donnelly, 2015). Methodological quality of the papers was assessed using the Consensus-Based Standards for the Selection of Health Measurement Instruments. Overall, the authors concluded that the SF-36 is a valid and reliable measure of HRQOL in breast cancer survivors, with acceptable to good internal consistency reliability (Ashing-Giwa, Padilla, Tejero, & Kim, 2004; Ashing-Giwa, Lam, & Xie, 2013; Ashing-Giwa & Rosales, 2013), good convergent validity with cancer-specific HRQOL measures (Ashing-Giwa et al., 2004; Ashing-Giwa & Rosales, 2013) and lymphedema-specific measures (Devoogdt, Van Kampen, Geraerts, Coremans, & Christiaens, 2011; Viehoff, van Genderen, & Wittink, 2008), and moderately good construct validity among various ethnic and language subgroups (Ashing-Giwa et al., 2004; Ashing-Giwa et al., 2013; Ashing-Giwa & Rosales, 2013). Interpretation of SF-36 scores may

differ slightly for non-English speaking groups, as translated versions of the survey may not equate with the original English language survey due to cultural factors and differences in interpretation of questions (Treanor & Donnelly, 2015). Additional details are listed in the Appendix.

***Convergent validity of the SF-36 with cancer-specific quality of life measures.*** Two studies have assessed convergent validity of the SF-36 with corresponding subscales of the Functional Assessment of Cancer Therapy, FACT-B and FACT-G (Ashing-Giwa et al., 2004; Ashing-Giwa & Rosales, 2013). The Fact-G (FACT-General) is a 33-item quality of life measure for patients undergoing cancer treatment (Cella et al., 1993). Domains assessed include physical, social/family, emotional, and functional wellbeing. The FACT-B consists of the FACT-G plus the Breast Cancer Subscale, which includes nine additional items specific to breast cancer (Brady et al., 1997). In two studies that examined convergent validity of the SF-36 with corresponding subscales of the FACT-B (Ashing-Giwa et al., 2004) and FACT-G (Ashing-Giwa & Rosales, 2013) among multiple language and ethnic groups, the strength and direction of associations between respective SF-36 and FACT subscales were similar across the total sample and across subgroups. SF-36 subscale scores equated with corresponding domain scores of the cancer-specific FACT measures (see Appendix for correlation coefficients).

***Convergent validity of the SF-36 subscales with lymphedema-specific measures.*** Two Dutch studies assessed convergent validity of the SF-36 subscales with lymphedema-specific measures in breast cancer survivors (Devoogdt et al., 2011; Viehoff et al., 2008). In both studies, the SF-36 bodily pain subscale and other physical subscales showed moderate correlations in the expected direction with corresponding subscales of the lymphedema measures (see Appendix for correlation coefficients).



***Validity of the SF-36 vitality subscale as a measure of fatigue.*** The SF-36 vitality subscale has been validated as a robust measure of fatigue in breast cancer survivors in numerous studies (Davies, Gibbons, Mackintosh, & Fitzpatrick, 2009; Ganz, 2002; Meeske et al., 2007; Stover et al., 2013). In a study of 800 women two to five years post-breast cancer diagnosis (Meeske et al., 2007), 41% of participants had clinically significant fatigue, as determined by a score of 4 or greater on the validated Piper Fatigue Scale-Revised (PFS-R). All eight subscale scores on the SF-36 were significantly lower ( $p < 0.0001$ ) for participants with fatigue than for those without fatigue (Appendix). Mean differences between participants with and without fatigue were greater for mental health than for physical health (Meeske et al., 2007). In another study, severity of fatigue in breast cancer survivors, as measured by a model of clinically significant threshold scores derived from the PFS-R, explained approximately 40% of the variance in the SF-36 physical component score and 30% of the variance in the mental component score (Stover et al., 2013). The SF-36 vitality subscale showed a high degree of correlation with scores on the PFS-R ( $r = -0.73$ ,  $p < 0.0001$ ) (Stover et al., 2013).

***Validity of the SF-36 in heart failure patients.*** Although psychometric properties of the SF-36 have not been evaluated specifically among breast cancer survivors with heart failure, the eight domain scores have been validated as sensitive indicators of decline in HRQOL among patients with heart failure. In a clinical study of 205 heart failure patients (84% male, mean age 54), HRQOL in all eight domains declined with increasing New York Heart Association (NYHA) functional class (Juenger et al., 2002). Increasing NYHA functional class (I, II, III, or IV) indicates worsening heart failure (Yancy et al., 2013). Patients with NYHA Class III heart failure, characterized by marked limitations in physical activity, had approximately one third the

score of the general population in physical functioning, role functioning physical, bodily pain, general health, vitality, and role functioning emotional (Juenger et al., 2002).

*Comparisons between the SF-36 and VR-12.* The VR-12 was derived from the SF-36 and assesses the same eight HRQOL subscales but with fewer questions. To make direct comparisons between SF-36 and VR-12 scores, the eight domain subscales from both surveys can be transformed to standardized t-scores using published algorithms (Fleishman, Selim, & Kazis, 2010). Based on psychometric evaluation of the SF-36, the VR-12 contains the twelve most essential items from the SF-36, plus two additional questions to assess change over the past year in physical and emotional health. Both surveys compute overall physical component and mental component scores based on weighted scores from each of the eight domain subscales. Reliability and validity of the VR-12 have been evaluated extensively in ambulatory care patient populations (Selim et al., 2007, 2010). Compared to the SF-36, the VR-12 is more responsive to change over time (Selim et al., 2007, 2010). The VR-12 has been used in numerous studies using SEER-MHOS data to assess HRQOL in cancer and non-cancer populations, including breast cancer survivors (Quach, Sanoff, Williams, Lyons, & Reeve, 2015; Reeve, Smith, Arora, & Hays, 2008; Reeve et al., 2009, 2012; Smith et al., 2008; Stover et al., 2013, 2014).

### **Activities of Daily Living Performance as a Measure of Functional Status in Older Adults**

Functional status is defined as an individual's ability to perform tasks required for living (Elsawy & Higgins, 2011). Two commonly used metrics to assess functional status in older adults are ability to perform activities of daily living (ADLs) and instrumental activities of daily living (IADLs). ADLs refer to daily self-care activities, such as eating, bathing, and dressing. Instrumental ADLs (IADLs) refer to activities required to live independently, such as housework, meal preparation, taking medication, and managing finances. A multidimensional

geriatric assessment for frail older adults includes measurement of ADL and IADL performance (Elsawy & Higgins, 2011).

ADLs are considered a more objective measure of function than IADLs, which are prone to cultural influences (Kautter & Pope, 2004). The Katz Index of Independence in Activities of Daily Living is a validated, widely used instrument that scores participants based on ability to perform six functions independently (yes/no): bathing, dressing, toileting, transferring, continence, and feeding (Elsawy & Higgins, 2011; Katz, Downs, Cash, & Grotz, 1970). ADLs have been used to assess functional status in older adults in multiple national surveys, including the Longitudinal Studies of Aging (National Center for Health Statistics, 2016) and the Health and Retirement Study (National Institute on Aging, 2016). Because impaired ADL performance in older adults predicts outcomes such as admission to nursing homes, use of home care services, hospitalization, and death, many insurance policies use ADL measures to determine eligibility for long-term care services (Wiener, Hanley, Clark, & Van Nostrand, 1990).

Although function in various domains (physical, social, and emotional) is a component of HRQOL measured on the Short Form-36, in the current study functional status has been conceptualized as ability to perform ADLs.

**Validation of the Medicare Health Outcomes Survey six-item scale for impairment in activities of daily living.** The six-item ADL measure used in the Medicare Health Outcomes Survey (MHOS) has been validated as a measure of functional impairment among Medicare enrollees. The survey asks, “Because of a health or physical problem, do you have any difficulty doing the following activities without special equipment or help from another person?” Six activities of daily living (bathing, dressing, eating, getting in/out of chairs, walking, and toileting) are measured on a three-point scale (1=unable to do this activity; 2=yes, I have

difficulty, 3=no, I do not have difficulty). These six ADL items comprise the core component of the CMS frailty adjustment model, a Medicare payment approach that pays managed care organizations according to the functional impairment of their community-dwelling enrollees (Kautter & Pope, 2004). The six-item ADL impairment measure in the MHOS is used as a frailty adjuster for enrollees in the Program of All-Inclusive Care for the Elderly (PACE), a Medicare program available in some states for provision of comprehensive medical care for frail community-dwelling older adults (Walsh, Nason, Moore, Khatutsky, & Caswell, 2003). The frailty adjustment model has been shown to explain Medicare expenditures better than diagnosis-based models (Kautter & Pope, 2004).

In a pilot study of PACE enrollees, results of the six-item ADL measure, as reported by patients or their proxies, were found to be comparable to nurse-administered assessments of ADLs, as well as ADLs reported in the medical record. A non-response analysis for the ADL impairment items was conducted using demographic data from the Medicare enrollment database and ADL impairment information from the medical record. Responders (individuals who completed all ADL items in the survey) were compared with non-responders (individuals who did not complete all ADL items). Non-responders did not differ significantly from responders in age, gender, mean number of ADL impairments, or distribution of ADL impairments (Walsh et al., 2003).

Kautter and Pope (2004) propose that a count measure of the number of impaired ADLs is the most promising measure of functional status for frailty adjustment, as the count measure improves statistical stability compared to using individual ADLs for frailty adjustment. A composite score for total ADL impairment (0-12 scale) has been derived from the six-item ADL measure on the MHOS, with higher scores indicating greater impairment. The composite

measure has been validated in a previous study of ADL impairment, chronic conditions, and HRQOL among older adults, with a Cronbach alpha of 0.88 (Barile et al., 2013). The composite measure for overall ADL impairment was also used in a SEER-MHOS study of HRQOL among older adults with and without colorectal cancer (Quach et al., 2015).

### **Utility of the Medicare Health Outcomes Survey to Measure Comorbidity in Older Adults**

The MHOS includes questions about the presence of twelve self-reported medical conditions. Several studies have used a simple count measure derived from the MHOS to evaluate comorbidity burden in older adults with or without a history of cancer (Barile et al., 2012, 2013; Kent et al., 2015, 2016; Kenzik et al., 2016). Other studies have used the MHOS to evaluate the presence of individual comorbid conditions in older adults with cancer (Leach et al., 2016; Quach et al., 2015; Reeve et al., 2009, 2012, 2008; Smith et al., 2008; Stover et al., 2013, 2014).

In a study to assess utility of the MHOS as a measure of comorbidity in older adults, self-reported conditions on the MHOS were validated against patient medical records. Patient-reported disease status for twelve conditions on the MHOS had acceptable specificity (70-94%) and sensitivity (65-85%) when compared with diagnostic codes from VA medical records. Agreement between the MHOS and medical record was assessed for twelve conditions: diabetes, hypertension, chronic lung disease, chronic low back pain from sciatica, arthritis, angina pectoris, congestive heart failure, heart attack, stroke, any cancer other than skin cancer, lung cancer, and colon cancer. Questions related to presence of diabetes, chronic lung disease, angina, CHF, stroke, and cancers had specificity of 85% or higher, indicating that patients who did not have these diseases listed in the medical record were unlikely to report them in the survey (Miller et al., 2008).

## **Summary and Remaining Gaps**

The contributions of this dissertation study are best viewed in the context of multimorbidity in aging cancer survivors. Aging of the US population will continue to shift the demographic towards older age groups, resulting in a projected 45% increase in cancer incidence by 2030 (Smith, Smith, Hurria, Hortobagyi, & Buchholz, 2009). Strategies to increase continuity of care while preserving HRQOL and reducing disability in cancer survivors with complex comorbidities will become increasingly important.

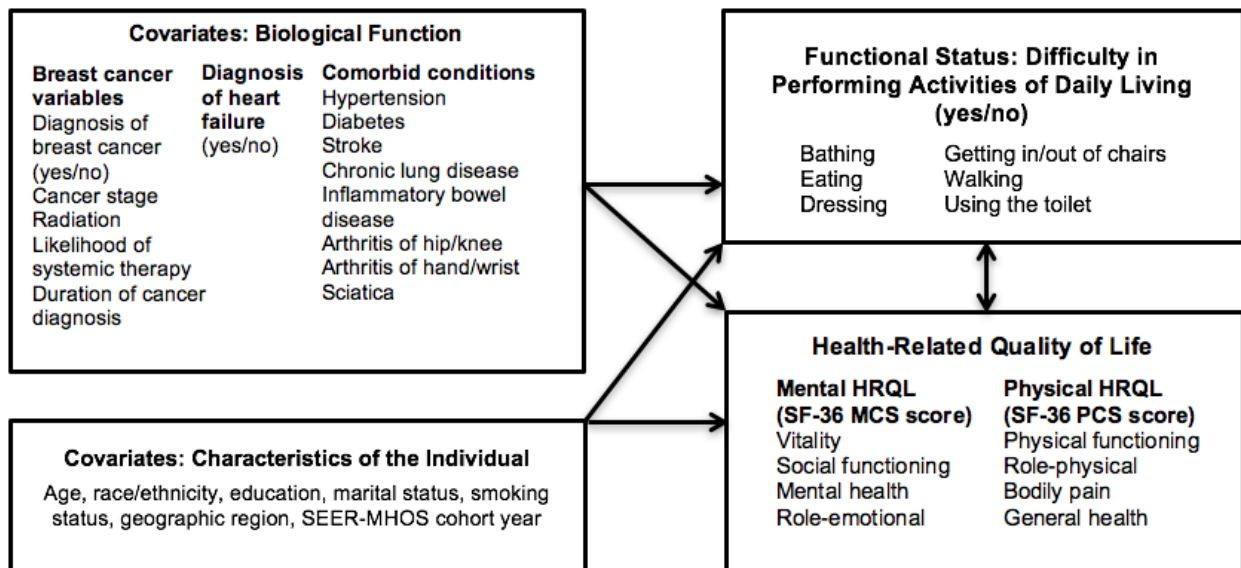
The co-occurrence of cancer and cardiovascular disease is a major public health issue, yet very little is known about older women with cancer and heart failure. Previous studies have primarily focused on the impact of individual chronic conditions on HRQOL and other patient outcomes, although the majority of older adults have multiple chronic conditions. The clustering of chronic conditions can influence the type and severity of health deficits that patients experience, particularly among cancer survivors (Fried, Bandeen-Roche, Kasper, & Guralnik, 1999; Kenzik et al., 2016). To address these gaps, we sought to characterize HRQOL, functional status, and long-term survival in a cohort of older women with breast cancer and heart failure, while examining the extent to which heart failure affects these outcomes.

## **Theoretical Framework**

The conceptual framework guiding this study (Figure 1.2) was informed by the Wilson and Cleary Model for HRQOL (Wilson & Cleary, 1995). The Wilson and Cleary model has been validated in heart failure patients (Heo et al., 2008; Rector, 2005) and cancer populations (Ferrans, 2010). According to this model, HRQOL is a multidimensional concept comprised of physical functioning, social functioning, role functioning, mental health, and general health perceptions. Biological variables and characteristics of the individual affect functional status and

HRQOL. The validated SF-36/VR-12 was used to evaluate overall mental and physical HRQOL (mental and physical component scores), in addition to eight domain subscales of HRQOL: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Mental Health, and Role-Emotional (Turner-Bowker, 2002). Each of the eight domain subscales measures a different aspect of HRQOL. Functional status was measured by patient-reported impairment (yes/no) in six activities of daily living. Study measures are listed in Table 1.1.

**Figure 1.2** Conceptual model informed by the Wilson and Cleary Model for Health-Related Quality of Life



**Table 1.1** Measures

<b>DEPENDENT VARIABLE: HRQOL measured by SF-36/VR-12</b> <i>(Healthcare Effectiveness Data and Information Set (HEDIS®) 2000 Volume 6: Specifications for the Medicare Health Outcomes Survey, 2000)</i>		
Scale	Description	Internal consistency reliability (Ashing-Giwa et al., 2004) <sup>†</sup>
<b>Physical Component Summary (PCS)</b>		
Physical functioning	The extent to which the respondent's health limits them in their performance of physical activities.	$\alpha = 0.88$ to $\alpha = 0.93$
Role-physical	The extent to which the physical health of the person completing the scale limits them in their work or other usual activities in terms of time and performance.	$\alpha = 0.86$ to $\alpha = 0.94$
Bodily pain	The severity of pain experienced by the respondent and the extent to which pain interferes with normal work, including work outside the home and housework.	$\alpha = 0.80$ to $\alpha = 0.86$
General health	Individual rates their current health status overall, their susceptibility to disease, and their expectations for health in the future.	$\alpha = 0.76$ to $\alpha = 0.84$
<b>Mental Component Summary (MCS)</b>		
Vitality	Subjective well-being rated in terms of energy and fatigue	$\alpha = 0.85$ to $\alpha = 0.90$
Social functioning	Limitations in normal social functioning due specifically to health-related problems.	$\alpha = 0.64$ to $\alpha = 0.88$
Mental Health	The frequency of feelings representing the major mental health dimensions.	$\alpha = 0.82$ to $\alpha = 0.86$
Role-emotional	Whether emotional problems have interfered with accomplishments at work or other usual activities in terms of time or performance.	$\alpha = 0.83$ to $\alpha = 0.88$
<b>DEPENDENT VARIABLE: FUNCTIONAL STATUS (MHOSv3.0 item 4)</b>		
<p><b>Because of a health or physical problem, do you have any difficulty doing the following activities without special equipment or help from another person?</b></p> <ul style="list-style-type: none"> <li>a) Bathing</li> <li>b) Eating</li> <li>c) Dressing</li> <li>d) Getting in or out of chairs</li> <li>e) Walking</li> <li>f) Toileting</li> </ul> <p><b>(1=Unable to do this activity; 2=Yes, I have difficulty; 3=No, I do not have difficulty)</b></p>		



<b>COVARIATES: BIOLOGICAL VARIABLES AND CHARACTERISTICS OF THE INDIVIDUAL</b>	
Variable	Data Source
<b>Biological variables</b>	
<b>Breast cancer variables:</b> Diagnosis of breast cancer (yes/no) Cancer stage Estrogen receptor status Treatment with radiation or surgery Duration of cancer diagnosis	SEER registry
<b>Heart failure diagnosis</b>	Patient self-report (yes/no) on MHOS
<b>Comorbid conditions</b>	Patient self-report (yes/no) on MHOS
<b>Characteristics of the Individual</b>	
Age, race/ethnicity	Patient self-report on MHOS/verification in Medicare database
Education, marital status, smoking status	Patient self-report on MHOS
SEER-MHOS catchment area (geographic region)	Medicare database

†SF-36 internal consistency reliability evaluated among n=703 breast cancer survivors, tested in total sample and within ethnic and language subgroups: African-American (n=135), European-American (n=179), Latina-American (n=183), Asian-American (n=206)

## References

- Accortt, E. E., Bower, J. E., Stanton, A. L., & Ganz, P. A. (2015). Depression and vasomotor symptoms in young breast cancer survivors: The mediating role of sleep disturbance. *Archives of Women's Mental Health, 18*(3), 565–8. <http://doi.org/10.1007/s00737-015-0504-5>
- Alberg, A. J., & Singh, S. (2001). Epidemiology of breast cancer in older women: Implications for future healthcare. *Drugs & Aging, 18*(10), 761–772.
- Alosco, M. L., Spitznagel, M. B., Sweet, L. H., Josephson, R., Hughes, J., & Gunstad, J. (2015). Cognitive dysfunction mediates the effects of poor physical fitness on decreased functional independence in heart failure. *Geriatrics and Gerontology International, 15*(2), 174–181. <http://doi.org/10.1111/ggi.12245>
- Ashing-Giwa, K., Lam, C. N., & Xie, B. (2013). Assessing health-related quality of life of Chinese-American breast cancer survivors: A measurement validation study. *Psycho-Oncology, 22*(3), 704–707. <http://doi.org/10.1002/pon.3030>
- Ashing-Giwa, K., Padilla, G., Tejero, J., & Kim, J. (2004). Breast cancer survivorship in a multiethnic sample - challenges in recruitment and measurement. *Cancer, 101*, 450–465. <http://doi.org/10.1002/cncr.20370>
- Ashing-Giwa, K., & Rosales, M. (2013). A cross-cultural validation of patient-reported outcomes measures: A study of breast cancers survivors. *Quality of Life Research, 22*(2), 295–308. <http://doi.org/10.1007/s11136-012-0140-8>
- Ashing, K., Rosales, M., Lai, L., & Hurria, A. (2014). Occurrence of comorbidities among African-American and Latina breast cancer survivors. *Journal of Cancer Survivorship, 8*(2), 312–318. <http://doi.org/10.1007/s11764-014-0342-x>

- Barac, A., Murtagh, G., Carver, J. R., Chen, M. H., Freeman, A. M., Herrmann, J., ... Douglas, P. S. (2015). Cardiovascular health of patients with cancer and cancer survivors: A roadmap to the next level. *Journal of the American College of Cardiology*, *65*(25), 2739–2746.  
<http://doi.org/10.1016/j.jacc.2015.04.059>
- Barile, J. P., Thompson, W. W., Zack, M. M., Krahn, G. L., Horner-Johnson, W., & Bowen, S. E. (2013). Multiple chronic medical conditions and health-related quality of life in older adults, 2004-2006. *Preventing Chronic Disease*, *10*(4), 120282.  
<http://doi.org/10.5888/pcd10.120282>
- Barile, J. P., Thompson, W. W., Zack, M. M., Krahn, G. L., Horner-Johnson, W., & Haffer, S. C. (2012). Activities of daily living, chronic medical conditions, and health-related quality of life in older adults. *The Journal of Ambulatory Care Management*, *35*(4), 292–303.  
<http://doi.org/10.1097/JAC.0b013e31826746f5>
- Bellizzi, K. M., Aziz, N. M., Rowland, J. H., Weaver, K., Arora, N. K., Hamilton, A. S., ... Keel, G. (2012). Double jeopardy? Age, race, and HRQOL in older adults with cancer. *Journal of Cancer Epidemiology*. <http://doi.org/10.1155/2012/478642>
- Blaney, J. M., McCollum, G., Lorimer, J., Bradley, J., Kennedy, R., & Rankin, J. P. (2015). Prospective surveillance of breast cancer-related lymphoedema in the first-year post-surgery: Feasibility and comparison of screening measures. *Supportive Care in Cancer*, *23*(6), 1549–59. <http://doi.org/10.1007/s00520-014-2504-9>
- Bower, J. E., Ganz, P. A., Desmond, K. A., Rowland, J. H., Meyerowitz, B. E., & Belin, T. R. (2000). Fatigue in breast cancer survivors: Occurrence, correlates, and impact on quality of life. *Journal of Clinical Oncology*, *18*(4), 743–753.
- Bower, J. E., & Lamkin, D. M. (2013). Inflammation and cancer-related fatigue: Mechanisms,

contributing factors, and treatment implications. *Brain, Behavior, and Immunity*.

<http://doi.org/10.1016/j.bbi.2012.06.011>

Brady, M. J., Cella, D. F., Mo, F., Bonomi, A. E., Tulsy, D. S., Lloyd, S. R., ... Shiimoto, G.

(1997). Reliability and validity of the functional assessment of cancer therapy-breast quality-of-life instrument. *Journal of Clinical Oncology*, *15*(3), 974–986.

Braithwaite, D., Satariano, W. A., Sternfeld, B., Hiatt, R. A., Ganz, P. A., Kerlikowske, K., ...

Caan, B. J. (2010). Long-term prognostic role of functional limitations among women with breast cancer. *Journal of the National Cancer Institute*, *102*(19), 1468–1477.

<http://doi.org/10.1093/jnci/djq344>

Brettschneider, C., Leicht, H., Bickel, H., Dahlhaus, A., Fuchs, A., Gensichen, J., ... MultiCare

Study Group. (2013). Relative impact of multimorbid chronic conditions on health-related quality of life -results from the MultiCare Cohort Study. *PLoS.One*.

<http://doi.org/10.1371/journal.pone.0066742>

Carmichael, A. R., & Bates, T. (2004). Obesity and breast cancer: A review of the literature.

*Breast*. <http://doi.org/10.1016/j.breast.2003.03.001>

Cella, D. F., Tulsy, D. S., Gray, G., Sarafian, B., Linn, E., Bonomi, A., ... et al. (1993). The

Functional Assessment of Cancer Therapy scale: Development and validation of the general measure. *Journal of Clinical Oncology*, *11*(3), 570–579. Retrieved from

<http://jco.ascopubs.org/content/11/3/570.full.pdf>

Charlson, M., Pompei, P., & Ales, K. (1987). A new method of classifying prognostic

comorbidity in longitudinal studies: Development and validation. *Journal of Chronic*

*Diseases*. [http://doi.org/10.1016/0021-9681\(87\)90171-8](http://doi.org/10.1016/0021-9681(87)90171-8)

Cianfrocca, M., & Goldstein, L. J. (2004). Prognostic and predictive factors in early-stage breast

- cancer. *The Oncologist*, 9(6), 606–16. <http://doi.org/10.1634/theoncologist.9-6-606>
- Davies, N., Gibbons, E., Mackintosh, A., & Fitzpatrick, R. (2009). A structured review of patient-reported outcome measures (PROMs) for women with breast cancer.
- Deimling, G. T., Arendt, J. A., Kypriotakis, G., & Bowman, K. F. (2009). Functioning of older, long-term cancer survivors: The role of cancer and comorbidities. In *Journal of the American Geriatrics Society* (Vol. 57). <http://doi.org/10.1111/j.1532-5415.2009.02515.x>
- DeSantis, C., Lin, C., Mariotto, A., Siegel, R., Stein, K., Kramer, J., ... Jemal, A. (2014). Cancer treatment and survivorship statistics, 2014. *CA: A Cancer Journal for Clinicians*, 64(4), 252–271.
- Devoogdt, N., Van Kampen, M., Geraerts, I., Coremans, T., & Christiaens, M.-R. (2011). Lymphoedema Functioning, Disability and Health Questionnaire (Lymph-ICF): Reliability and validity. *Physical Therapy*, 91(6), 944–57. <http://doi.org/10.2522/ptj.20100087>
- DiSipio, T., Rye, S., Newman, B., & Hayes, S. (2013). Incidence of unilateral arm lymphoedema after breast cancer: A systematic review and meta-analysis. *The Lancet Oncology*, 14(6), 500–515. [http://doi.org/10.1016/S1470-2045\(13\)70076-7](http://doi.org/10.1016/S1470-2045(13)70076-7)
- Dodd, M. J., Cho, M. H., Cooper, B. A., & Miaskowski, C. (2010). The effect of symptom clusters on functional status and quality of life in women with breast cancer. *European Journal of Oncology Nursing*, 14(2), 101–110. <http://doi.org/10.1016/j.ejon.2009.09.005>
- Dunlay, S. M., Manemann, S. M., Chamberlain, A. M., Cheville, A. L., Jiang, R., Weston, S. A., & Roger, V. L. (2015). Activities of daily living and outcomes in heart failure. *Circulation: Heart Failure*, 8(2), 261–7. <http://doi.org/10.1161/CIRCHEARTFAILURE.114.001542>
- Eastwood, J., Moser, D. K., Riegel, B. J., Albert, N. M., Pressler, S., Chung, M. L., ... Lennie, T. A. (2012). Commonalities and differences in correlates of depressive symptoms in men and

- women with heart failure. *European Journal of Cardiovascular Nursing*, 11(3), 356–65.  
<http://doi.org/10.1177/1474515112438010>
- Eley, J. W., Hill, H. A., Chen, V. W., Austin, D. F., Wesley, M. N., Muss, H. B., ... Edwards, B. K. (1994). Racial differences in survival from breast cancer: Results of the National Cancer Institute Black/White Cancer Survival Study. *Journal of the American Medical Association*, 272(12), 947–954.
- Elsawy, B., & Higgins, K. E. (2011). The geriatric assessment. *American Family Physician*, 83(1), 48–56. <http://doi.org/http://dx.doi.org/10.1159/000228650>
- Extermann, M. (2012). Integrating a geriatric evaluation in the clinical setting. *Seminars in Radiation Oncology*. <http://doi.org/10.1016/j.semradonc.2012.05.003>
- Fallowfield, L., & Jenkins, V. (2015). Psychosocial/survivorship issues in breast cancer: Are we doing better? *Journal of the National Cancer Institute*, 107(1), 335.  
<http://doi.org/10.1093/jnci/dju335>
- Fayers, P., Aaronson, N., & Bjordal, K. (2001). *EORTC QLQ-C30 scoring manual*. EORTC.  
Retrieved from  
<http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:EORTC+QLQ-C30+Scoring+Manual#0>
- Ferrans, C. E. (2010). Advances in measuring quality-of-life outcomes in cancer care. *Seminars in Oncology Nursing*, 26(1), 2–11. <http://doi.org/10.1016/j.soncn.2009.11.002>
- Files, J. A., Ko, M. G., & Pruthi, S. (2010). Managing aromatase inhibitors in breast cancer survivors: Not just for oncologists. *Mayo Clinic Proceedings*, 85(6), 560–566.  
<http://doi.org/10.4065/mcp.2010.0137>
- Fleishman, J. A., Selim, A. J., & Kazis, L. E. (2010). Deriving SF-12v2 physical and mental

- health summary scores: A comparison of different scoring algorithms. *Quality of Life Research*, 19(2), 231–241. <http://doi.org/10.1007/s11136-009-9582-z>
- Fried, L. P., Bandeen-Roche, K., Kasper, J. D., & Guralnik, J. M. (1999). Association of comorbidity with disability in older women: The Women's Health and Aging Study. *Journal of Clinical Epidemiology*, 52(1), 27–37. [http://doi.org/10.1016/S0895-4356\(98\)00124-3](http://doi.org/10.1016/S0895-4356(98)00124-3)
- Fu, M. R., Axelrod, D., Guth, A. A., Cleland, C. M., Ryan, C. E., Weaver, K. R., ... Melkus, G. D. (2015). Comorbidities and quality of life among breast cancer survivors: A prospective study. *Journal of Personalized Medicine*, 5(3), 229–42. <http://doi.org/10.3390/jpm5030229>
- Ganz, P. A. (2002). Quality of life in long-term, disease-free survivors of breast cancer: A follow-up study. *CancerSpectrum Knowledge Environment*, 94(1), 39–49. <http://doi.org/10.1093/jnci/94.1.39>
- Ganz, P. A., Kwan, L., Stanton, A. L., Bower, J. E., & Belin, T. R. (2011). Physical and psychosocial recovery in the year after primary treatment of breast cancer. *J Clin Oncol*, 29(9), 1101–1109. <http://doi.org/10.1200/JCO.2010.28.8043>
- Giordano, S. H., Duan, Z., Kuo, Y.-F., Hortobagyi, G. N., & Goodwin, J. S. (2006). Use and outcomes of adjuvant chemotherapy in older women with breast cancer. *Journal of Clinical Oncology*, 24(18), 2750–6. <http://doi.org/10.1200/JCO.2005.02.3028>
- Goodlin, S., Wingate, S., Albert, N., Pressler, S., Houser, J., Kwon, J., ... PAIN-HF Investigators. (2012). Investigating pain in heart failure patients: The pain assessment, incidence, and nature in heart failure (PAIN-HF) study. *Journal of Cardiac Failure*, 18(10), 776–783.
- Greenlee, H., Shi, Z., Sardo Molmenti, C. L., Rundle, A., & Tsai, W. Y. (2016). Trends in

obesity prevalence in adults with a history of cancer: Results From the US National Health Interview Survey, 1997 to 2014. *Journal of Clinical Oncology*, 34.

<http://doi.org/10.1200/JCO.2016.66.4391>

Haas, J. S., Liang, S.-Y., Hassett, M. J., Shiboski, S., Elkin, E. B., & Phillips, K. A. (2011). Gene expression profile testing for breast cancer and the use of chemotherapy, serious adverse effects, and costs of care. *Breast Cancer Research and Treatment*, 130(2), 619–26.

<http://doi.org/10.1007/s10549-011-1628-6>

Harris, D. J., & Douglas, P. S. (2000). Enrollment of women in cardiovascular clinical trials funded by the National Heart, Lung, and Blood Institute. *The New England Journal of Medicine*, 343(7), 475–480. <http://doi.org/10.1097/00006254-200101000-00022>

Harrison, J. M., Pressler, S. J., & Friese, C. R. (2016). Cardiotoxic heart failure in breast cancer survivors: A concept analysis. *Journal of Advanced Nursing*, 72(7), 1518–28.

<http://doi.org/10.1111/jan.12988>

Hassett, M. J., Silver, S. M., Hughes, M. E., Blayney, D. W., Edge, S. B., Herman, J. G., ... Weeks, J. C. (2012). Adoption of gene expression profile testing and association with use of chemotherapy among women with breast cancer. *Journal of Clinical Oncology*, 30(18), 2218–26. <http://doi.org/10.1200/JCO.2011.38.5740>

Health and Retirement Study. (2016). Retrieved from

[http://hrsonline.isr.umich.edu/?\\_ga=1.55809517.799118545.1479739120](http://hrsonline.isr.umich.edu/?_ga=1.55809517.799118545.1479739120)

*Healthcare Effectiveness Data and Information Set (HEDIS®) 2000 Volume 6: Specifications for the Medicare Health Outcomes Survey*. (2000). Washington, DC.

*Healthy People 2020 Foundation Health Measure Report: Health-Related Quality of Life and Well-Being*. (2010). Washington, DC. Retrieved from



<http://www.healthypeople.gov/sites/default/files/HRQoLWBFullReport.pdf>

Heiat, A., Gross, C. P., & Krumholz, H. M. (2002). Representation of the elderly, women, and minorities in heart failure clinical trials. *Archives of Internal Medicine*, *162*(15), 1682–8.

<http://doi.org/10.1001/archinte.162.15.1682>

Heo, S., Doering, L. V., Widener, J., & Moser, D. K. (2008). Predictors and effect of physical symptom status on health-related quality of life in patients with heart failure. *American Journal of Critical Care*, *17*(2), 124–132.

Howlader, N., Noone, A., Krapcho, M., Miller, D., Bishop, K., Altekruse, S., ... Cronin, K. (2016). *SEER Cancer Statistics Review, 1975-2013*. Bethesda, MD. Retrieved from

[http://seer.cancer.gov/csr/1975\\_2013/](http://seer.cancer.gov/csr/1975_2013/)

Hung, W. W., Ross, J. S., Boockvar, K. S., & Siu, A. L. (2011). Recent trends in chronic disease, impairment and disability among older adults in the United States. *BMC Geriatrics*, *11*, 47.

<http://doi.org/10.1186/1471-2318-11-47>

Jiang, W., Alexander, J., Christopher, E., Kuchibhatla, M., Gauden, L. H., Cuffe, M. S., ...

O'Connor, C. M. (2001). Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Archives of Internal Medicine*, *161*(15), 1849–56.

Juenger, J., Schellberg, D., Kraemer, S., Haunstetter, A., Zugck, C., Herzog, W., & Haass, M. (2002). Health related quality of life in patients with congestive heart failure: Comparison

with other chronic diseases and relation to functional variables. *Heart*, *87*(3), 235–241.

Katz, S., Downs, T. D., Cash, H. R., & Grotz, R. C. (1970). Progress in Development of the Index of ADL. *The Gerontologist*, *10*(1 Part 1), 20–30.

[http://doi.org/10.1093/geront/10.1\\_Part\\_1.20](http://doi.org/10.1093/geront/10.1_Part_1.20)

- Kautter, J., & Pope, G. C. (2004). CMS frailty adjustment model. *Health Care Financing Review*, 26(2), 1–19.
- Kent, E. E., Ambs, A., Mitchell, S. A., Clauser, S. B., Smith, A. W., & Hays, R. D. (2015). Health-related quality of life in older adult survivors of selected cancers: Data from the SEER-MHOS linkage. *Cancer*, 121(5), 758–65. <http://doi.org/10.1002/cncr.29119>
- Kent, E. E., Malinoff, R., Rozjabek, H. M., Ambs, A., Clauser, S. B., Topor, M. A., ... DeMichele, K. (2016). Revisiting the surveillance epidemiology and end results cancer registry and medicare health outcomes survey (SEER-MHOS) linked data resource for patient-reported outcomes research in older adults with cancer. *Journal of the American Geriatrics Society*, 64(1), 186–192. <http://doi.org/10.1111/jgs.13888>
- Kenzik, K. M., Kent, E. E., Martin, M. Y., Bhatia, S., & Pisu, M. (2016). Chronic condition clusters and functional impairment in older cancer survivors: A population-based study. *Journal of Cancer Survivorship*. <http://doi.org/10.1007/s11764-016-0553-4>
- Klabunde, C. N., Legler, J. M., Warren, J. L., Baldwin, L. M., & Schrag, D. (2007). A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. *Annals of Epidemiology*, 17(8), 584–590. <http://doi.org/10.1016/j.annepidem.2007.03.011>
- Klabunde, C. N., Potosky, A. L., Legler, J. M., & Warren, J. L. (2000). Development of a comorbidity index using physician claims data. *Journal of Clinical Epidemiology*, 53(12), 1258–1267. [http://doi.org/10.1016/S0895-4356\(00\)00256-0](http://doi.org/10.1016/S0895-4356(00)00256-0)
- Klein, S., Burke, L. E., Bray, G. A., Blair, S., Allison, D. B., Pi-Sunyer, X., ... Eckel, R. H. (2004). Clinical implications of obesity with specific focus on cardiovascular disease. *Circulation American Heart Association*, 110(18), 2952–2967.

<http://doi.org/10.1161/01.CIR.0000145546.97738.1E>

- Kumar, R., Woo, M. A., MacEy, P. M., Fonarow, G. C., Hamilton, M. A., & Harper, R. M. (2011). Brain axonal and myelin evaluation in heart failure. *Journal of the Neurological Sciences*, 307(1–2), 106–113. <http://doi.org/10.1016/j.jns.2011.04.028>
- Kushi, L. H., Kwan, M. L., Lee, M. M., & Ambrosone, C. B. (2007). Lifestyle Factors and Survival in Women with Breast Cancer. *Journal of Nutrition*, 137(5), 236S–242S.
- Leach, C. R., Bellizzi, K. M., Hurria, A., & Reeve, B. B. (2016). Is it my cancer or am I just getting older?: Impact of cancer on age-related health conditions of older cancer survivors. *Cancer*, 122(12), 1946–1953. <http://doi.org/10.1002/cncr.29914>
- Leach, C. R., Weaver, K. E., Aziz, N. M., Alfano, C. M., Bellizzi, K. M., Kent, E. E., ... Rowland, J. H. (2015). The complex health profile of long-term cancer survivors: prevalence and predictors of comorbid conditions. *Journal of Cancer Survivorship : Research and Practice*, 9(2), 239–51. <http://doi.org/10.1007/s11764-014-0403-1>
- Lee, K. S., Song, E. K., Lennie, T. A., Frazier, S. K., Chung, M. L., Heo, S., ... Moser, D. K. (2010). Symptom clusters in men and women with heart failure and their impact on cardiac event-free survival. *The Journal of Cardiovascular Nursing*, 25(4), 263–272. <http://doi.org/10.1097/JCN.0b013e3181cfbb88>
- Lewis, J. H. (2003). Participation of patients 65 years of age or older in cancer clinical trials. *Journal of Clinical Oncology*. <http://doi.org/10.1200/JCO.2003.08.010>
- Lindenfeld, J., & Kelly, P. A. (2010). Developing a cardiology-oncology clinical practice guideline. *Progress in Cardiovascular Diseases*, 53(2), 173–179. <http://doi.org/10.1016/j.pcad.2010.06.001>
- Louwman, W. J., Janssen-Heijnen, M. L. G., Houterman, S., Voogd, A. C., van der Sangen, M.

- J. C., Nieuwenhuijzen, G. A. ., & Coebergh, J. W. W. (2005). Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: A population-based study. *European Journal of Cancer*, *41*(5), 779–785. <http://doi.org/10.1016/j.ejca.2004.12.025>
- Meeske, K., Smith, A. W., Alfano, C. M., McGregor, B. a., McTiernan, A., Baumgartner, K. B., ... Bernstein, L. (2007). Fatigue in breast cancer survivors two to five years post diagnosis: A HEAL Study report. *Quality of Life Research*, *16*(6), 947–960. <http://doi.org/10.1007/s11136-007-9215-3>
- Miller, D. R., Rogers, W. H., Kazis, L. E., Spiro, A., Ren, X. S., & Haffer, S. C. (2008). Patients' self-report of diseases in the Medicare Health Outcomes Survey based on comparisons with linked survey and medical data from the Veterans Health Administration. *The Journal of Ambulatory Care Management*, *31*(2), 161–77. <http://doi.org/10.1097/01.JAC.0000314707.88160.9c>
- Moslehi, J. (2013). The cardiovascular perils of cancer survivorship. *New England Journal of Medicine*, *368*(11), 1055–1056. <http://doi.org/10.1056/NEJMe1215300>
- Moslehi, J. (2016). Cardiovascular toxic effects of targeted cancer therapies. *New England Journal of Medicine*, *375*(15), 1457–1467. <http://doi.org/10.1056/NEJMra1100265>
- Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., ... Turner, M. B. (2015). Heart disease and stroke statistics - 2016 update: A report from the american heart association. *Circulation*, *133*(4), e38–e360. <http://doi.org/10.1161/CIR.0000000000000350>
- National Cancer Institute. (2011). Cancer of the Breast (Female) - SEER Stat Fact Sheets. Retrieved from <http://seer.cancer.gov/statfacts/html/breast.html>
- National Center for Health Statistics. (2016). LSOA - Longitudinal Studies of Aging Homepage.

Retrieved from <http://www.cdc.gov/nchs/lsoa/>

- Patnaik, J. L., Byers, T., DiGuseppi, C., Dabelea, D., & Denberg, T. D. (2011). Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: A retrospective cohort study. *Breast Cancer Research, 13*(3), R64. <http://doi.org/10.1186/bcr2901>
- Patnaik, J. L., Byers, T., Diguseppi, C., Denberg, T. D., & Dabelea, D. (2011). The influence of comorbidities on overall survival among older women diagnosed with breast cancer. *Journal of the National Cancer Institute, 103*(14), 1101–1111. <http://doi.org/10.1093/jnci/djr188>
- Piccirillo, J. F., Tierney, R., Costas, I., Grove, L., & Spitznagel, E. (2004). Prognostic importance of comorbidity in a hospital based cancer registry. *Journal of the American Medical Association, 291*(20), 2441–2447.
- Pinder, M. C., Duan, Z., Goodwin, J. S., Hortobagyi, G. N., & Giordano, S. H. (2007). Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *Journal of Clinical Oncology, 25*(25), 3808–3815. <http://doi.org/10.1200/JCO.2006.10.4976>
- Pressler, S. J. (2016). Women with heart failure are disproportionately studied as compared with prevalence: A review of published studies from 2013. *The Journal of Cardiovascular Nursing, 31*(1), 84–8. <http://doi.org/10.1097/JCN.0000000000000212>
- Protani, M., Coory, M., & Martin, J. H. (2010). Effect of obesity on survival of women with breast cancer: Systematic review and meta-analysis. *Breast Cancer Research and Treatment, 123*(3), 627–635. <http://doi.org/10.1007/s10549-010-0990-0>
- Quach, C., Sanoff, H. K., Williams, G. R., Lyons, J. C., & Reeve, B. B. (2015). Impact of

- colorectal cancer diagnosis and treatment on health-related quality of life among older Americans: A population-based, case-control study. *Cancer*, 121(6), 943–50.  
<http://doi.org/10.1002/cncr.29125>
- Rector, T. S. (2005). A conceptual model of quality of life in relation to heart failure. *Journal of Cardiac Failure*, 11(3), 173–176. <http://doi.org/10.1016/j.cardfail.2004.09.002>
- Reeve, B. B., Potosky, A. L., Smith, A. W., Han, P. K., Hays, R. D., Davis, W. W., ... Clauser, S. B. (2009). Impact of cancer on health-related quality of life of older americans. *Journal of the National Cancer Institute*, 101(12), 860–868. <http://doi.org/10.1093/jnci/djp123>
- Reeve, B. B., Smith, A. W., Arora, N. K., & Hays, R. D. (2008). Reducing bias in cancer research: Application of propensity score matching. *Health Care Financing Review*, 29(4), 69–80.
- Reeve, B. B., Stover, A. M., Jensen, R. E., Chen, R. C., Taylor, K. L., Clauser, S. B., ... Potosky, A. L. (2012). Impact of diagnosis and treatment of clinically localized prostate cancer on health-related quality of life for older Americans: A population-based study. *Cancer*.  
<http://doi.org/10.1002/cncr.27578>
- Reyes-Gibby, C., Morrow, P. K., Bennett, M. I., Jensen, M. P., & Shete, S. (2010). Neuropathic pain in breast cancer survivors: using the ID pain as a screening tool. *Journal of Pain and Symptom Management*, 39(5), 882–9. <http://doi.org/10.1016/j.jpainsymman.2009.09.020>
- Roiland, R. A., & Heidrich, S. M. (2011). Symptom clusters and quality of life in older adult breast cancer survivors. *Oncology Nursing Forum*, 38(6), 672–80.  
<http://doi.org/10.1188/11.ONF.672-680>
- Schmidt, M. E., Chang-Claude, J., Seibold, P., Vrieling, A., Heinz, J., Flesch-Janys, D., & Steindorf, K. (2014). Determinants of long-term fatigue in breast cancer survivors: Results

of a prospective patient cohort study. *Psycho-Oncology*, 46(May 2014), 40–46.

<http://doi.org/10.1002/pon.3581>

Schmitz, K. H., Prosnitz, R. G., Schwartz, A. L., & Carver, J. R. (2012). Prospective surveillance and management of cardiac toxicity and health in breast cancer survivors. *Cancer*, 118(SUPPL.8), 2270–2276.

Sehl, M., Lu, X., Silliman, R., & Ganz, P. A. (2013). Decline in physical functioning in first 2 years after breast cancer diagnosis predicts 10-year survival in older women. *Journal of Cancer Survivorship*, 7(1), 20–31. <http://doi.org/10.1007/s11764-012-0239-5>

Selim, A. J., Berlowitz, D., Kazis, L. E., Rogers, W., Wright, S. M., Qian, S. X., ... Fincke, B. G. (2010). Comparison of health outcomes for male seniors in the Veterans Health Administration and Medicare Advantage plans. *Health Services Research*, 45(2), 376–96. <http://doi.org/10.1111/j.1475-6773.2009.01068.x>

Selim, A. J., Kazis, L. E., Rogers, W., Qian, S. X., Rothendler, J. A., Spiro, A., ... Fincke, B. G. (2007). Change in health status and mortality as indicators of outcomes: Comparison between the Medicare Advantage Program and the Veterans Health Administration. *Quality of Life Research*, 16(7), 1179–91. <http://doi.org/10.1007/s11136-007-9216-2>

Seo, Y., Roberts, B. L., Piña, I., Dolansky, M., Seo Y, Roberts BL, ... Dolansky M. (2008). Predictors of motor tasks essential for daily activities among persons with heart failure. *Journal of Cardiac Failure*, 14(4), 296–302. <http://doi.org/10.1016/j.cardfail.2008.01.005>

Shelburne, N., Adhikari, B., Brell, J., Davis, M., Desvigne-Nickens, P., Freedman, A., ... Remick, S. C. (2014). Cancer treatment–related cardiotoxicity: Current state of knowledge and future research priorities. *Journal of the National Cancer Institute*, 106(9). <http://doi.org/10.1093/jnci/dju232>

- Smith, A. W., Reeve, B. B., Bellizzi, K. M., Harlan, L. C., Klabunde, C. N., Amsellem, M., ...  
Hays, R. D. (2008). Cancer, comorbidities, and health-related quality of life of older adults.  
*Health Care Financing Review, 29*(4), 41–56.
- Smith, B. D., Smith, G. L., Hurria, A., Hortobagyi, G. N., & Buchholz, T. A. (2009). Future of  
cancer incidence in the united states: Burdens upon an aging, changing nation. *Journal of  
Clinical Oncology, 27*(17), 2758–2765. <http://doi.org/10.1200/JCO.2008.20.8983>
- Sogaard, M., Thomsen, R. W., Bossen, K. S., Sorensen, H. T., & Norgaard, M. (2013). The  
impact of comorbidity on cancer survival: A review. *Clinical Epidemiology*.  
<http://doi.org/10.2147/CLEP.S47150>
- Sparano, J. A., Gray, R. J., Makower, D. F., Pritchard, K. I., Albain, K. S., Hayes, D. F., ...  
Sledge, G. W. (2015). Prospective validation of a 21-gene expression assay in breast cancer.  
*New England Journal of Medicine, 373*(21), 150927220039001.  
<http://doi.org/10.1056/NEJMoa1510764>
- Stover, A. M., Mayer, D. K., Muss, H., Wheeler, S. B., Lyons, J. C., & Reeve, B. B. (2014).  
Quality of life changes during the pre- to postdiagnosis period and treatment-related  
recovery time in older women with breast cancer. *Cancer, 120*(12), 1881–9.  
<http://doi.org/10.1002/cncr.28649>
- Stover, A. M., Reeve, B. B., Piper, B. F., Alfano, C. M., Smith, A. W., Mitchell, S. A., ...  
Ballard-Barbash, R. (2013). Deriving clinically meaningful cut-scores for fatigue in a cohort  
of breast cancer survivors: a Health, Eating, Activity, and Lifestyle (HEAL) Study. *Quality  
of Life Research, 22*(9), 2279–92. <http://doi.org/10.1007/s11136-013-0360-6>
- Tammemagi, C. M., Nerenz, D., Neslund-Dudas, C., Feldkamp, C., & Nathanson, D. (2005).  
Comorbidity and survival disparities among black and white patients with breast cancer.



*JAMA : The Journal of the American Medical Association*, 294(14), 1765–1772.

<http://doi.org/10.1001/jama.294.14.1765>

Treanor, C., & Donnelly, M. (2015). A methodological review of the Short Form Health Survey 36 (SF-36) and its derivatives among breast cancer survivors. *Quality of Life Research*, 24(2), 339–62. <http://doi.org/10.1007/s11136-014-0785-6>

Turner-Bowker, D., Bartley, P., & Ware, J. (Eds.). (2002). *SF-36VR Health Survey & “SF” Bibliography: Third Edition (1988-2000)*. Lincoln, RI: Quality-Metric, Inc.

Tymkew, H., & Templin, L. (2011). Patients with chronic obstructive pulmonary disease or congested heart failure in a home health setting are at a high fall risk: A descriptive study. *American Physical Therapy*, 22(4), 25.

Viehoff, P. B., van Genderen, F. R., & Wittink, H. (2008). Upper limb lymphedema 27 (ULL27): Dutch translation and validation of an illness-specific health-related quality of life questionnaire for patients with upper limb lymphedema. *Lymphology*, 41(3), 131–8.

Vijayvergia, N., & Denlinger, C. (2015). Lifestyle factors in cancer survivorship: Where we are and where we are headed. *Journal of Personalized Medicine*, 5(3), 243–263.  
<http://doi.org/10.3390/jpm5030243>

Vogeli, C., Shields, A. E., Lee, T. A., Gibson, T. B., Marder, W. D., Weiss, K. B., & Blumenthal, D. (2007). Multiple chronic conditions: Prevalence, health consequences, and implications for quality, care management, and costs. *Journal of General Internal Medicine*, 22(SUPPL. 3), 391–395. <http://doi.org/10.1007/s11606-007-0322-1>

Volkova, M., & Russell, R. (2011). Anthracycline cardiotoxicity: Prevalence, pathogenesis and treatment. *Current Cardiology Reviews*, 7(4), 214–220.  
<http://doi.org/10.2174/157340311799960645>

- Von Ah, D., Habermann, B., Carpenter, J. S., & Schneider, B. L. (2013). Impact of perceived cognitive impairment in breast cancer survivors. *European Journal of Oncology Nursing*, *17*(2), 236–241. <http://doi.org/10.1016/j.ejon.2012.06.002>
- Von Ah, D., & Tallman, E. F. (2015). Perceived cognitive function in breast cancer survivors: Evaluating relationships with objective cognitive performance and other symptoms using the functional assessment of cancer therapy-cognitive function instrument. *Journal of Pain and Symptom Management*, *49*(4), 697–706. <http://doi.org/10.1016/j.jpainsymman.2014.08.012>
- Walker, L. O., & Avant, K. C. (2011). *Strategies for Theory Construction in Nursing* (5th ed.). Upper Saddle River, NJ: Pearson Prentice Hall.
- Walsh, E. G., Nason, C. A., Moore, A., Khatutsky, G., & Caswell, C. (2003). *Pilot Test of the Medicare Health Survey for PACE and EverCare: PACE Pilot Report*. Baltimore, MD. Retrieved from <http://www.rti.org/pubs/pilottestpace.pdf>
- Weaver, K. E., Forsythe, L. P., Reeve, B. B., Alfano, C. M., Rodriguez, J. L., Sabatino, S. a, ... Rowland, J. H. (2012). Mental and physical health-related quality of life among U.S. cancer survivors: population estimates from the 2010 National Health Interview Survey. *Cancer Epidemiology, Biomarkers & Prevention*, *21*(11), 2108–17. <http://doi.org/10.1158/1055-9965.EPI-12-0740>
- Wenger, N. K. (2002). Women, heart failure, and heart failure therapies. *Circulation*, *105*(13), 1526–1528. <http://doi.org/10.1161/01.CIR.0000014121.94868.81>
- Wiener, J. M., Hanley, R. J., Clark, R., & Van Nostrand, J. F. (1990). Measuring the activities of daily living: Comparisons across national surveys. *Journal of Gerontology*, *45*(6), S229–S237. <http://doi.org/10.1093/geronj/45.6.S229>

Wilson, I., & Cleary, P. (1995). Linking clinical variables with health-related quality of life: A conceptual model of patient outcomes. *Journal of the American Medical Association*, 273(1), 59–65. <http://doi.org/10.1001/jama.1995.03520250075037>

Yancik, R., Wesley, M. N., Ries, L. a, Havlik, R. J., Edwards, B. K., & Yates, J. W. (2001). Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. *Journal of the American Medical Association*, 285(7), 885–892. <http://doi.org/10.1001/jama.285.7.885>

Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Drazner, M. H., ... Wilkoff, B. L. (2013). 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*, 128(16), 240–327. <http://doi.org/10.1161/CIR.0b013e31829e8776>

## Chapter 2

### Cardiotoxic Heart Failure in Breast Cancer Survivors: A Concept Analysis

Previously published in *Journal of Advanced Nursing* (Harrison, Pressler, & Friese, 2016)

#### Abstract

**Aim.** To report an analysis of the concept of cardiotoxic heart failure in breast cancer survivors.

**Background.** Despite numerous studies describing cardiotoxic effects of breast cancer therapies, the literature lacks consistent terminology to describe cancer treatment-induced heart failure, defined by the authors as ‘cardiotoxic heart failure.’ Breast cancer survivors who develop heart failure may not fit existing conceptual models. A concept analysis of cardiotoxic heart failure in breast cancer survivors is needed to integrate previous research findings and establish the scientific foundation for future intervention research.

**Design.** Concept analysis.

**Data sources.** An integrative review (1999-2014) was conducted to examine etiologies and risk factors for heart failure in female breast cancer survivors. Databases searched were CINAHL, Cochrane Library, EmBase, Medline and Scopus.

**Methods.** Walker and Avant’s method for concept analysis includes: select concept; determine purpose; identify uses; define attributes; identify model case; describe borderline, related and contrary cases; identify antecedents/consequences; define empirical referents.

**Results.** In the literature, substantial variation was noted in terminology for breast cancer treatment-induced cardiotoxicity. The authors define cardiotoxic heart failure in breast cancer

survivors as chronic heart failure resulting from breast cancer treatment-induced cardiotoxicity among women without preexisting heart failure diagnosis. No studies were found that described quality of life or tested interventions to preserve quality of life for this population.

**Conclusions.** Prospective studies are needed to develop interventions for symptom management to improve quality of life in breast cancer survivors with heart failure. New conceptual paradigms may be needed to improve outcomes for this vulnerable population.

## Introduction

Increased awareness of the cardiac damage that can result from cancer treatment has prompted development of cardio-oncology as a distinct clinical discipline. Clinicians must routinely monitor patients for potential cardiotoxic effects after treatment with chemotherapeutic agents, radiation and other targeted therapies. According to the European Society for Medical Oncology, it is critical for clinicians to monitor cardiac function before, during and after cancer treatment and plan accordingly to minimize cardiac damage while maintaining the effectiveness of treatment (Bovelli et al., 2010). Cardiotoxicity from cancer treatment has been recognized as an issue internationally, as evidenced by formation of the International Cardio-Oncology Society (ICOS Leadership, 2014).

Breast cancer patients and survivors are particularly susceptible to heart failure and the statistics are alarming. An estimated one quarter of women treated for breast cancer with anthracycline chemotherapy and trastuzumab will develop left ventricular systolic dysfunction that may progress to heart failure (Wadhwa et al., 2009). With the combined effects of chemotherapy, chest radiation and biologic therapies that are known to be cardiotoxic, patients who receive these treatments are at high risk for developing chronic heart failure during or after treatment (Carver et al., 2007). The true prevalence of heart failure in breast cancer survivors has yet to be quantified and the risk varies depending on the type of treatment received (Giordano & Hortobagyi, 2007). However, in a recent study of breast cancer patients over age 65 who were treated with trastuzumab, 19% of patients developed heart failure or cardiomyopathy within three years after treatment (Ezaz, Long, Gross, & Chen, 2014). While survival has improved over time, the overall five-year mortality rate for all heart failure patients is 50% (Go et al., 2014). Detailed survival rates are not available for heart failure patients with breast cancer. In

addition to the high mortality rate, heart failure has a high symptom burden that often includes dyspnea, depression, fatigue, pain, loss of balance and cognitive impairment (Goodlin et al., 2012; Lee et al., 2010; Tymkew & Templin, 2011).

### **Select a Concept: Cardiotoxic Heart Failure in Breast Cancer Survivors**

Despite robust research on the mechanisms of cancer treatment-induced cardiotoxicity, the literature lacks consistent terminology to describe heart failure resulting from cancer treatment (Shelburne et al., 2014). For the purposes of this concept analysis, heart failure resulting from cancer treatment will be defined as ‘cardiotoxic heart failure.’ Various terms are used to describe cardiotoxic effects of chemotherapy, radiotherapy, trastuzumab and other breast cancer therapies. However, the narrow focus on individual cardiotoxic agents does not account for the synergistic effects of these agents and their interaction with women’s personal cardiac risk factors. Breast cancer survivors who develop cardiotoxic heart failure have not been sufficiently distinguished as a separate population whose characteristics may differ from other heart failure patients. It remains unclear whether extant research that examines the patterns, correlates and outcomes of heart failure can be generalized to women with breast cancer.

### **Background**

Breast cancer survivors with cardiotoxic heart failure represent a substantial population of patients who have been excluded from heart failure research. Heart failure and cardiovascular disease have traditionally been subject to gender biases with males as the normative model (Wenger, 2002). Women are consistently underrepresented in heart failure clinical trials (Harris & Douglas, 2000; Heiat, Gross, & Krumholz, 2002; Pressler, 2016), despite potential gender differences in heart failure symptoms, etiologies and response to drugs and other therapies (Harris & Douglas, 2000). Furthermore, patients with cancer are typically excluded from heart

failure clinical trials because cancer is considered a potentially life-limiting condition (Wenger, 2002). Clinical guidelines for treatment of heart failure were developed based on clinical trials that excluded patients with cancer and the applicability of established guidelines to breast cancer survivors with cardiotoxic heart failure is questionable (Wenger, 2002).

Women who develop heart failure after breast cancer treatment have unique circumstances that may not fit existing conceptual models of heart failure. Numerous models of heart failure exist in the literature, which describe biologic mechanisms of heart failure (Mann & Bristow, 2005) and describe quality of life (Rector, 2005). The relevance of symptom-specific models in breast cancer survivors with heart failure, such as the model of physical and psychological symptoms of heart failure developed by Lee and colleagues (2013), is unknown. The symptom experience and impact on health-related quality of life (HRQOL) in this subset of women may differ from the experience of other heart failure patients. Women with cardiotoxic heart failure may require different interventions for symptom management. To develop a situation-specific conceptual model of cardiotoxic heart failure in breast cancer survivors for use in research, a clearer definition of this concept is required than is currently available. This analysis is needed to establish the foundation for future research and development of interventions to improve care and optimize HRQOL for women who develop heart failure as a result of breast cancer treatment.

### **Study Purpose**

The purpose of this concept analysis is to develop an operational definition for the term ‘cardiotoxic heart failure’ for use in research, while distinguishing this phenomenon from ischemic heart failure as a separate entity with distinct attributes. Using the methods of Walker and Avant (2011), the concept of cardiotoxic heart failure was examined in the context of female



breast cancer survivors, a population at high risk for cancer treatment-induced heart failure. An eight-step method was used to guide this analysis: select a concept; determine the purpose of the analysis; identify uses of the concept in the literature; define attributes; identify a model case; describe borderline, related and contrary cases; identify antecedents and consequences; and identify empirical referents (Walker & Avant, 2011).

### **Data Sources**

An integrative review was conducted to examine etiologies and risk factors for development of heart failure in female breast cancer survivors. The following databases were searched: Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library of Systematic Reviews, EmBase, Ovid Medline and Scopus. The search was limited to articles published between 1999 and 2014. Other inclusion criteria were English language and discussion of etiologies and/or risk factors for heart failure in breast cancer survivors. Exclusion criteria were magazine or news articles, molecular biology studies without human samples, animal studies and case reports. Search terms were grouped into four main concepts: heart failure, breast cancer, cancer treatment and survivors. A combination of keywords and subject headings were used (Table 2.1). Using Boolean search terms, synonyms for each concept were combined with ‘OR,’ and the four concepts were combined with ‘AND.’ After articles were screened, the search yielded a total of 49 articles, including 35 review articles, 12 original data-based studies and two systematic reviews with breast cancer subgroups. One systematic review examined the incidence of long-term cardiac and pulmonary toxicity secondary to cancer treatment (Carver et al., 2007) and the other examined the usefulness of advanced echocardiographic techniques to diagnose cardiotoxicity in oncology patients (Thavendiranathan et al., 2014).

**Table 2.1** Literature Search Terms

<b>Concept 1: Heart Failure</b>	<b>Concept 2: Breast Cancer</b>	<b>Concept 3: Cancer Treatment</b>	<b>Concept 4: Survivors</b>
Subject heading “heart failure”  Keyword: Heart failure	Subject heading “breast neoplasm”  Keyword: Breast cancer OR breast neoplasm	Subject heading “drug therapy” OR “radiotherapy”  Keyword: Drug therap* OR drug treatment* OR chemotherap* OR radiation therap* OR radiation treatment* OR radiotherap*	Subject heading “survivor”  Keyword: survivor

Based on results of the literature review, cardiotoxic heart failure was defined and uses of the concept were identified. Results were then organized into two major subtopics: 1) treatment-related etiologies of cardiotoxic heart failure in breast cancer survivors; 2) patient-related risk factors for cardiotoxic heart failure in breast cancer survivors.

## **Results**

### **Definition of the Concept**

The authors define cardiotoxic heart failure in breast cancer survivors as chronic heart failure resulting from breast cancer treatment-induced cardiotoxicity among women with no heart failure diagnosis prior to treatment. Cardiotoxic heart failure may occur in various different cancer populations, but it is particularly common in breast cancer survivors due to the type of treatment received.

Cardiotoxicity in patients undergoing cancer treatment is typically defined as a drop in left ventricular ejection fraction (LVEF) from baseline (Thavendiranathan et al., 2014). Although the specific parameters vary, a common definition of cardiotoxicity is a 5% reduction in LVEF

for symptomatic patients, or 10% reduction for asymptomatic patients, to an LVEF below 55% (Seidman et al., 2002). However, decreased LVEF is considered a late sign of anthracycline cardiotoxicity. Diastolic dysfunction may occur prior to systolic dysfunction and subsequent decline in LVEF (Sheppard, Berger, & Sebag, 2013). Even in patients who are asymptomatic, prolonged left ventricular dysfunction leads to cardiomyopathy, a condition where remodeling of the heart muscle reduces its ability to pump efficiently. If treated early, cardiomyopathy is often reversible with medication, but without treatment, cardiomyopathy may progress to chronic heart failure (Antman & Marks, 2005).

### **Uses of the Concept ‘Cardiotoxic Heart Failure’**

This search of the literature revealed wide variation in terms used to describe cardiotoxic side effects of breast cancer treatment. Terms used to describe diagnoses that could be classified as cardiotoxic heart failure included the following: chemotherapy-induced cardiovascular toxicity (Carver et al., 2007), cancer treatment-induced cardiotoxicity (Schmitz, Prosnitz, Schwartz, & Carver, 2012), treatment-induced chronic toxicities (Yardley, 2010), anthracycline-induced cardiotoxicity (Hershman & Shao, 2009), long-term cardiac toxicity (Giordano & Hortobagyi, 2007), cancer therapy-associated decreased LVEF (Yoon et al., 2010), radiotherapy-related heart disease and targeted drug cardiotoxicity (Bovelli et al., 2010). The variation in terminology reinforces the need for a concept to integrate previous research findings.

#### ***Treatment-Related Etiologies of Cardiotoxic Heart Failure in Breast Cancer Survivors.***

Although the survival benefits of life-saving cancer treatments often outweigh the risk of chronic heart failure, breast cancer survivors must receive appropriate cardiac surveillance during and after cancer treatment. In women with breast cancer, two of the most common medications associated with cardiotoxicity are anthracycline chemotherapy, particularly

doxorubicin, and trastuzumab, a monoclonal antibody given to women whose tumors overexpress the human epidermal growth factor receptor – 2 (HER2) protein (Schmitz et al., 2012). HER2-positive tumors occur in approximately 15-20% of women with breast cancer and are associated with more aggressive disease and worse prognosis (Schmitz et al., 2012). Trastuzumab and other monoclonal antibodies used to target tumor cells are referred as biological therapies, or targeted therapies (Barroso-Sousa, Santana, Testa, de Melo Gagliato, & Mano, 2013). Doxorubicin is a commonly used chemotherapeutic agent in breast cancer treatment known to cause cumulative, dose-dependent cardiomyocyte death (Schmitz et al., 2012). Conversely, left ventricular dysfunction caused by trastuzumab is nonstructural and may be related to interruption of cardiac HER2 signaling pathways (Chen et al., 2011).

Ewer and Ewer developed the terms ‘type I’ and ‘type II’ to describe cancer treatment-induced cardiotoxicity (Ewer & Ewer, 2010). ‘Type I toxicity’ refers to chronic, irreversible damage leading to a decrease in left ventricular function, such as the cumulative damage caused by anthracyclines. The threshold of doxorubicin-induced cardiotoxicity was previously thought to occur at a cumulative dose of 450 mg/m<sup>2</sup>; however, recent evidence suggests that anthracyclines are cardiotoxic at any dose and patients with existing cardiac risk factors may experience cardiac dysfunction at lower cumulative doses (Ryberg et al., 2008; Schmitz et al., 2012). ‘Type II toxicity’ refers to trastuzumab-induced heart failure, which is often acute and reversible with standard heart failure medications. Unlike cardiotoxicity from radiation and chemotherapy, trastuzumab toxicity is not dose dependent. Patients may experience asymptomatic type I or type II cardiotoxicity manifested as a decrease in LVEF from baseline, but ventricular remodeling can progress over time to symptomatic heart failure (Ewer & Ewer, 2010).

The iron-chelating agent dexrazoxane reduces the risk and severity of anthracycline-induced cardiotoxicity (Marty et al., 2006; Van Dalen, Caron, Dickinson, & Kremer, 2008; Yancy et al., 2013). However, in 2011, the United States Food and Drug Administration restricted the use of dexrazoxane to adult patients with advanced or metastatic breast cancer, due to reports of acute myeloid leukemia and myelodysplastic syndrome in children receiving dexrazoxane (Center for Drug Evaluation and Research, 2011).

Other etiologies of heart failure in breast cancer survivors include alkylating agents such as cyclophosphamide, cytotoxic drugs such as paclitaxel and 5-fluorouracil, endocrine therapies, hematopoietic growth factors and radiation therapy (Bovelli et al., 2010; Schmitz et al., 2012). High cumulative doses of radiation and/or chemotherapy, as well as delivery of radiation to the internal mammary chain, chest wall, or breast, increase the risk of cardiotoxicity (Carver et al., 2007; Hooning et al., 2007). Treatment with a combination of multiple chemotherapy agents or treatment with anthracyclines in combination with mediastinal radiation increases the risk of cardiotoxicity (Carver et al., 2007; Hooning et al., 2007). Radiation therapy and platinum-based chemotherapy treatments induce endothelial damage and premature atherosclerosis (Carver et al., 2007). Radiation may result in valvular and myocardial damage, in addition to diastolic dysfunction (Bovelli et al., 2010). Radiation-induced cardiotoxicity is thought to be progressive, developing over time after treatment (Bovelli et al., 2010).

Aromatase inhibitors, an endocrine therapy for treatment and long-term prevention of breast cancer in post-menopausal women, may increase the risk of clinically significant hypercholesterolemia, ischemic heart disease and heart failure (Coates et al., 2007; Files, Ko, & Pruthi, 2010; Howell et al., 2005). In comparison, tamoxifen, another endocrine therapy that can be used in pre- or post-menopausal women, may have a lipid lowering effect but increases the

risk for venous thromboembolic events (Early Breast Cancer Trialists' Collaborative Group, 2005; Files et al., 2010).

### ***Patient-Related Risk Factors for Cardiotoxic Heart Failure in Breast Cancer***

**Survivors.** Predictors, or risk factors, that predispose breast cancer survivors to developing heart failure include abnormal baseline LVEF (Yardley, 2010); existing coronary artery disease or other cardiovascular disease (Carver et al., 2007); existing cardiac risk factors such hypertension, hypercholesterolemia, diabetes and obesity (Hershman & Shao, 2009); and smoking (Hooning et al., 2007). Patients over age 65 are at highest risk for developing cardiotoxic heart failure, likely due to increased prevalence of cardiac risk factors (Carver et al., 2007; Schmitz et al., 2012). In a retrospective study of breast cancer patients over age 65 who received trastuzumab, factors that increased women's risk of heart failure or cardiomyopathy were chemotherapy treatment, age > 75 years, coronary artery disease, diabetes, hypertension, renal failure and atrial fibrillation or atrial flutter (Ezaz et al., 2014). Genetic predisposition to cardiovascular disease may increase the risk of developing heart failure from cancer treatment; however, the genetic mechanisms of cardiotoxicity in breast cancer survivors are not well understood (Volkova & Russell, 2011).

### **Defining Attributes**

Walker and Avant (2011) describe defining attributes as the characteristics most often associated with the concept that provide the greatest insight into its meaning. For the concept of cardiotoxic heart failure in breast cancer survivors, the population of interest was adult women over 18 years of age who have undergone treatment for breast cancer. Heart failure must have developed during or after cancer treatment, without a pre-existing diagnosis of heart failure. The heart failure diagnosis must be chronic. Due to the wide variation in clinical manifestations of

heart failure and lack of a single test for diagnosis, no other restrictions were placed on the type of heart failure (systolic or diastolic) or method of diagnosis.

Because cardiotoxic side effects may take years to appear, no time limits were placed for development of heart failure; patients may develop cardiotoxic heart failure at any point after cancer treatment is initiated. The median time frame for anthracycline-induced heart failure is three months after treatment is finished; however, heart failure may appear decades after treatment (Antman & Marks, 2005).

Although breast cancer treatment can cause many different cardiac side effects, including valvular disease, arrhythmias and accelerated coronary artery disease (Antman & Marks, 2005), these conditions were defined as related cases of cardiotoxicity, not cardiotoxic heart failure. However, related cases of cardiotoxic side effects may subsequently lead to development of cardiotoxic heart failure later in life.

### **Case Studies**

A series of four case studies were used to demonstrate the defining attributes of breast cancer treatment-induced cardiotoxic heart failure. The case studies include examples and analyses of a model case, borderline case, related case and contrary case.

***Model Case: Chronic Cardiotoxic Heart Failure.*** A model case is an exemplar that demonstrates all the defining attributes of the concept (Walker & Avant, 2011). This model case is loosely based on a previously published case study (Moore, 2012). The case study described J.G., a woman diagnosed with stage I breast cancer at age 56. J.G.'s cardiac risk factors included hypertension, obesity and a sedentary lifestyle. However, an electrocardiogram and multigated acquisition scan showed that her cardiac function before treatment was within the normal range with an LVEF of 61%. After a lumpectomy and sentinel node biopsy, she was treated with four

cycles of doxorubicin plus cyclophosphamide, followed by six weeks of radiation to her right breast where the tumor occurred. She saw her cardiologist and surgeon for regular follow-up appointments over the next five years. However, at age 64, she began to notice increasing fatigue, a dry cough and unexplained weight gain. She developed severe orthopnea and had to sleep seated in a chair. She had pitting edema in her legs, a heart rate of 122 and respirations of 30. Concerned that the cancer had recurred, this time in her lungs, she returned to her oncologist. After a series of tests, she was found to have an elevated BNP (B-type natriuretic peptide) level of 1,542 pg/mL (a normal BNP value is <100 pg/mL (Antman & Marks, 2005). Her LVEF was 10%. She was diagnosed with heart failure and admitted to a telemetry unit, treated with diuretics and started on a medication regimen and low sodium diet. After several months of this treatment regimen, her LVEF improved to 20% and her BNP level decreased to 849 pg/nL. However, she was diagnosed with chronic congestive heart failure, New York Heart Association (NYHA) Class III, on the basis of marked limitations of physical activity with symptoms of fatigue, dyspnea and palpitations.

J.G.'s case demonstrated all the defining attributes of cardiotoxic heart failure in a breast cancer survivor: an adult woman with no pre-existing diagnosis of heart failure, breast cancer treatment and development of chronic heart failure as a result of treatment. J.G.'s case also demonstrated the potential for cancer treatment to interact with existing cardiac risk factors to increase the risk of heart failure. This case underscores the importance of long-term cardiac monitoring for breast cancer survivors. Even if cardiotoxicity is not immediately apparent following treatment, its effects can appear years later.

***Borderline Case: Acute Cardiotoxic Heart Failure.*** A borderline case contains most of the defining attributes but not all (Walker & Avant, 2011). The elements of this borderline case



are based on a case report of acute heart failure in a woman receiving treatment for breast cancer (Modesto Dos Santos, Thommen Teles, & Alves Leite, 2012). S.M. was a 48-year-old woman undergoing treatment for stage II ductal invasive breast cancer. Although she had a history of type II diabetes and hypertension, her cardiac function before treatment was normal with an LVEF of 74%. After a lumpectomy and lymph node dissection, she was treated with four cycles of doxorubicin, cyclophosphamide and paclitaxel and four cycles of trastuzumab. Her oncologist planned to administer several more rounds of trastuzumab, but S.M. began to develop fatigue, tachycardia and dyspnea with activity. Her LVEF declined to 57%. She was treated with an ACE inhibitor and her oncologist reduced the remaining doses of chemotherapy by 25%. S.M. finished treatment and continued taking the ACE inhibitor. A year after finishing treatment, her LVEF had increased to 72% and her cardiac symptoms appeared to have resolved.

Although this case was a clear example of acute treatment-induced heart failure, S.M.'s symptoms resolved after treatment was stopped. Because her cardiac function returned to normal, her case was a borderline example of cardiotoxic heart failure. Despite demonstrating all the other defining attributes of cardiotoxic heart failure, her symptoms did not progress to chronic heart failure.

***Related Case: Cardiotoxic Arrhythmias.*** A related case is an example of a concept that is connected to the main concept and contains some of the same defining attributes, yet differs in some way (Walker & Avant, 2011). This related case is based on a breast cancer case report (Slovacek, Ansorgova, Macingova, Haman, & Petera, 2008). T.A. was a 56-year-old woman diagnosed with estrogen-receptor positive carcinoma in her right breast. Her treatment involved a partial mastectomy with axillary lymph node excision, followed by endocrine therapy and radiation. She also took a retinoid drug called acitretin for a skin disorder. Three weeks after

starting radiation treatment, T.A. began to feel tired and dizzy. She felt a pressure on the inside of her chest. An electrocardiogram showed sinus bradycardia at 45 beats per minute with QT prolongation. After ruling out ischemic heart disease and hypothyroidism, the medical team suspected the arrhythmia had been caused by an interaction between tamoxifen and acitretin. They discovered that acitretin inhibits the metabolism of tamoxifen, a hormonal therapy known to cause QT prolongation. They stopped administration of both drugs and substituted a different hormonal treatment for tamoxifen. The next day, T.A. did not experience any symptoms. Over time, her heart rate and QT interval returned to normal.

This related case is an example of other cardiotoxic effects that may occur from breast cancer treatment. Although this case involved neither heart failure nor an irreversible condition, QT interval prolongation is a dangerous side effect that may lead to fatal arrhythmias (Kitagawa et al., 2012). A prospective study of breast cancer patients in Japan found significant QT interval prolongation in women treated with a regimen of epirubicin, cyclophosphamide and 5-fluorouracil (Kitagawa et al., 2012). Clinicians may be unaware of underlying arrhythmias in patients who are asymptomatic and cases such as this one provide further evidence of the need for cardiac evaluation in patients receiving breast cancer treatment.

***Contrary Case: Ischemic Heart Failure.*** A contrary case acts as a counterexample of the concept being analyzed (Walker & Avant, 2011). The fictional subject of this contrary case is R.B., a 62-year-old woman with a twenty-year history of hypertension, hyperlipidemia and type 2 diabetes. R.B had a body mass index of 32 and didn't find much time to exercise. She had smoked since age 17 and had a 45 pack-year history. Her father had coronary artery disease and died from myocardial infarction. Over the last several months, she had been feeling tired and short of breath with activity but attributed it to getting older. She also seemed to be retaining

fluid in her legs. One day, she was walking to her car after work when she noticed a feeling of pressure on her chest and severe shortness of breath. Feeling anxious, she drove to the emergency department. On assessment, the nurse practitioner in the emergency department observed that R.B. had a systolic heart murmur, mild jugular venous distension and 2+ edema in her lower extremities. Test results showed a BNP level of 1,340 pg/mL, LVEF of 28% and moderate pulmonary edema on the chest x-ray. She was admitted to a telemetry unit, treated with diuretics and started on a medication regimen. She was instructed to limit sodium and fluid intake and quit smoking. After being discharged and following the prescribed diet and medication regimen, she began to improve, although she still had shortness of breath with activity. She was diagnosed with chronic heart failure, NYHA Class II, on the basis of slight limitations of physical activity due to symptoms of fatigue, dyspnea and palpitations.

This case was a clear example of ischemic heart failure that was not cardiotoxic in origin. R.B.'s risk factors for ischemic heart failure included advanced age, hypertension, hyperlipidemia, diabetes, smoking, obesity, sedentary lifestyle and extensive family history of cardiovascular disease (D'Agostino et al., 2008).

### **Antecedents**

Antecedents are defined by Walker and Avant (2011) as the elements that must be present for the concept to occur. Unlike defining attributes, antecedents are precursors to the concept under examination. Cardiotoxic heart failure in breast survivors has two antecedents: (1) diagnosis of breast cancer; (2) treatment for breast cancer with one or more of the following: a) Systemic chemotherapy (traditional drugs); b) Endocrine therapy; c) Radiation therapy; d) Biological therapy (trastuzumab or other biological agents). These antecedents must precede the diagnosis of heart failure for it to be classified as cardiotoxic.

## **Consequences**

Because heart failure often causes debilitating symptoms that impair quality of life, HRQOL is an important outcome to consider for patients with heart failure. Although the author found no studies that described HRQOL in women who develop cardiotoxic heart failure resulting from breast cancer treatment, the consequences of heart failure include increased risk of mortality (Go et al., 2014), high symptom burden (Lee et al., 2010) and poor HRQOL (Heo, Doering, Widener, & Moser, 2008). Both mental and physical symptoms contribute to poor HRQOL in patients with heart failure. Two main symptom clusters are common in both men and women with heart failure: a physical symptom cluster (dyspnea, fatigue, sleep disturbance) and an emotional symptom cluster (anxiety, depression, cognitive problems) (Lee et al., 2010). In a study of symptom clusters and level of distress in heart failure patients (65% male), women were more likely than men to be distressed by symptoms of depression, as well as physical symptoms of fatigue and sleep disturbance (Lee et al., 2010). When compared with men, women with heart failure have higher symptom burden and greater incidence of depression (Eastwood et al., 2012). Among women with heart failure, depressive symptoms are associated with anxiety, low perceived control and higher body mass index (Eastwood et al., 2012). Furthermore, heart failure patients with depression have lower adherence with therapy, more frequent hospitalizations and higher mortality rates (Jiang et al., 2001).

## **Empirical Referents**

The American College of Cardiology Foundation/American Heart Association Guidelines for Management of Heart Failure provide standards for identification and diagnosis of heart failure. Patients with symptoms of dyspnea, fatigue, activity intolerance, edema, or other cardiac symptoms such as arrhythmia should be evaluated for heart failure. Patients receiving treatment

for breast cancer should be monitored closely for these symptoms. Heart failure diagnosis is based on a combination of clinical assessment and diagnostic testing. The most reliable diagnostic test is a two-dimensional echocardiogram with Doppler flow studies to determine ejection fraction and identify structural abnormalities of the heart. Asymptomatic decreased LVEF increases the risk for congestive heart failure and death, but early treatment of decreased LVEF with beta-blockers and ACE inhibitors or angiotensin receptor blockers decreases mortality risk (Yancy et al., 2013).

The European Society for Medical Oncology guidelines recommend that all patients to be treated with anthracyclines receive a baseline cardiac evaluation and electrocardiogram. For high-risk patients, including patients older than age 60 and those with a history of cardiac risk factors such as hypertension, hypercholesterolemia, diabetes, or obesity, the guidelines recommend assessment of baseline systolic and diastolic function with echocardiogram before treatment with anthracyclines or monoclonal antibodies. Further guidelines are listed for monitoring LVEF in patients based on cumulative anthracycline dose and type of anthracycline received. Aggressive treatment of decreased LVEF with beta-blockers and ACE inhibitors is mandatory (Bovelli et al., 2010).

### **Discussion**

As illustrated by the previous case studies, cardiotoxic effects of breast cancer treatment can be life threatening. Additional studies to examine cardiotoxic heart failure in breast cancer survivors are important for several reasons. First, despite substantial research on breast cancer treatment-related etiologies of heart failure, the author found no studies that examined HRQOL or interventions to preserve HRQOL in breast cancer survivors who develop heart failure. Second, with more advanced and effective cancer treatments, the population of cancer survivors

is expanding rapidly. Of the 3.1 million breast cancer survivors in the United States, approximately 72% are over the age of 60 (DeSantis et al., 2014) and at increased risk of cardiotoxicity from cancer treatment due to advanced age (Schmitz et al., 2012). In addition, a recent report from the National Cancer Institute suggests that the current level of funding for research on cancer treatment-related cardiotoxicity is insufficient to address the full magnitude of the problem, with research on this topic accounting for less than 0.1% of NIH-funded studies for fiscal year 2012 (Shelburne et al., 2014). Despite the potential lack of research funding, numerous new biological therapies for breast cancer have been developed and recently approved. Biologic therapies may effectively increase breast cancer survival rates, but the toxicity profiles and synergistic effects of these drugs with chemotherapy and other treatments are uncertain and in some cases may be life-threatening (Barroso-Sousa et al., 2013).

### **Limitations**

For breast cancer survivors who develop heart failure years or even decades after cancer treatment, distinguishing the etiology of heart failure becomes more difficult. For researchers, this issue may present a measurement challenge in identifying women who have developed heart failure as a result of cancer treatment, as opposed to other etiologies. In addition, breast cancer patients who develop heart failure during treatment could potentially be considered a separate population from long-term survivors who develop heart failure. Further research is needed to identify subgroups of patients with cardiotoxic heart failure.

### **Conclusions**

Breast cancer patients and survivors who develop cardiotoxic heart failure likely have complex health needs, both physically and psychologically. Interdisciplinary providers can develop programs for cardiac surveillance to ensure early detection and treatment of

cardiotoxicity in oncology patients. Patients with a history of breast cancer (past or present) should be closely monitored for symptoms of dyspnea, fatigue, edema and activity intolerance. Management of these patients may require long-term interdisciplinary collaboration and advanced practice nurses can play an important role in coordinating the treatment and long-term management of this population. McKenney (2005) cites the need for nurse practitioners specializing in care of women with breast cancer to provide increased continuity of care.

Finally, nursing and interdisciplinary researchers need to fill the current gaps in the literature by conducting large-scale investigations on cardiotoxic heart failure in breast cancer survivors, including a focus on their symptoms, comorbidities and factors that influence their quality of life. Although prevention of cardiotoxicity is ideal, prospective studies are needed to develop targeted interventions for symptom management to improve quality of life in women who develop cardiotoxic heart failure. After experiencing two catastrophic illnesses, breast cancer survivors may require a different approach to treatment and management of heart failure. Further investigation is necessary to develop a situation-specific conceptual model of cardiotoxic heart failure that fits the unique characteristics of this population.

## References

- Antman, K., & Marks, A. R. (2005). *The patient with cardiovascular disease and cancer*. (D. P. Zipes, P. Libby, R. O. Bonow, & E. Braunwald, Eds.) (7th ed.). Philadelphia: Elsevier Saunders.
- Barroso-Sousa, R., Santana, I. A., Testa, L., de Melo Gagliato, D., & Mano, M. S. (2013). Biological therapies in breast cancer: Common toxicities and management strategies. *Breast*, 22(6), 1009–1018. <http://doi.org/10.1016/j.breast.2013.09.009>
- Bovelli, D., Plataniotis, G., Roila, F., & ESMO Guidelines Working Group. (2010). Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines. *Annals of Oncology: Official Journal of the European Society for Medical Oncology*, 21 Suppl 5, v277-82.
- Carver, J. R., Shapiro, C. L., Ng, A., Jacobs, L., Schwartz, C., Virgo, K. S., ... Vaughn, D. J. (2007). American society of clinical oncology clinical evidence review on the ongoing care of adult cancer survivors: Cardiac and pulmonary late effects. *Journal of Clinical Oncology*, 25(25), 3991–4008.
- Center for Drug Evaluation and Research. (2011). *Drug Safety and Availability - FDA Statement on Dexrazoxane*. Center for Drug Evaluation and Research. Retrieved from <http://www.fda.gov/Drugs/DrugSafety/ucm263729.htm>
- Chen, T., Xu, T., Li, Y., Liang, C., Chen, J., Lu, Y., ... Wu, S. (2011). Risk of cardiac dysfunction with trastuzumab in breast cancer patients: A meta-analysis. *Cancer Treatment Reviews*, 37(4), 312–320. <http://doi.org/10.1016/j.ctrv.2010.09.001>
- Coates, A. S., Keshaviah, A., Thürlimann, B., Mouridsen, H., Mauriac, L., Forbes, J. F., ... Goldhirsch, A. (2007). Five years of letrozole compared with tamoxifen as initial adjuvant



therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. *Journal of Clinical Oncology*, 25(5), 486–92.

<http://doi.org/10.1200/JCO.2006.08.8617>

D'Agostino, R. B., Vasan, R. S., Pencina, M. J., Wolf, P. A., Cobain, M., Massaro, J. M., & Kannel, W. B. (2008). General cardiovascular risk profile for use in primary care. *Circulation*, 117(6).

DeSantis, C., Lin, C., Mariotto, A., Siegel, R., Stein, K., Kramer, J., ... Jemal, A. (2014). Cancer treatment and survivorship statistics, 2014. *CA: A Cancer Journal for Clinicians*, 64(4), 252–271.

Early Breast Cancer Trialists' Collaborative Group. (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*, 365(9472), 1687–717. [http://doi.org/10.1016/S0140-6736\(05\)66544-0](http://doi.org/10.1016/S0140-6736(05)66544-0)

Eastwood, J., Moser, D. K., Riegel, B. J., Albert, N. M., Pressler, S., Chung, M. L., ... Lennie, T. A. (2012). Commonalities and differences in correlates of depressive symptoms in men and women with heart failure. *European Journal of Cardiovascular Nursing*, 11(3), 356–65. <http://doi.org/10.1177/1474515112438010>

Ewer, M. S., & Ewer, S. M. (2010). Cardiotoxicity of anticancer treatments: What the cardiologist needs to know. *Nature Reviews Cardiology*, 7(10), 564–575. <http://doi.org/10.1038/nrcardio.2010.121>

Ezaz, G., Long, J. B., Gross, C. P., & Chen, J. (2014). Risk prediction model for heart failure and cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *Journal of the American Heart Association*, 3, e000472. <http://doi.org/10.1161/JAHA.113.000472>

- Files, J. A., Ko, M. G., & Pruthi, S. (2010). Managing aromatase inhibitors in breast cancer survivors: Not just for oncologists. *Mayo Clinic Proceedings*, *85*(6), 560–566.  
<http://doi.org/10.4065/mcp.2010.0137>
- Giordano, S. H., & Hortobagyi, G. N. (2007). Local recurrence or cardiovascular disease: Pay now or later. *Journal of the National Cancer Institute*, *99*(5), 340–341.
- Go, A. S., Mozaffarian, D., Roger, V. L., Benjamin, E. J., Berry, J. D., Blaha, M. J., ... Turner, M. B. (2014). Heart disease and stroke statistics - 2014 update: A report from the American Heart Association. *Circulation*, *129*, e28–e292.  
<http://doi.org/10.1161/01.cir.0000441139.02102.80>
- Goodlin, S., Wingate, S., Albert, N., Pressler, S., Houser, J., Kwon, J., ... PAIN-HF Investigators. (2012). Investigating pain in heart failure patients: The pain assessment, incidence, and nature in heart failure (PAIN-HF) study. *Journal of Cardiac Failure*, *18*(10), 776–783.
- Harris, D. J., & Douglas, P. S. (2000). Enrollment of women in cardiovascular clinical trials funded by the National Heart, Lung, and Blood Institute. *The New England Journal of Medicine*, *343*(7), 475–480. <http://doi.org/10.1097/00006254-200101000-00022>
- Harrison, J. M., Pressler, S. J., & Friese, C. R. (2016). Cardiotoxic heart failure in breast cancer survivors: A concept analysis. *Journal of Advanced Nursing*, *72*(7), 1518–28.  
<http://doi.org/10.1111/jan.12988>
- Heiat, A., Gross, C. P., & Krumholz, H. M. (2002). Representation of the elderly, women, and minorities in heart failure clinical trials. *Archives of Internal Medicine*, *162*(15), 1682–8.  
<http://doi.org/10.1001/archinte.162.15.1682>
- Heo, S., Doering, L. V., Widener, J., & Moser, D. K. (2008). Predictors and effect of physical

- symptom status on health-related quality of life in patients with heart failure. *American Journal of Critical Care*, 17(2), 124–132.
- Hershman, D. L., & Shao, T. (2009). Anthracycline cardiotoxicity after breast cancer treatment. *Oncology (Williston Park, N.Y.)*, 23(3), 227–34.
- Hooning, M. J., Botma, A., Aleman, B. M. P., Baaijens, M. H. A., Bartelink, H., Klijn, J. G. M., ... van Leeuwen, F. E. (2007). Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *Journal of the National Cancer Institute*, 99(5), 365–375.  
<http://doi.org/10.1093/jnci/djk064>
- Howell, A., Cuzick, J., Baum, M., Buzdar, A., Dowsett, M., Forbes, J. F., ... Tobias, J. S. (2005). Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet*, 365(9453), 60–2.  
[http://doi.org/10.1016/S0140-6736\(04\)17666-6](http://doi.org/10.1016/S0140-6736(04)17666-6)
- ICOS Leadership: International Cardioncology Society, North America. (2014). Retrieved December 31, 2015, from <http://icosna.org/leadership-team/>
- Jiang, W., Alexander, J., Christopher, E., Kuchibhatla, M., Gauden, L. H., Cuffe, M. S., ... O'Connor, C. M. (2001). Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Archives of Internal Medicine*, 161(15), 1849–56.
- Kitagawa, K., Kawada, K., Morita, S., Inada, M., Mitsuma, A., Sawaki, M., ... Ando, Y. (2012). Prospective evaluation of corrected QT intervals and arrhythmias after exposure to epirubicin, cyclophosphamide, and 5-fluorouracil in women with breast cancer. *Annals of Oncology*, 23(3), 743–747. <http://doi.org/10.1093/annonc/mdr296>
- Lee, C. S., Gelow, J. M., Denfeld, Q. E., Mudd, J. O., Burgess, D., Green, J. K., ... Jurgens, C.

- Y. (2013). Physical and psychological symptom profiling and event-free survival in adults with moderate to advanced heart failure. *The Journal of Cardiovascular Nursing*, 0(0), 1–9. <http://doi.org/10.1097/JCN.0b013e318285968a>
- Lee, K. S., Song, E. K., Lennie, T. A., Frazier, S. K., Chung, M. L., Heo, S., ... Moser, D. K. (2010). Symptom clusters in men and women with heart failure and their impact on cardiac event-free survival. *The Journal of Cardiovascular Nursing*, 25(4), 263–272. <http://doi.org/10.1097/JCN.0b013e3181cfbb88>
- Mann, D. L., & Bristow, M. R. (2005). Mechanisms and models in heart failure: The biomechanical model and beyond. *Circulation*, 111(21), 2837–49. <http://doi.org/10.1161/CIRCULATIONAHA.104.500546>
- Marty, M., Espié, M., Llombart, A., Monnier, A., Rapoport, B. L., & Stahalova, V. (2006). Multicenter randomized phase III study of the cardioprotective effect of dexrazoxane (Cardioxane) in advanced/metastatic breast cancer patients treated with anthracycline-based chemotherapy. *Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO*, 17(4), 614–22. <http://doi.org/10.1093/annonc/mdj134>
- McKenney, S. A. (2005). The role of the nurse practitioner in the care of young women with breast cancer. *Breast Disease*, 23, 115–21.
- Modesto Dos Santos, V., Thommen Teles, L., & Alves Leite, V. (2012). Reversible cardiotoxicity in a 54-year-old woman treated with trastuzumab. *Revista Medica de Chile*, 140(6), 763–766.
- Moore, S. (2012). Heart failure in a breast cancer survivor. *Oncology Nursing Forum*, 39(2), 147–150.
- Pressler, S. J. (2016). Women with heart failure are disproportionately studied as compared with

- prevalence: A review of published studies from 2013. *The Journal of Cardiovascular Nursing*, 31(1), 84–8. <http://doi.org/10.1097/JCN.0000000000000212>
- Rector, T. S. (2005). A conceptual model of quality of life in relation to heart failure. *Journal of Cardiac Failure*, 11(3), 173–176. <http://doi.org/10.1016/j.cardfail.2004.09.002>
- Ryberg, M., Nielsen, D., Cortese, G., Nielsen, G., Skovsgaard, T., & Andersen, P. K. (2008). New insight into epirubicin cardiac toxicity: Competing risks analysis of 1097 breast cancer patients. *Journal of the National Cancer Institute*, 100(15), 1058–1067. <http://doi.org/10.1093/jnci/djn206>
- Salzer, W. L., Devidas, M., Carroll, W. L., Winick, N., Pullen, J., Hunger, S. P., & Camitta, B. A. (2010). Long-term results of the pediatric oncology group studies for childhood acute lymphoblastic leukemia 1984-2001: A report from the children's oncology group. *Leukemia*, 24(2), 355–70. <http://doi.org/10.1038/leu.2009.261>
- Schmitz, K. H., Prosnitz, R. G., Schwartz, A. L., & Carver, J. R. (2012). Prospective surveillance and management of cardiac toxicity and health in breast cancer survivors. *Cancer*, 118(SUPPL.8), 2270–2276.
- Seidman, A., Hudis, C., Kathryn Pierri, M., Shak, S., Paton, V., Ashby, M., ... Keefe, D. (2002). Cardiac dysfunction in the trastuzumab clinical trials experience. *Journal of Clinical Oncology*, 20(5), 1215–1221. <http://doi.org/10.1200/JCO.20.5.1215>
- Shelburne, N., Adhikari, B., Brell, J., Davis, M., Desvigne-Nickens, P., Freedman, A., ... Remick, S. C. (2014). Cancer treatment-related cardiotoxicity: Current state of knowledge and future research priorities. *Journal of the National Cancer Institute*, 106(9). <http://doi.org/10.1093/jnci/dju232>
- Sheppard, R. J., Berger, J., & Sebag, I. A. (2013). Cardiotoxicity of cancer therapeutics: Current

- issues in screening, prevention, and therapy. *Frontiers in Pharmacology*, 4, 19.
- Slovacek, L., Ansorgova, V., Macingova, Z., Haman, L., & Petera, J. (2008). Tamoxifen-induced QT interval prolongation. *Journal of Clinical Pharmacy and Therapeutics*, 33(4), 453–455.  
<http://doi.org/10.1111/j.1365-2710.2008.00928.x>
- Tebbi, C. K., London, W. B., Friedman, D., Villaluna, D., De Alarcon, P. A., Constine, L. S., ... Schwartz, C. L. (2007). Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. *Journal of Clinical Oncology*, 25(5), 493–500.  
<http://doi.org/10.1200/JCO.2005.02.3879>
- Thavendiranathan, P., Poulin, F., Lim, K. D., Plana, J. C., Woo, A., & Marwick, T. H. (2014). Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: A systematic review. *Journal of the American College of Cardiology*, 63(25A), 2751–2768.
- Tymkew, H., & Templin, L. (2011). Patients with chronic obstructive pulmonary disease or congested heart failure in a home health setting are at a high fall risk: A descriptive study. *American Physical Therapy*, 22(4), 25.
- Van Dalen, E. C., Caron, H. N., Dickinson, H. O., & Kremer, L. C. M. (2008). Cardioprotective interventions for cancer patients receiving anthracyclines. *The Cochrane Database of Systematic Reviews*, (2), CD003917. <http://doi.org/10.1002/14651858.CD003917.pub3>
- Volkova, M., & Russell, R. (2011). Anthracycline cardiotoxicity: Prevalence, pathogenesis and treatment. *Current Cardiology Reviews*, 7(4), 214–220.  
<http://doi.org/10.2174/157340311799960645>
- Wadhwa, D., Fallah-Rad, N., Grenier, D., Krahn, M., Fang, T., Ahmadie, R., ... Jassal, D.

- (2009). Trastuzumab mediated cardiotoxicity in the setting of adjuvant chemotherapy for breast cancer: a retrospective study. *Breast Cancer Research & Treatment*, *117*(2), 357–364.
- Walker, L. O., & Avant, K. C. (2011). *Strategies for Theory Construction in Nursing* (5th ed.). Upper Saddle River, NJ: Pearson Prentice Hall.
- Wenger, N. K. (2002). Women, heart failure, and heart failure therapies. *Circulation*, *105*(13), 1526–1528. <http://doi.org/10.1161/01.CIR.0000014121.94868.81>
- Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Drazner, M. H., ... Wilkoff, B. L. (2013). 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*, *128*(16), 240–327. <http://doi.org/10.1161/CIR.0b013e31829e8776>
- Yardley, D. A. (2010). Integrating bevacizumab into the treatment of patients with early-stage breast cancer: Focus on cardiac safety. *Clinical Breast Cancer*, *10*(2), 119–129. <http://doi.org/10.3816/CBC.2010.n.016>
- Yoon, G. J., Telli, M. L., Kao, D. P., Matsuda, K. Y., Carlson, R. W., & Witteles, R. M. (2010). Left ventricular dysfunction in patients receiving cardiotoxic cancer therapies: Are clinicians responding optimally? *Journal of the American College of Cardiology*, *56*(20), 1644–1650. <http://doi.org/10.1016/j.jacc.2010.07.023>

## Chapter 3

### Functional Status and Quality of Life Among Breast Cancer Survivors with Heart Failure:

#### Results from the Medicare Health Outcomes Survey

Previously published in *Supportive Care in Cancer* (Harrison et al., 2017)

#### Abstract

**Purpose.** The purpose of this population-based study was to examine health-related quality of life (HRQOL) and functional status among breast cancer survivors with heart failure.

**Methods.** We examined Medicare Health Outcomes Survey data from women aged 65 and older diagnosed with breast cancer in the past five years. Surveys were linked to Surveillance, Epidemiology, and End Results cancer registries. Each woman identified with self-reported heart failure (n=239) was matched to controls without heart failure (n=685) using propensity scores. The Short Form-36/Veterans Rand-12 measured eight domains of HRQOL. Functional status impairment was measured by limitations in six activities of daily living (ADLs). Linear models estimated associations between heart failure status and HRQOL. Logistic regression models estimated odds ratios for associations between heart failure and ADL impairment. We examined associations for the total study population and subgroups stratified by cancer stage.

**Results.** Among all study participants, heart failure was associated with significant deficits in every HRQOL domain and impairment in all ADLs ( $p < 0.01$ , ORs ranged from 1.74-2.47). After stratification by cancer stage, heart failure was associated with physical HRQOL deficits across all cancer stages (physical function, vitality, general health) and mental HRQOL deficits only in



women with stage I/II cancer (role-emotional, social function). Women with early-stage cancer experienced the greatest HRQOL deficits associated with heart failure.

**Conclusions.** Heart failure in breast cancer survivors is associated with substantial HRQOL deficits and functional status impairment, particularly in early-stage cancer. Tailored interventions are needed to improve physical function and mental wellbeing in this high-risk population.

## Introduction

With the development of more effective breast cancer therapies over the last several decades, the population of breast cancer survivors in the United States has expanded to over 3.1 million women (DeSantis et al., 2014). Despite excellent survival rates for early-stage breast cancer, many women experience chronic, unmanaged symptoms that impair health-related quality of life (HRQOL) long after treatment is finished (Fallowfield & Jenkins, 2015). Of particular interest are women with chronic heart failure, a disabling, life-limiting, high-cost condition that disproportionately affects breast cancer survivors (Mozaffarian et al., 2015; Schmitz, Prosnitz, Schwartz, & Carver, 2012).

The increase in cancer survivorship, combined with an aging population and marked growth of chronic disease, has led to new challenges for the US health care system (DeSantis et al., 2014; Vogeli et al., 2007). An estimated 72% of breast cancer survivors in the US are aged 60 and older (DeSantis et al., 2014). The advanced age of many women with breast cancer places them at increased risk of cardiovascular comorbidities (Carver et al., 2007). The combined effects of anthracycline chemotherapy, radiation, and biological therapies such as trastuzumab for treatment of breast cancer increase women's risk for developing heart failure (Carver et al., 2007; Schmitz et al., 2012). Women with preexisting heart failure or cardiovascular disease may also experience greater or more prolonged HRQOL deficits following cancer treatment. In addition to a high mortality rate, heart failure patients often experience significant burden from symptoms of dyspnea, depression, fatigue, pain, loss of balance, and cognitive impairment (Goodlin et al., 2012; Lee et al., 2010; Pressler et al., 2010; Pressler et al., 2011; Tang, Yu, & Yeh, 2010; Tymkew & Templin, 2011).

Heart failure is associated with known deficits in HRQOL and functional status, but due to a dearth of focused research, the extent of these deficits for breast cancer survivors is unknown (Harrison, Pressler, & Friese, 2016; Heo, Doering, Widener, & Moser, 2008; Juenger et al., 2002). Our extant understanding of HRQOL in heart failure originated from clinical trials in which women were consistently underrepresented and patients with cancer were systematically excluded (Harris & Douglas, 2000; Heiat, Gross, & Krumholz, 2002; Heo et al., 2014; Wenger, 2002). Despite extensive research on breast cancer treatment-related etiologies of heart failure, the implications of heart failure for HRQOL in this subset of women are not well understood.

We conducted a cross-sectional, population-based study to examine the relationship between heart failure and functional status and HRQOL among breast cancer survivors using data from the Medicare Health Outcomes Survey (MHOS) linked to Surveillance, Epidemiology, and End Results (SEER) cancer registries. We hypothesized that heart failure would be associated with clinically significant deficits in physical and mental HRQOL and greater functional status impairment among older women with breast cancer. Findings from these analyses can inform clinicians who care for breast cancer patients by clarifying the implications of a heart failure diagnosis in this population and informing interventions to prevent deterioration of patients' function and quality of life.

## **Methods**

### **Data Source**

The SEER-MHOS linked database is a collaborative effort between the National Cancer Institute and the Center for Medicare & Medicaid Services to investigate health outcomes among cancer patients and survivors enrolled in Medicare managed care plans (Clauser & Haffer, 2008).

The MHOS is a self-administered mailed survey that evaluates HRQOL in terms of physical and mental health status. Surveys are distributed annually to 1200 randomly selected Medicare beneficiaries from each participating managed care plan across the US. The MHOS is longitudinal, with the same survey administered at baseline and follow-up questionnaires sent two years later. MHOS respondents with a history of cancer are linked to SEER registries to obtain detailed clinical data related to past cancer diagnoses. The overall response rate for SEER-linked MHOS surveys has ranged from 60-87% (SEER-MHOS, 2016). Our study used baseline MHOS data. Because the date of heart failure diagnosis was unknown, the sequence of breast cancer and heart failure could not be determined.

### **Study Population**

The initial sample included 42,335 women with breast cancer from 14 SEER-MHOS cohorts (survey years 1998-2013) (Figure 3.1). Inclusion criteria for this study were: female; age  $\geq 65$  years; completed the MHOS (survey administered after breast cancer diagnosis); previous diagnosis of breast cancer within the past 5 years; and no history of other primary cancers listed in the SEER registry. Inclusion criteria for the case group was a diagnosis of heart failure as determined by self-report on the MHOS. Inclusion criteria for the control group were no self-reported history of heart failure, angina/coronary artery disease, myocardial infarction, or other heart conditions on the MHOS, due to potential for subclinical cardiovascular disease. Exclusion criteria for both groups included missing physical or mental component score, heart failure status, or cancer stage. Women with *in situ* tumors (stage 0) were also excluded, as this stage is pre-cancerous and non-invasive.

We identified 239 women with heart failure who met criteria for the case group. A sample of 2,640 women without heart failure met criteria for the control group.

**Propensity score matching.** We used nearest-neighbor propensity score matching to select the final study sample and balance covariates between the two groups (Reeve, Smith, Arora, & Hays, 2008). We matched each of the 239 women with heart failure to controls based on probability of having heart failure. The number of controls selected for each case was allowed to vary between one and four depending on the number of close matches (Stuart, 2010). Our propensity score model included sociodemographic characteristics (age, race, ethnicity, education, marital status), smoking status, preexisting comorbidities, SEER-MHOS catchment area, and cohort year (Table 1) (Alberg & Singh, 2001; Ballinger & Fallowfield, 2009; Stover et al., 2014). Of the 2,640 women who met criteria for the control group, 685 controls whose propensity scores matched women in the heart failure group most closely were selected for inclusion in the final sample. Propensity score matching was performed in R using the *optmatch* package (Hansen & Klopfer, 2006; R Development Core Team, 2010).

## **Measures**

**Health-related quality of life.** From 1998 to 2006, MHOS used the SF-36 to measure HRQOL (Turner-Bowker, Bartley, & Ware, 2002). The SF-36 has been validated in numerous populations, including cancer and heart failure (Turner-Bowker et al., 2002). In 2006, MHOS switched to the Veterans Rand 12-Item Health Survey (VR-12) with the same eight subscales but fewer items (Iqbal et al., 2008). Measures of HRQOL to be derived from the SF-36/VR-12 surveys include the Physical Component Score (PCS), Mental Component Score (MCS), and eight domain subscale scores. Higher scores on the SF-36/VR-12 indicate better HRQOL. To make direct comparisons between SF-36 and VR-12 scores, the eight domain subscales from both surveys were transformed to standardized t-scores using published algorithms (Fleishman, Selim, & Kazis, 2010). All scales are based on a standardized t-score of 0-100 (mean=50,

SD=10), with published US population norms available – a score of 50 can be interpreted as the population average (Fleishman et al., 2010). The minimal clinically important differences in scores to indicate an appreciable difference in HRQOL are defined as 2-point (2%) differences in the PCS and MCS, or 3-point (3%) differences in each of the eight domain subscales (Hays, Farivar, & Liu, 2005).

**Functional status.** To measure functional status, we examined the relationship between heart failure and patient-rated performance of activities of daily living (ADLs) on the MHOS. The six-item measure of ADLs used in the MHOS has been validated as a measure of functional status among Medicare enrollees (Kautter & Pope, 2004; Walsh, Nason, Moore, Khatutsky, & Caswell, 2003). Respondents were asked, “Because of a health or physical problem, do you have any difficulty doing the following activities without special equipment or help from another person?” Six basic ADLs (bathing, dressing, eating, getting in/out of chairs, walking, and using the toilet) were measured on a three-point scale (i.e., “Unable to do this activity”; “Yes, I have difficulty”, or “No, I do not have difficulty”). To calculate odds ratios for functional status impairment, we collapsed the three response categories for each ADL into binary categories (“Yes, I have difficulty or am unable to perform this activity”; or “No, I do not have difficulty”) (Quach, Sanoff, Williams, Lyons, & Reeve, 2015).

**Covariates.** SEER registry data provide information on cancer site, stage, age at diagnosis, month/year of diagnosis, and number of past cancer diagnoses. The database also includes information on cancer treatment (i.e., surgery versus radiation). We extracted data on other self-reported medical conditions (Table 1) from the MHOS for inclusion as covariates in our statistical models.

The SEER-MHOS dataset does not provide detail of chemotherapy and hormonal or biological therapies. As the specific treatment would likely affect HRQOL, we identified women as being low-, medium-, or high-risk for clinical treatment with systemic therapy (chemotherapy) based on breast cancer stage and estrogen receptor status, according to the National Comprehensive Cancer Network Clinical Practice Guidelines for Breast Cancer (2016).

### **Statistical Analysis**

We used multiple linear regression to examine the relationship between heart failure status and each of the eight HRQOL domain scores. Effect estimates for heart failure were computed for the total study population and separately by breast cancer stage. We controlled for propensity for heart failure diagnosis, time since cancer diagnosis, and comorbidities not sufficiently balanced through propensity score matching. We also explored adjustment for being low-, medium-, or high-risk for treatment with systemic therapy. Power to detect group differences in the eight domain scores is 0.98, assuming predictor estimated SD ~10.0, detectable effect 0.03 (3% changes in HRQOL, defined as clinically significant changes), false-positive rate  $\alpha=0.05$ , and unequal sample sizes of  $n_1=239$  and  $n_2=685$  (Champely et al., 2015; Lenth, 2001).

Logistic regression was used to estimate odds ratios for the relationship between heart failure status and ADL impairment controlling for the same covariates as our HRQOL models. Odds ratios for impairment in the heart failure group were estimated for the overall sample and for subgroups stratified by cancer stage, with matched breast cancer controls as the reference group.

Except for the propensity score matching algorithm, all analyses were performed in Stata version 14.0 (College Station, TX) (StataCorp, 2015). For all analyses we used two-sided tests

with  $\alpha=0.05$  based on complete case analysis. Missing values were assumed to be missing at random.

## **Results**

### **Study Participant Characteristics**

Among the breast cancer survivors included in our study, the 239 women with heart failure were similar to the 685 matched controls without heart failure, indicating balanced covariates between the two groups ( $p=0.998$ ) (Bowers, Fredrickson, & Hansen, 2016) (Table 3.1). Several variables were more common in the heart failure group: use of a proxy for survey completion and the comorbidities of stroke, respiratory disease, inflammatory bowel disease, and diabetes. Race varied between the two groups ( $p=0.001$ ) – the heart failure group included fewer Asian women (5.0%) and more black women (14.6%) compared to the control group (9.6% and 8.0%, respectively). The heart failure group included a greater proportion of patients with stage III/IV cancer and more women classified as medium- or high-risk for treatment with systemic therapy but fewer women treated with radiation. Across both groups, duration of cancer diagnosis ranged from less than one month to five years. Multicollinearity diagnostics (variance inflation factor) were all less than three (mean VIF=1.37), indicating no evidence of multicollinearity.

### **Heart Failure and Health-Related Quality of Life**

Among all study participants, heart failure was associated with clinically and statistically significant deficits in all eight physical and mental domains of HRQOL, as well as overall PCS and MCS ( $p<0.01$  for all) (Figure 3.2). Breast cancer survivors with heart failure reported greater HRQOL deficits than matched controls, but the contribution of heart failure to these deficits varied by breast cancer stage.



Examined separately by cancer stage, heart failure was associated with clinically significant physical HRQOL deficits across all stages, including overall PCS and the domains of physical function, vitality, and general health. Only women with early-stage cancer (I/II) experienced significant mental HRQOL deficits associated with heart failure, which occurred in all domains for women with stage I cancer and in role-emotional and social function for women with stage II cancer. Among women with stage I cancer, heart failure was associated with clinically significant deficits in all eight domains. Women with heart failure and advanced cancer stage (III/IV) reported the lowest HRQOL in all physical domains and some mental domains, including physical functioning, bodily pain, general health, vitality, social functioning, and mental health. However, the relative contribution of heart failure to physical and mental HRQOL deficits was greatest for women with early-stage cancer, particularly for role-physical, role-emotional, and social functioning (Figure 3.2). Results did not change appreciably with inclusion of additional covariates not sufficiently balanced through propensity score matching: clinical subgroup (likelihood of systemic therapy), treatment with radiation, mastectomy, race/ethnicity, or use of a proxy for survey completion. Similarly, associations persisted in analyses restricted to breast cancer survivors within one year of cancer diagnosis.

### **Heart Failure and Functional Status**

Compared with controls, breast cancer survivors with heart failure were more likely to report impairments across all six ADLs,  $p < 0.001$  for all (Figure 3.3). Among the heart failure group, 73.2% of women reported having impairment in any ADL compared to 46.6% of matched controls ( $p = 0.03$ ). The greatest functional deficits reported by the heart failure group were bathing, walking, and dressing. Respectively, 11.7%, 10.0%, and 6.7% of women with heart failure reported they were unable to do these activities. Almost 70% of surveyed women with

heart failure reported difficulty walking. Women with heart failure and advanced stage cancer (III/IV) reported the greatest frequency of impairment.

In adjusted models, heart failure was associated with greater odds of impairment in all six ADLs examined ( $p < 0.01$  for all) – ORs varied from 1.74 (95% CI: 1.27, 2.40) for difficulty getting in/out of chairs to 2.47 (95% CI: 1.77, 3.44) for difficulty walking (Figure 3.4).

Examined separately by cancer stage, associations were not consistent. The odds of ADL impairment associated with heart failure were relatively consistent among women with early-stage cancer (I/II) but more variable in women with advanced cancer stage (III/IV). No dose-response effect was observed for advancing cancer stage and likelihood of ADL impairment.

### **Discussion**

To our knowledge, this is the first study to examine HRQOL and functional status among a diverse sample of breast cancer survivors with heart failure. Although we cannot presume that women in this study developed heart failure as a result of breast cancer treatment, due to lack of key clinical data such as chemotherapy regimens and duration of heart failure diagnoses, we have documented the collective burden of these two comorbid conditions on HRQOL and functional status.

The most consistent HRQOL deficits associated with heart failure across all cancer stages were physical deficits, including reduced physical function, vitality, and general health. The magnitude of these deficits varied little by cancer stage. Physical function on the SF-36/VR-12 is measured in terms of ability to climb several flights of stairs and perform moderate physical activities such moving a table, pushing a vacuum cleaner, bowling, or playing golf (Iqbal et al., 2008). Vitality is measured in terms of perceived energy level, and general health is measured with one question about overall perception of health (Iqbal et al., 2008). Our findings were

consistent with the heart failure literature. Dyspnea, fatigue, and muscle weakness limit heart failure patients' ability to perform physical activities (Seo et al., 2008). Based on our findings, interventions are needed to improve physical function and manage fatigue among breast cancer survivors with heart failure. However, existing physical activity interventions targeted toward breast cancer survivors were not designed for women also living with chronic heart failure. Symptoms of fatigue, in particular, may present a challenge for maintaining physical activity. Development of interventions to preserve physical function may require collaboration with physical and occupational therapy, cardiology, and/or physical medicine and rehabilitation.

Among women with stage I and II cancer, heart failure was associated with deficits in role-emotional and social function. Role-emotional refers to the degree to which emotional problems such as depression or anxiety interfere with normal work or activities, and social function is the degree to which physical health or emotional problems interfere with social activities (Iqbal et al., 2008). Both breast cancer and heart failure are associated with high rates of psychological morbidity (Kissane et al., 2004; Rutledge, Reis, Linke, Greenberg, & Mills, 2006), and the presence of both conditions may increase psychological distress. Because depression is associated with worse prognosis in patients with heart failure, the American Heart Association recommends screening for depression using the Patient Health Questionnaire-9 to identify patients in need of mental health referral (Kroenke, Spitzer, & Williams, 2001; Lichtman et al., 2008).

The finding that heart failure-associated HRQOL deficits were more common in women with early-stage cancer may be due to lower cancer-related morbidity in this group. Although older women diagnosed with early-stage breast cancer typically experience a lapse in HRQOL for the first six months following cancer diagnosis, their HRQOL often improves over time

(Stover et al., 2013). For this group, the relative burden of heart failure may be more overwhelming than cancer, warranting increased awareness and intervention. Regular assessment of physical function and mental wellbeing during clinic follow-up will allow for early intervention, and patients may benefit from tailored interventions to address their unique concerns. Evaluation of new strategies to follow symptoms with mobile phone apps and interactive voice response may be beneficial for this vulnerable subgroup.

In addition to limiting the individual's ability to live independently, the functional status impairment we observed is associated with increased risk of mortality and all-cause hospitalization in heart failure patients (Dunlay et al., 2015). Functional deficits are common in heart failure and become more severe with advancing disease (Dunlay et al., 2015). Dyspnea and activity intolerance contribute to deconditioning and loss of muscle strength over time (Seo et al., 2008). However, community-based interventions have successfully reduced functional deficits in older adults. An example is the Health Enhancement Program, an intervention designed to improve health and functional status among community-dwelling older adults through optimization of individual risk factors for functional decline, such as unmanaged diabetes, physical inactivity, and social isolation (Phelan, Williams, Penninx, LoGerfo, & Leveille, 2004). Given the impairment we observed, a similar intervention adapted to patients with heart failure may be beneficial for this population.

This study had several limitations. The study population was limited to women aged 65 and older enrolled in Medicare Advantage plans. Identification of women with heart failure was based on patient self-report within the MHOS. Other comorbid conditions were also self-reported, and patients may have had additional unmeasured comorbidities. Some surveys (16%) were completed by proxies. Significant results from this analysis should be confirmed in

prospective studies that include key clinical data, including chemotherapy regimens, tumor type, receipt of trastuzumab, heart failure type and stage, and duration of heart failure diagnosis. Despite these limitations, strengths of this study included national data with a diverse and representative sample of women in the US, well-validated survey measures, and a propensity score approach to minimize observed differences between women with heart failure and controls.

In conclusion, clinicians should be aware that breast cancer survivors with heart failure are at risk for substantially greater deficits in physical function and mental health than similar patients without cardiovascular comorbidity. Women with early-stage cancer experienced the greatest physical and mental HRQOL deficits associated with heart failure. Tailored interventions are needed to improve physical function and mental wellbeing in this growing patient population, and patients may benefit from automatic referral to physical/occupational therapy to preserve their physical function. Further investigation of these results in prospective studies will inform development of evidence-based interventions to preserve functional status and HRQOL among the notable number of breast cancer survivors living with chronic heart failure.

**Table 3.1** Characteristics of Study Participants According to Heart Failure Status

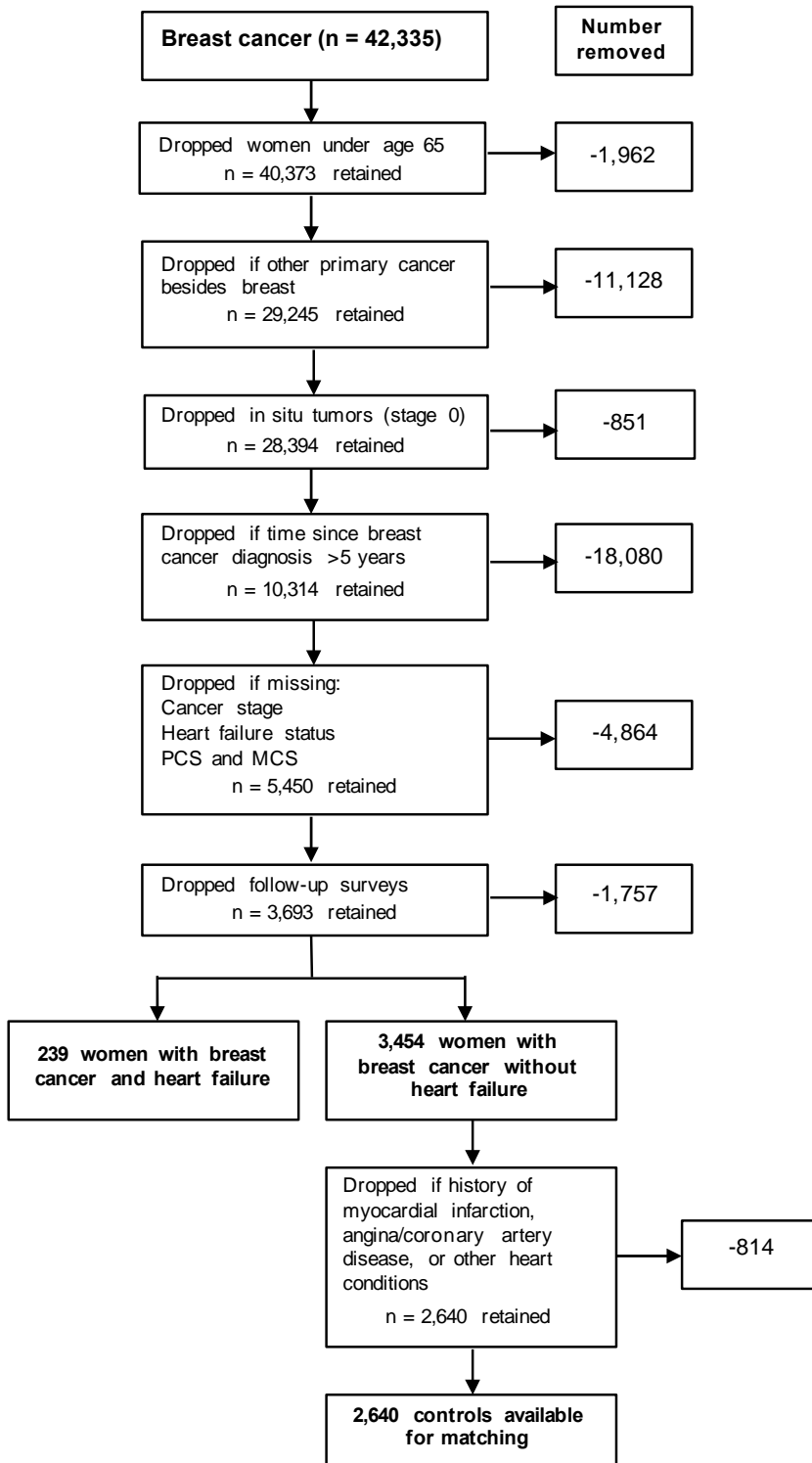
Characteristic	With Heart Failure, n = 239	Without Heart Failure (matched controls), n = 685	p-value*
<b>Sociodemographic Characteristics and Comorbidities<sup>†</sup></b>			
<b>Age at time of survey, n (%)</b>			0.18
65-69 y	36 (15.1)	113 (16.5)	
70-74 y	54 (22.6)	150 (21.9)	
75-79 y	51 (21.3)	190 (27.7)	
80-84 y	54 (22.6)	139 (20.3)	
85+ y	44 (18.4)	93 (13.6)	
<b>Race/ethnicity, n (%)</b>			< 0.01
White	158 (66.1)	483 (70.5)	
Asian/Pacific Islander	12 (5.0)	66 (9.6)	
Hispanic	35 (14.6)	55 (8.0)	
Black/African American	21 (8.8)	65 (9.5)	
Other	13 (5.4)	16 (2.3)	
<b>Education level, n (%)</b>			0.49
High school graduate or less	155 (64.9)	450 (65.7)	
Some college or 2-year degree	60 (25.1)	146 (21.3)	
College graduate or higher	19 (8.0)	70 (10.2)	
Unknown	-- **	19 (2.8)	
<b>Marital status, n (%)</b>			0.47
Married	158 (66.1)	423 (61.8)	
Divorced, separated, widowed or never married	75 (31.4)	245 (35.8)	
Unknown	-- **	17 (2.5)	
<b>Proxy for survey completion, n (%)</b>			0.01
Yes	52 (21.8)	96 (14.0)	
No	172 (72.0)	529 (77.2)	
Unknown	15 (6.3)	60 (8.8)	
<b>Smoking status n (%)</b>			0.71
Current smoker	17 (7.1)	60 (8.8)	
Not current smoker	188 (78.7)	525 (76.6)	
Unknown	34 (14.2)	100 (14.6)	
<b>Comorbidities, n (%)</b>			
Hypertension	200 (83.7)	548 (80.0)	0.31
Angina/CAD	107 (44.8)	--	--
Myocardial infarction	124 (51.9)	--	--
Other heart conditions	-- **	--	--
Stroke	56 (23.4)	86 (12.6)	< 0.001
Emphysema, asthma, or COPD	71 (29.7)	140 (20.4)	< 0.001
Crohn's/ulcerative colitis/IBD	19 (8.0)	34 (5.0)	0.04
Arthritis of hip or knee	127 (53.1)	338 (49.3)	0.55
Arthritis of hand/wrist	112 (46.9)	303 (44.2)	0.73
Sciatica	81 (33.9)	180 (26.3)	0.07
Diabetes	104 (43.5)	240 (35.0)	0.03
<sup>†</sup> Demographic and clinical covariates were matched between women with and without self-reported heart failure; p-value for overall balance of covariates between groups = 0.998. Exclusion criteria for non-heart failure controls included history of angina/coronary artery disease, myocardial infarction, and other heart conditions.			

<b>Cancer Characteristics</b>			
<b>Cancer stage, n (%)</b>			0.04
Stage I	120 (50.2)	416 (60.7)	
Stage II	81 (33.9)	189 (27.6)	
Stage III/IV	38 (15.9)	80 (11.7)	
<b>Time from cancer diagnosis to survey, months, n (%)</b>			0.18
0-12 mos.	61 (25.5)	213 (31.1)	
13-24 mos.	57 (23.9)	188 (27.5)	
25-36 mos.	43 (18.0)	100 (14.6)	
37-48 mos.	43 (18.0)	106 (15.5)	
49-60 mos.	35 (14.6)	78 (11.4)	
<b>Estrogen receptor status, n (%)</b>			0.91
Positive	171 (71.6)	514 (75.0)	
Negative	35 (14.6)	96 (14.0)	
Borderline/Unknown	33 (13.8)	75 (10.9)	
<b>Likelihood of systemic therapy, n (%)</b>			0.04
Low	88 (36.8)	325 (47.5)	
Medium	95 (39.8)	224 (32.7)	
High	25 (10.5)	65 (9.5)	
Unknown	31 (13.0)	71 (10.4)	
<b>Treatment with Radiation, n (%)</b>			< 0.01
Yes	94 (39.3)	348 (50.8)	
No	141 (59.0)	367 (53.6)	
Unknown	-- **	83 (12.1)	
<b>Mastectomy, n (%)</b>			0.34
Yes	93 (38.9)	235 (34.3)	
No	115 (48.1)	367 (53.6)	
Unknown	31 (13.0)	83 (12.1)	
<b>Health-Related Quality of Life and Functional Status Impairment</b>			
<b>SF-36/VR-12 Scores, mean (SE)</b>			
Physical Component Score	28.12 (0.67)	35.86 (0.43)	< 0.001
Mental Component Score	44.62 (0.81)	49.33 (0.45)	< 0.001
Physical Functioning	26.19 (0.79)	34.72 (0.50)	< 0.001
Role-Physical	33.05 (0.68)	37.97 (0.47)	< 0.001
Bodily Pain	36.54 (0.74)	41.30 (0.44)	< 0.001
General Health	33.27 (0.75)	41.86 (0.42)	< 0.001
Vitality	36.54 (0.73)	44.75 (0.43)	< 0.001
Social Functioning	37.20 (0.94)	43.73 (0.50)	< 0.001
Role-Emotional	40.30 (0.90)	44.50 (0.50)	< 0.001
Mental Health	43.58 (0.87)	48.13 (0.46)	< 0.001
<b>ADL Impairment (Yes/No), n (%)</b>			
Difficulty bathing	99 (41.4)	144 (21.0)	< 0.001
Difficulty dressing	82 (34.3)	110 (16.1)	< 0.001
Difficulty eating	35 (14.6)	38 (5.6)	< 0.001
Difficulty walking	161 (67.4)	274 (40.0)	< 0.001
Difficulty getting in/out of chairs	122 (51.1)	225 (32.9)	< 0.001
Difficulty using the toilet	67 (28.0)	85 (12.4)	< 0.001

\*P-value compares study participants with and without heart failure.

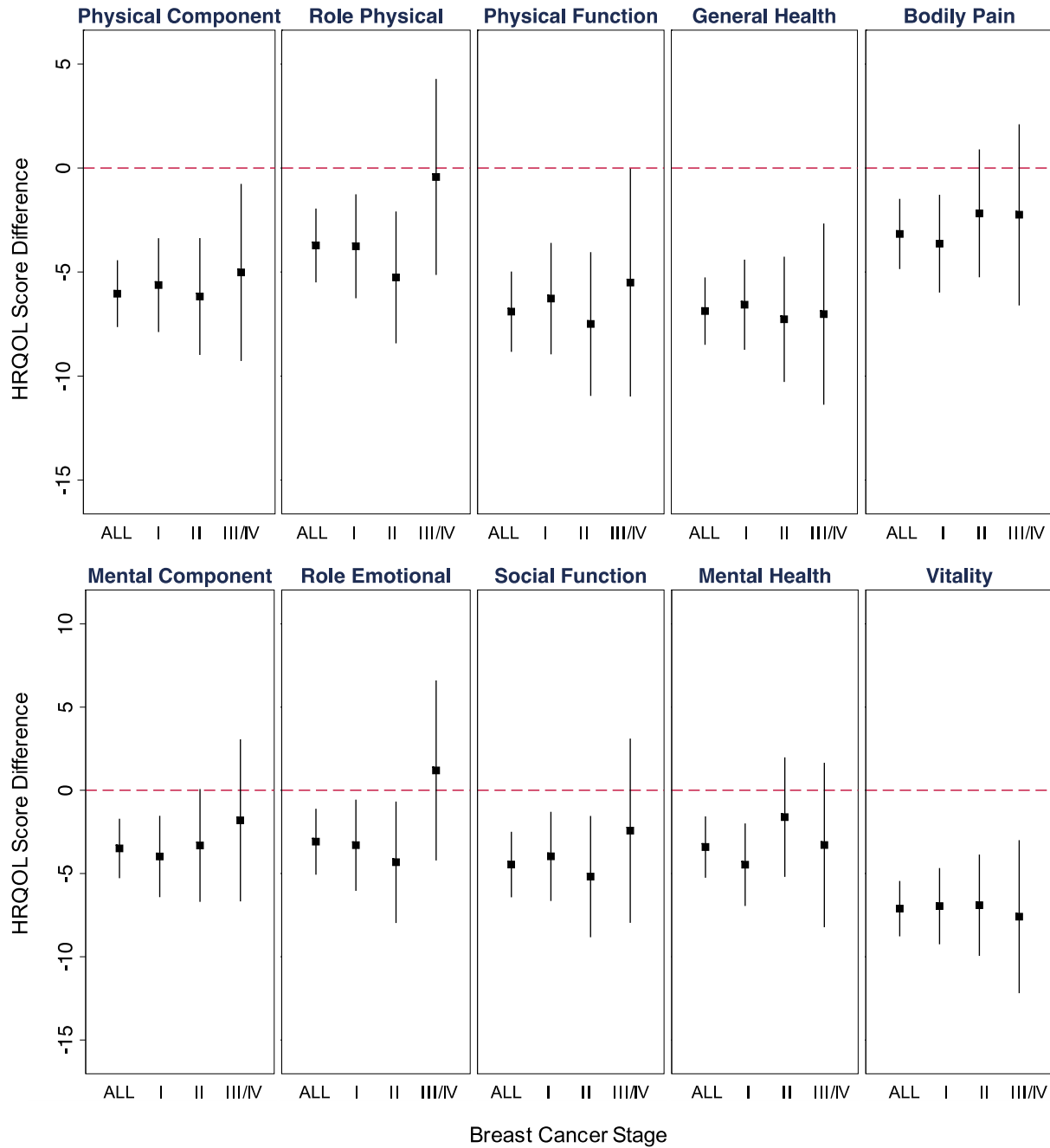
\*\*Data suppressed for confidentiality.

**Figure 3.1** Selection of Breast Cancer Sample from SEER-MHOS Database



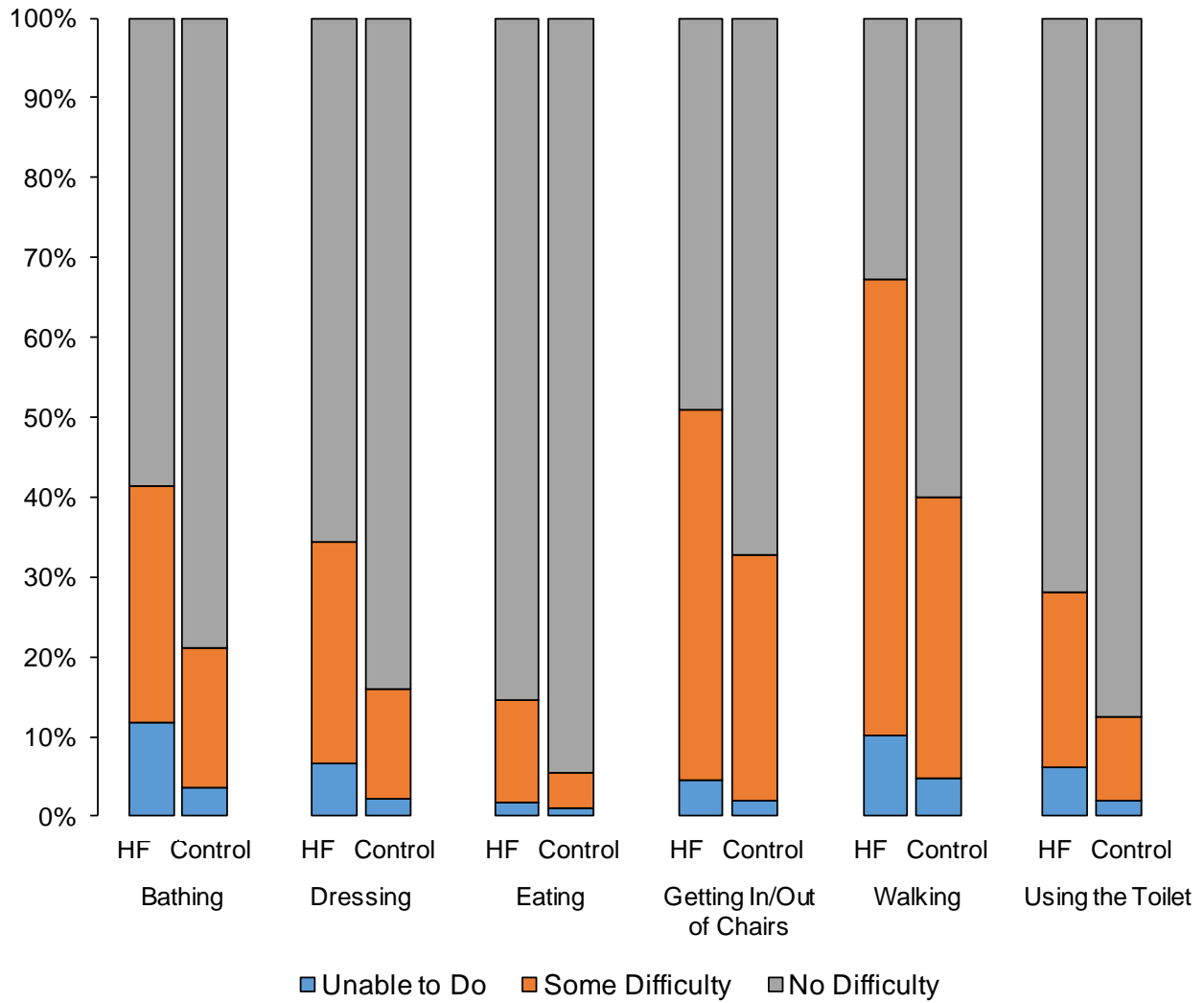


**Figure 3.2** Mean Difference (95% Confidence Intervals) in SF-36 Health-Related Quality of Life Scores Among Breast Cancer Survivors According to Heart Failure Status\*



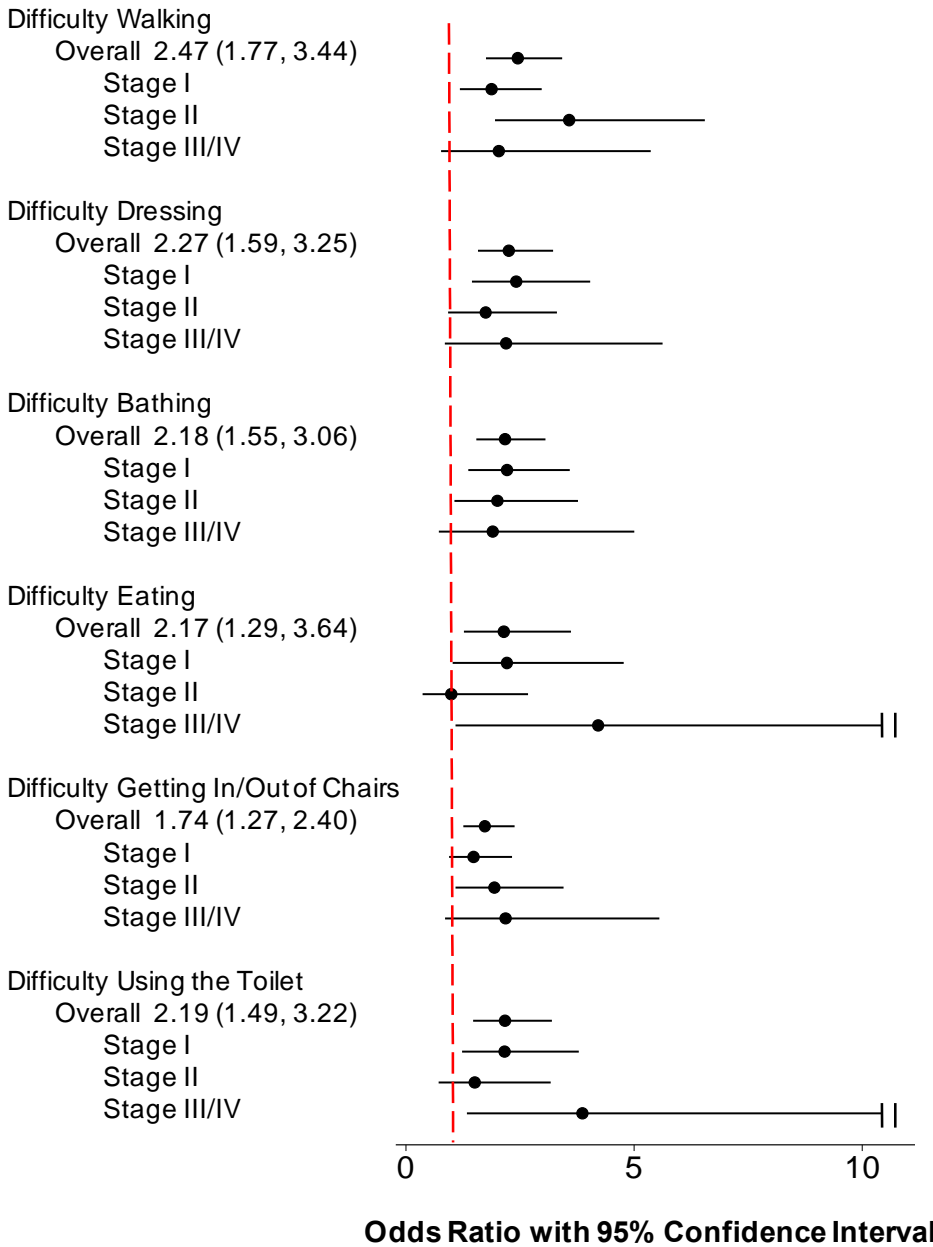
\*Negative coefficients on the y-axis reflect deficits for the heart failure group. Referent group are matched breast cancer controls without heart failure. Adjusted for time since cancer diagnosis, propensity scores, and presence of respiratory disease, stroke, inflammatory bowel disease, and diabetes. Clinically significant differences are 2-point differences in physical or mental component score, or 3-point differences in the eight domain scores (Hays et al., 2005). The VR-12 was administered to all respondents after 2006.

**Figure 3.3** Activities of Daily Living Impairment Among Breast Cancer Survivors with Heart Failure Compared with Matched Controls\*



\*HF = heart failure;  $p < 0.001$  for all differences between heart failure and control group

**Figure 3.4** Adjusted Odds Ratios (95% Confidence Intervals) for the Association Between Heart Failure and Activities of Daily Living Impairment Among Breast Cancer Survivors\*



\*Referent group are matched breast cancer controls without heart failure. Adjusted for time since cancer diagnosis, propensity scores, and presence of respiratory disease, stroke, inflammatory bowel disease, and diabetes.

## References

- Alberg, A. J., & Singh, S. (2001). Epidemiology of breast cancer in older women: Implications for future healthcare. *Drugs & Aging, 18*(10), 761–772.
- Ballinger, R. S., & Fallowfield, L. J. (2009). Quality of life and patient-reported outcomes in the older breast cancer patient. *Clinical Oncology, 21*(2), 140–155.  
<http://doi.org/10.1016/j.clon.2008.11.003>
- Bowers, J., Fredrickson, M., & Hansen, B. (2016). RITools: Randomized Inference Tools.
- Carver, J. R., Shapiro, C. L., Ng, A., Jacobs, L., Schwartz, C., Virgo, K. S., ... Vaughn, D. J. (2007). American society of clinical oncology clinical evidence review on the ongoing care of adult cancer survivors: Cardiac and pulmonary late effects. *Journal of Clinical Oncology, 25*(25), 3991–4008.
- Champely, S., Ekstrom, C., Dalgaard, P., Gill, J., Wunder, J., & Rosario, H. De. (2015). Package “pwr.” Retrieved from <https://github.com/heliosdrm/pwr>
- Clauser, S. B., & Haffer, S. C. (2008). SEER-MHOS: A new federal collaboration on cancer outcomes research. *Health Care Financing Review, 29*(4), 1–4.
- DeSantis, C., Lin, C., Mariotto, A., Siegel, R., Stein, K., Kramer, J., ... Jemal, A. (2014). Cancer treatment and survivorship statistics, 2014. *CA: A Cancer Journal for Clinicians, 64*(4), 252–271.
- Dunlay, S. M., Manemann, S. M., Chamberlain, A. M., Cheville, A. L., Jiang, R., Weston, S. A., & Roger, V. L. (2015). Activities of daily living and outcomes in heart failure. *Circulation: Heart Failure, 8*(2), 261–7. <http://doi.org/10.1161/CIRCHEARTFAILURE.114.001542>
- Fallowfield, L., & Jenkins, V. (2015). Psychosocial/survivorship issues in breast cancer: Are we doing better? *Journal of the National Cancer Institute, 107*(1), 335.

<http://doi.org/10.1093/jnci/dju335>

Fleishman, J. A., Selim, A. J., & Kazis, L. E. (2010). Deriving SF-12v2 physical and mental health summary scores: A comparison of different scoring algorithms. *Quality of Life Research, 19*(2), 231–241. <http://doi.org/10.1007/s11136-009-9582-z>

Goodlin, S., Wingate, S., Albert, N., Pressler, S., Houser, J., Kwon, J., ... PAIN-HF Investigators. (2012). Investigating pain in heart failure patients: The pain assessment, incidence, and nature in heart failure (PAIN-HF) study. *Journal of Cardiac Failure, 18*(10), 776–783.

Hansen, B. B., & Klopfer, S. O. (2006). Optimal full matching and related designs via network flows. *Journal of Computational and Graphical Statistics, 15*(3), 609–627.

Harris, D. J., & Douglas, P. S. (2000). Enrollment of women in cardiovascular clinical trials funded by the National Heart, Lung, and Blood Institute. *The New England Journal of Medicine, 343*(7), 475–480. <http://doi.org/10.1097/00006254-200101000-00022>

Harrison, J. M., Davis, M. A., Barton, D. L., Janz, N. K., Pressler, S. J., & Friese, C. R. (2017). Functional status and quality of life among breast cancer survivors with heart failure: results of the Medicare Health Outcomes Survey. *Supportive Care in Cancer*. Advance online publication. <http://doi.org/10.1007/s00520-017-3653-4>

Harrison, J. M., Pressler, S. J., & Friese, C. R. (2016). Cardiotoxic heart failure in breast cancer survivors: A concept analysis. *Journal of Advanced Nursing, 72*(7), 1518–28. <http://doi.org/10.1111/jan.12988>

Hays, R. D., Farivar, S. S., & Liu, H. (2005). Approaches and recommendations for estimating minimally important differences for health-related quality of life measures. *COPD, 2*(1), 63–67. <http://doi.org/10.1081/COPD-200050663>

- Heiat, A., Gross, C. P., & Krumholz, H. M. (2002). Representation of the elderly, women, and minorities in heart failure clinical trials. *Archives of Internal Medicine*, *162*(15), 1682–8. <http://doi.org/10.1001/archinte.162.15.1682>
- Heo, S., Doering, L. V., Widener, J., & Moser, D. K. (2008). Predictors and effect of physical symptom status on health-related quality of life in patients with heart failure. *American Journal of Critical Care*, *17*(2), 124–132.
- Heo, S., Moser, D. K., Pressler, S. J., Dunbar, S. B., Mudd-Martin, G., & Lennie, T. A. (2014). Psychometric properties of the symptom status questionnaire - heart failure. *The Journal of Cardiovascular Nursing*, *0*(0), 1–9. <http://doi.org/10.1097/JCN.0000000000000102>
- Iqbal, S. U., Rogers, W., Selim, A. J., Qian, S. X., Lee, A., Ren, X. S., ... Kazis, L. E. (2008). *The Veterans Rand 12 Item Health Survey (VR-12): What It Is and How It Is Used*. Retrieved from [http://www.hosonline.org/globalassets/hos-online/publications/veterans\\_rand\\_12\\_item\\_health\\_survey\\_vr-12\\_2007.pdf](http://www.hosonline.org/globalassets/hos-online/publications/veterans_rand_12_item_health_survey_vr-12_2007.pdf)
- Juenger, J., Schellberg, D., Kraemer, S., Haunstetter, A., Zugck, C., Herzog, W., & Haass, M. (2002). Health related quality of life in patients with congestive heart failure: Comparison with other chronic diseases and relation to functional variables. *Heart*, *87*(3), 235–241.
- Kautter, J., & Pope, G. C. (2004). CMS frailty adjustment model. *Health Care Financing Review*, *26*(2), 1–19.
- Kissane, D. W., Grabsch, B., Love, A., Clarke, D. M., Blosch, S., & Smith, G. C. (2004). Psychiatric disorder in women with early stage and advanced breast cancer: A comparative analysis. *Australian and New Zealand Journal of Psychiatry*, *38*(5), 320–326. <http://doi.org/10.1111/j.1440-1614.2004.01358.x>
- Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). The PHQ-9: Validity of a brief

depression severity measure. *Journal of General Internal Medicine*, 16(9), 606–613.

<http://doi.org/10.1046/j.1525-1497.2001.016009606.x>

Lee, K. S., Song, E. K., Lennie, T. A., Frazier, S. K., Chung, M. L., Heo, S., ... Moser, D. K.

(2010). Symptom clusters in men and women with heart failure and their impact on cardiac event-free survival. *The Journal of Cardiovascular Nursing*, 25(4), 263–272.

<http://doi.org/10.1097/JCN.0b013e3181cfbb88>

Lenth, R. V. (2001). Some practical guidelines for effective sample size determination. *The*

*American Statistician*. <http://doi.org/10.1198/000313001317098149>

Lichtman, J. H., Bigger, J. T., Blumenthal, J. a, Frasure-Smith, N., Kaufmann, P. G., Lespérance,

F., ... Froelicher, E. S. (2008). Depression and coronary heart disease: Recommendations for screening, referral, and treatment. *Circulation*, 118(17), 1768–75.

<http://doi.org/10.1161/CIRCULATIONAHA.108.190769>

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., ...

Turner, M. B. (2015). Heart disease and stroke statistics—2015 update. *Circulation*, 131(4), 29–322.

National Comprehensive Cancer Network. (2016). NCCN Practice Guidelines. Retrieved from

[https://www.nccn.org/professionals/physician\\_gls/f\\_guidelines](https://www.nccn.org/professionals/physician_gls/f_guidelines)

Phelan, E. A., Williams, B., Penninx, B. W., LoGerfo, J. P., & Leveille, S. G. (2004). Activities

of daily living function and disability in older adults in a randomized trial of the Health Enhancement Program. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, 59(8), 838–843.

Pressler, S. J., Subramanian, U., Perkins, S. M., Gradus-Pizlo, I., Kareken, D., Kim, J., ... Sloan,

R. (2011). Measuring depressive symptoms in heart failure: Validity and reliability of the

patient health Questionnaire-8. *American Journal of Critical Care*, 20(2), 146–152.

<http://doi.org/10.4037/ajcc2010931>

Pressler, S., Subramanian, U., Kareken, D., Perkins, S., Gradus-Pizlo, I., Sauve, M., ... Shaw, R. (2010). Cognitive deficits and health-related quality of life in chronic heart failure. *Journal of Cardiovascular Nursing*, 25(3), 189–198.

Quach, C., Sanoff, H. K., Williams, G. R., Lyons, J. C., & Reeve, B. B. (2015). Impact of colorectal cancer diagnosis and treatment on health-related quality of life among older Americans: A population-based, case-control study. *Cancer*, 121(6), 943–50.

<http://doi.org/10.1002/cncr.29125>

R Development Core Team. R: A language and environment for statistical computing. (2010). Vienna, Austria: R Foundation for Statistical Computing. Retrieved from <http://www.r-project.org>

Reeve, B. B., Smith, A. W., Arora, N. K., & Hays, R. D. (2008). Reducing bias in cancer research: Application of propensity score matching. *Health Care Financing Review*, 29(4), 69–80.

Rutledge, T., Reis, V. A., Linke, S. E., Greenberg, B. H., & Mills, P. J. (2006). Depression in heart failure. *Journal of the American College of Cardiology*, 48(8), 1527–1537.

<http://doi.org/10.1016/j.jacc.2006.06.055>

Schmitz, K. H., Prosnitz, R. G., Schwartz, A. L., & Carver, J. R. (2012). Prospective surveillance and management of cardiac toxicity and health in breast cancer survivors. *Cancer*, 118(SUPPL.8), 2270–2276.

SEER-Medicare Health Outcomes Survey (SEER-MHOS) Linked Database: MHOS Survey Instruments. (2017). Retrieved from <http://healthcaredelivery.cancer.gov/seer-mhos/>



- Seo, Y., Roberts, B. L., Piña, I., Dolansky, M., Seo Y, Roberts BL, ... Dolansky M. (2008). Predictors of motor tasks essential for daily activities among persons with heart failure. *Journal of Cardiac Failure*, 14(4), 296–302. <http://doi.org/10.1016/j.cardfail.2008.01.005>
- StataCorp. (2015). Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.
- Stover, A. M., Mayer, D. K., Muss, H., Wheeler, S. B., Lyons, J. C., & Reeve, B. B. (2014). Quality of life changes during the pre- to postdiagnosis period and treatment-related recovery time in older women with breast cancer. *Cancer*, 120(12), 1881–9. <http://doi.org/10.1002/cncr.28649>
- Stover, A. M., Reeve, B. B., Piper, B. F., Alfano, C. M., Smith, A. W., Mitchell, S. A., ... Ballard-Barbash, R. (2013). Deriving clinically meaningful cut-scores for fatigue in a cohort of breast cancer survivors: a Health, Eating, Activity, and Lifestyle (HEAL) Study. *Quality of Life Research*, 22(9), 2279–92. <http://doi.org/10.1007/s11136-013-0360-6>
- Stuart, E. A. (2010). Matching methods for causal inference: A review and a look forward. *Statistical Science*, 25(1), 1–21. <http://doi.org/10.1214/09-STS313>
- Tang, W., Yu, C., & Yeh, S. (2010). Fatigue and its related factors in patients with chronic heart failure. *Journal of Clinical Nursing*, 19(1–2), 69–78. <http://doi.org/10.1111/j.1365-2702.2009.02959.x>.
- Turner-Bowker, D., Bartley, P., & Ware, J. (Eds.). (2002). *SF-36VR Health Survey & “SF” Bibliography: Third Edition (1988-2000)*. Lincoln, RI: Quality-Metric, Inc.
- Tymkew, H., & Templin, L. (2011). Patients with chronic obstructive pulmonary disease or congested heart failure in a home health setting are at a high fall risk: A descriptive study. *American Physical Therapy*, 22(4), 25.
- Vogeli, C., Shields, A. E., Lee, T. A., Gibson, T. B., Marder, W. D., Weiss, K. B., &

- Blumenthal, D. (2007). Multiple chronic conditions: Prevalence, health consequences, and implications for quality, care management, and costs. *Journal of General Internal Medicine*, 22(SUPPL. 3), 391–395. <http://doi.org/10.1007/s11606-007-0322-1>
- Walsh, E. G., Nason, C. A., Moore, A., Khatutsky, G., & Caswell, C. (2003). *Pilot Test of the Medicare Health Survey for PACE and EverCare: PACE Pilot Report*. Baltimore, MD. Retrieved from <http://www.rti.org/pubs/pilottestpace.pdf>
- Wenger, N. K. (2002). Women, heart failure, and heart failure therapies. *Circulation*, 105(13), 1526–1528. <http://doi.org/10.1161/01.CIR.0000014121.94868.81>

## **Chapter 4**

### **Heart Failure and Long-Term Survival Among Older Women with Breast Cancer**

#### **Introduction**

Breast cancer patients aged 65 and older experience disproportionately high rates of chronic heart failure. Increasing clinician concerns for patients with diagnoses of cancer and heart disease has catalyzed an emerging cross-disciplinary field of cardio-oncology (Moslehi, 2013, 2016). The scope of cardio-oncology encompasses prevention and treatment of cardiovascular disease during cancer treatment and throughout cancer survivorship (Moslehi, 2013, 2016). In a cohort study of over 40,000 women diagnosed with breast cancer between ages 66 to 70, ten-year prevalence of heart failure ranged from 29% in women who received no chemotherapy to 38% in women treated with anthracyclines (Pinder, Duan, Goodwin, Hortobagyi, & Giordano, 2007). Comparatively, overall prevalence of heart failure in American women aged 60 to 79 is 5% (Mozaffarian et al., 2015). Multiple factors account for the high prevalence of heart failure in this population. Cardiovascular disease and breast cancer share many risk factors, including advanced age, obesity, physical inactivity, and smoking (Lindenfeld & Kelly, 2010; Schmitz, Prosnitz, Schwartz, & Carver, 2012). At the time of breast cancer diagnosis, many older women have preexisting comorbidities such as coronary artery disease, hypertension, and diabetes (Lindenfeld & Kelly, 2010; Schmitz et al., 2012). Furthermore, many breast cancer therapies are cardiotoxic and interact synergistically with existing cardiovascular risk factors to increase the risk of heart failure (Lindenfeld & Kelly, 2010; Schmitz et al., 2012).

Breast cancer patients with comorbidities such as heart failure are typically excluded from oncology clinical trials (Lewis, 2003); and clinical studies with limited follow-up time underestimate the long-term survival impact of heart failure in patients with breast cancer (Pinder et al., 2007). Thus, little is known about the association between heart failure and long-term survival among older women with breast cancer. Furthermore, it is unclear how the relative contribution of heart failure to mortality risk varies by breast cancer stage – an important consideration, as the competing mortality risk of heart failure must be weighed against the benefits of cancer treatment for each individual. Therefore, we conducted a retrospective cohort study to examine the association between chronic heart failure and long-term survival among older women with breast cancer.

### **Methods**

We used data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) cancer registries linked to the annual Medicare Health Outcomes Survey (MHOS) for survey years 1998 to 2013 (Kent et al., 2016). SEER data contain robust clinical information on cancer diagnosis, disease stage, and mortality. The MHOS is a self-administered mailed survey distributed annually to randomly selected enrollees in Medicare managed care plans (i.e., Medicare Advantage) that collects information on health status and self-reported chronic conditions. We used the MHOS data to identify individuals in SEER who had self-reported heart failure. Self-reported conditions on the MHOS have acceptable sensitivity and specificity when validated against diagnostic codes from patient medical records (Miller et al., 2008).

Our study population included women aged 65 years or older who had a previous diagnosis of invasive breast cancer, completed the MHOS survey within five years of breast

cancer diagnosis, and had no history of other primary cancers. Summing across 14 years of SEER-MHOS cohorts, we initially identified 42,335 women with breast cancer. We then excluded women with *in situ* tumors (stage 0) and those with missing data for either cancer stage, date of cancer diagnosis, or heart failure status. Our final sample included 3,689 women, including 239 with self-reported heart failure in the MHOS survey and 3,450 without heart failure (Figure 4.1).

Among women who died, survival time was calculated as the number of months between date of cancer diagnosis and date of death reported in the Medicare enrollment database. Date of last follow-up was November 30, 2014; therefore, all women who had not died by that date were censored and survival time was calculated from date of diagnosis.

We collected information on cancer site, cancer stage, age at diagnosis, and month/year of diagnosis from SEER data and self-reported medical conditions (e.g., heart failure, hypertension, diabetes, etc.) obtained from the MHOS survey.

Survival was calculated using the Kaplan-Meier Estimator for the entire cohort and separately by heart failure status (heart failure diagnosis reported yes/no). We used Cox proportional hazards regression to examine the association between heart failure status and mortality up to ten years after cancer diagnosis overall and by breast cancer stage. In our adjusted models we controlled for age, race/ethnicity, smoking status, use of a proxy for survey completion, cancer stage, breast tumor estrogen receptor status, diabetes, stroke, and chronic lung disease. All analyses were performed in Stata version 14.0 (College Station, TX) (StataCorp, 2015) using two-sided statistical tests with alpha level of 0.05. We used complete cases analysis and missing values were assumed to be missing completely at random.

## Results

Women with heart failure differed from those without heart failure in several ways (Table 4.1). Women with heart failure were slightly older (mean age 78 years vs. 76 years) and were more likely to be Non-Hispanic Black compared to those without heart failure (15% vs 8%,  $p<0.001$ ). Women with heart failure were more likely to report comorbid conditions, for instance: hypertension, diabetes, other cardiovascular conditions, chronic lung disease, and arthritis. The heart failure group also included a greater proportion of patients with advanced stage (III/IV) cancer than women without heart failure (16% vs. 10%,  $p<0.01$ ).

Survival rates were lower among women with heart failure compared to those without heart failure throughout follow-up (Table 4.2, Figure 4.2). Five-year survival rates in women with heart failure exceeded 70% for women with stage I or II cancer and were 49% for stage III/IV cancer (Table 4.2). At ten years after cancer diagnosis, survival rates in women with heart failure and stage I, II, or III/IV cancer fell to 55%, 51%, and 27%, respectively. The contrast in survivorship between participants with and without heart failure was greater at ten years. Among all study participants, heart failure was independently and significantly associated with increased likelihood of death (adjusted hazard ratio: 1.62, 95% CI: 1.32, 2.00). Other significant predictors, in addition to age and cancer stage, were smoking, diabetes, stroke, and chronic lung disease (HRs ranged from 1.23 to 1.87,  $p<0.01$  for all).

After stratification by cancer stage and adjustment for covariates, heart failure was associated with higher likelihood of death in women with stage I and II cancer up to ten years after diagnosis (HR 1.72, 95% CI: 1.24, 2.38 and HR 2.06, 95% CI: 1.46, 2.93, respectively) but not in women with advanced stage (III/IV) cancer (HR 1.27, 95% CI: 0.82, 1.98).

## Discussion

We found that heart failure is associated with significantly lower short- and long-term survival rates only among older women with early-stage (I/II) breast cancer. This finding may seem counterintuitive, as early-stage breast cancer is generally associated with better prognosis. Prevention and management of cardiovascular disease should remain a high priority for this patient population. As expected, women with heart failure also had greater comorbidity burden that may contribute to mortality risk.

Survival rates among women without heart failure were comparable to population survival rates for postmenopausal women with invasive breast cancer (Howlander et al., 2016). However, we found that five-year survival among the heart failure group (72.4%) exceeded typical survival estimates for older women with heart failure. In a population-based cohort study of women diagnosed with heart failure between 1996 and 2000 (mean age 75 years), 5-year survival was 54% (Roger et al., 2004). The observed difference in survival may be related to variation in heart failure type (systolic vs. diastolic) and/or heart failure stage, which were unavailable for the participants in this study.

To minimize the cardiovascular risk of cancer treatment, the European Society of Cardiology recommends thorough assessment and optimization of baseline cardiovascular risk factors in patients with cancer (Zamorano et al., 2016). Before treatment with cardiotoxic agents such as anthracyclines or trastuzumab, patients should see a cardiologist for assessment of baseline cardiac function (Zamorano et al., 2016). Clinical guidelines vary in regards to recommended frequency of cardiac surveillance in oncology patients. The European Society of Cardiology recommends continued surveillance with echocardiography after every four cycles of trastuzumab or 200 mg/m<sup>2</sup> of doxorubicin, and more frequent surveillance may be necessary for

patients with cardiac risk factors or abnormal baseline cardiac function (Zamorano et al., 2016). Comparatively, the American Society of Clinical Oncology recommends routine surveillance with echocardiography for individuals with cardiovascular risk factors undergoing treatment with cardiotoxic agents (anthracyclines, trastuzumab, and mediastinal radiation), with the frequency of screening at the discretion of providers based on clinical judgment (Armenian et al., 2016). Prophylactic treatment with ACE inhibitors and beta-blockers benefits patients with preexisting cardiovascular disease, but the benefit for patients with low baseline risk is unclear (Zamorano et al., 2016). Cardiovascular risk stratification may be useful to identify patients in need of more frequent screening and subsequent intervention (Ezaz, Long, Gross, & Chen, 2014; Francis, Cheng, Arteaga, & Moslehi, 2014). In addition, breast cancer patients with comorbidity may benefit from follow-up with a general practitioner for medical management of existing health issues.

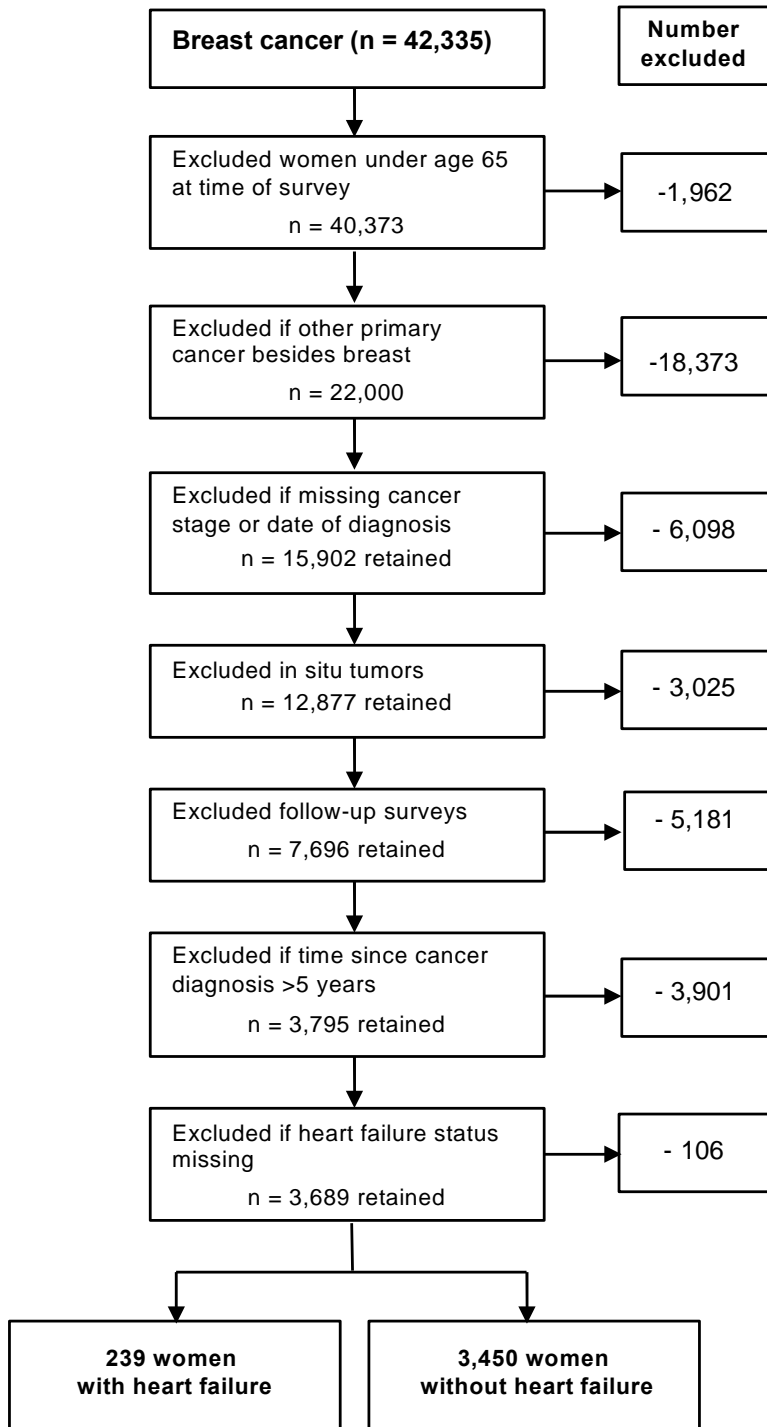
The increased mortality risk associated with cardiovascular disease in women with breast cancer may not manifest for a number of years after cancer diagnosis (Schmitz et al., 2012). The contrast in survivorship we observed between participants with and without heart failure became apparent approximately three years post-cancer diagnosis and increased over time. In a related study, Bradshaw et al. (2016) found that breast cancer survivors experienced greater cardiovascular disease-related mortality compared to women without breast cancer beginning approximately seven years after cancer diagnosis. Prospective longitudinal studies are needed to examine the trajectory of cardiovascular disease development in aging cancer survivors. In order to conduct epidemiologic studies that inform cancer treatment decisions and survivorship care, the National Cancer Institute has proposed development of a national registry of cardiovascular outcomes in oncology patients (Shelburne et al., 2014).



To our knowledge, no prior study has examined the association between comorbid heart failure and overall survival at ten years among a diverse sample of women with breast cancer. However, several limitations of our study must be acknowledged. First, our sample was limited to women aged 65 and older enrolled in Medicare Advantage plans. Second, heart failure and other comorbid conditions were self-reported on the MHOS, and temporality of heart failure diagnosis in relation to breast cancer diagnosis was unknown. Third, clinical data regarding heart failure type and stage and details of chemotherapy regimens and hormonal therapies were unavailable. Despite these limitations, this study included a large national dataset with a representative sample of the US population and detailed cancer data.

In summary, heart failure is associated with significantly worse prognosis for older women with early-stage breast cancer. Prevention and management of cardiovascular comorbidities and other chronic conditions in this population should remain a priority after cancer diagnosis, and prospective research can inform strategies for risk-adapted cardiac surveillance in breast cancer survivors.

**Figure 4.1** Selection of Breast Cancer Sample from SEER-MHOS Database



**Table 4.1** Characteristics of Study Participants According to Heart Failure Status

Characteristic	With Heart Failure, n = 239	Without Heart Failure, n = 3,450	p-value*
<b>Sociodemographic Characteristics and Comorbidities</b>			
Age at time of survey, n (%)			<0.001
65-74 y	91 (38.1)	1,790 (51.9)	
75-84 y	104 (43.5)	1,350 (39.1)	
85+ y	44 (18.4)	310 (9.0)	
Race/ethnicity, n (%)			<0.01
Non-Hispanic White	159 (66.5)	2,528 (73.3)	
Non-Hispanic Black	35 (14.6)	260 (7.5)	
Hispanic	20 (8.4)	282 (8.2)	
Other	25 (10.5)	380 (11.0)	
Proxy for survey completion, n (%)			<0.001
Yes	50 (20.9)	326 (9.5)	
No	174 (72.8)	2,917 (84.5)	
Unknown	15 (6.3)	207 (6.0)	
Smoking status n (%)			0.80
Current smoker	16 (6.7)	245 (7.1)	
Not current smoker	187 (78.2)	2,635 (76.4)	
Unknown	36 (15.1)	570 (16.5)	
Comorbidities, n (%)			
Hypertension	202 (84.5)	2,216 (64.2)	<0.001
Angina/CAD	107 (44.8)	237 (6.9)	<0.001
Myocardial infarction	81 (33.9)	142 (4.1)	<0.001
Other heart conditions	138 (57.7)	626 (18.1)	<0.001
Stroke	55 (23.0)	266 (7.7)	<0.001
Emphysema, asthma, or COPD	71 (29.7)	451 (13.1)	<0.001
Crohn's/ulcerative colitis/IBD	20 (8.4)	152 (4.4)	<0.01
Arthritis of hip or knee	128 (53.6)	1,593 (46.2)	0.03
Arthritis of hand/wrist	113 (47.3)	1,423 (41.3)	0.07
Sciatica	82 (34.3)	818 (23.7)	<0.001
Diabetes	104 (43.5)	734 (21.3)	<0.001
<b>Cancer Characteristics</b>			
Cancer stage, n (%)			<0.01
Stage I	119 (49.8)	2,074 (60.1)	
Stage II	83 (34.7)	1,029 (29.8)	
Stage III/IV	37 (15.5)	347 (10.1)	
Estrogen receptor status, n (%)			0.30
Positive	172 (72.0)	2,634 (76.3)	
Negative	36 (15.0)	452 (13.1)	
Borderline/Unknown	31 (13.0)	364 (10.6)	

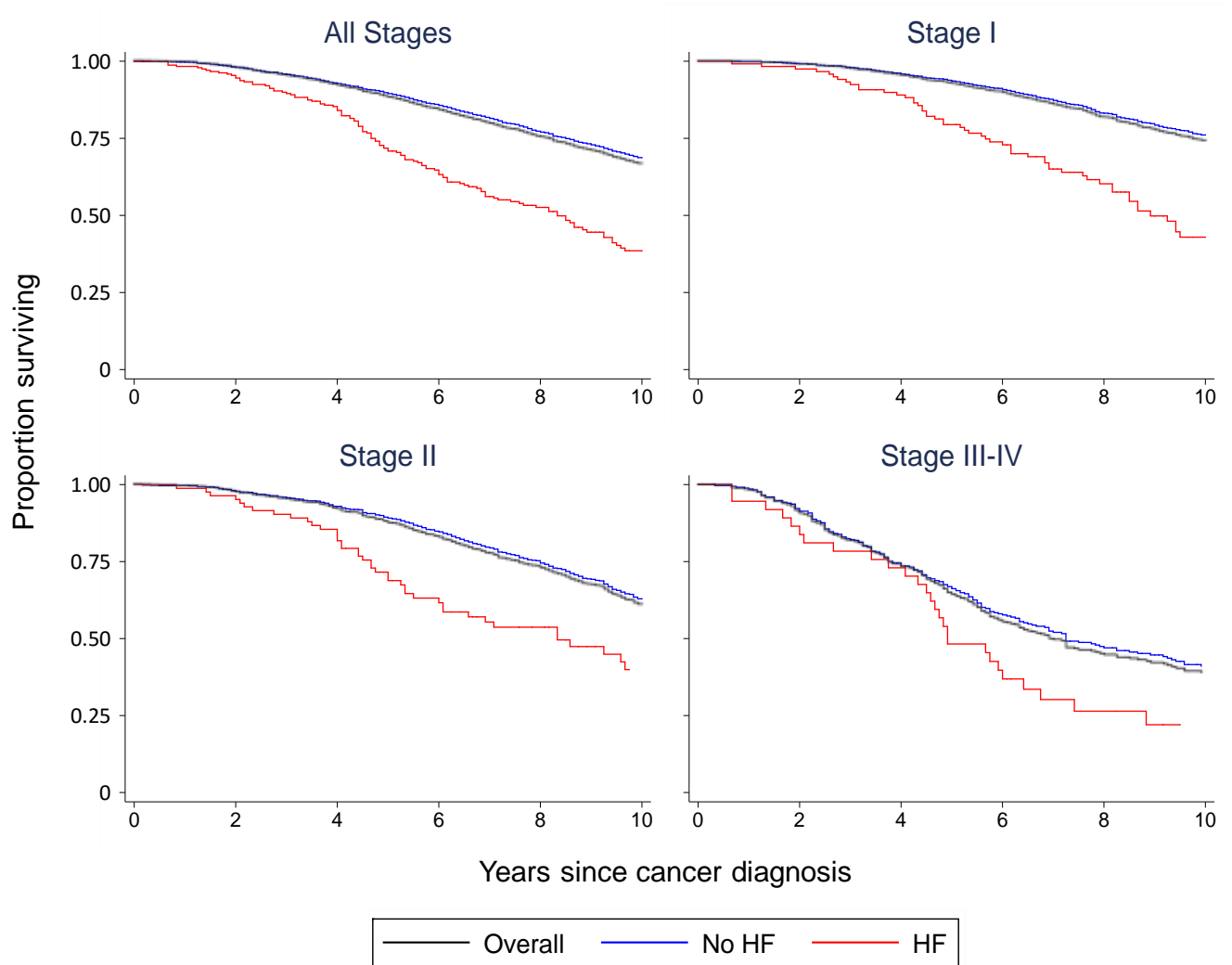
\*p-value compares study participants with and without heart failure using chi-square tests

**Table 4.2** Five- and Ten-Year Survival Rates Among Breast Cancer Patients According to Heart Failure Status

	With Heart Failure, n = 239	Without Heart Failure, n = 3,450	p-value*
Five-Year Survival (%)			
All Stages	72.4	90.1	<0.001
Stage I	79.8	94.0	<0.001
Stage II	72.3	89.7	<0.001
Stage III/IV	48.6	67.7	0.04
Ten-Year Survival (%)			
All Stages	49.0	74.9	<0.001
Stage I	54.6	81.1	<0.001
Stage II	50.6	71.2	<0.001
Stage III/IV	27.0	48.7	0.01

\*p-value compares study participants with and without heart failure using log-rank tests

**Figure 4.2** Survival Curves Overall and by Heart Failure Status Among Older Women with Breast Cancer



HF = Heart Failure

## References

- Armenian, S. H., Lacchetti, C., Barac, A., Carver, J., Constine, L. S., Denduluri, N., ... Lenihan, D. (2017). Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 35(8), 893–911. <http://doi.org/10.1200/JCO.2016.70.5400>
- Bradshaw, P. T., Stevens, J., Khankari, N., Teitelbaum, S. L., Neugut, A. I., & Gammon, M. D. (2016). Cardiovascular disease mortality among breast cancer survivors. *Epidemiology*, 27(1), 6–13. <http://doi.org/10.1097/EDE.0000000000000394>
- Ezaz, G., Long, J. B., Gross, C. P., & Chen, J. (2014). Risk prediction model for heart failure and cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *Journal of the American Heart Association*, 3, e000472. <http://doi.org/10.1161/JAHA.113.000472>
- Francis, S. A., Cheng, S., Arteaga, C. L., & Moslehi, J. (2014). Heart failure and breast cancer therapies: Moving towards personalized risk assessment. *Journal of the American Heart Association*, 3(1), e000780. <http://doi.org/10.1161/JAHA.113.000780>
- Howlader, N., Noone, A., Krapcho, M., Miller, D., Bishop, K., Altekruse, S., ... Cronin, K. (2016). *SEER Cancer Statistics Review, 1975-2013*. Bethesda, MD. Retrieved from [http://seer.cancer.gov/csr/1975\\_2013/](http://seer.cancer.gov/csr/1975_2013/)
- Kent, E. E., Malinoff, R., Rozjabek, H. M., Ambros, A., Clauser, S. B., Topor, M. A., ... DeMichele, K. (2016). Revisiting the surveillance epidemiology and end results cancer registry and medicare health outcomes survey (SEER-MHOS) linked data resource for patient-reported outcomes research in older adults with cancer. *Journal of the American Geriatrics Society*, 64(1), 186–192. <http://doi.org/10.1111/jgs.13888>

- Lewis, J. H. (2003). Participation of patients 65 years of age or older in cancer clinical trials. *Journal of Clinical Oncology*. <http://doi.org/10.1200/JCO.2003.08.010>
- Lindenfeld, J., & Kelly, P. A. (2010). Developing a cardiology-oncology clinical practice guideline. *Progress in Cardiovascular Diseases*, 53(2), 173–179. <http://doi.org/10.1016/j.pcad.2010.06.001>
- Miller, D. R., Rogers, W. H., Kazis, L. E., Spiro, A., Ren, X. S., & Haffer, S. C. (2008). Patients' self-report of diseases in the Medicare Health Outcomes Survey based on comparisons with linked survey and medical data from the Veterans Health Administration. *The Journal of Ambulatory Care Management*, 31(2), 161–77. <http://doi.org/10.1097/01.JAC.0000314707.88160.9c>
- Moslehi, J. (2013). The cardiovascular perils of cancer survivorship. *New England Journal of Medicine*, 368(11), 1055–1056. <http://doi.org/10.1056/NEJMe1215300>
- Moslehi, J. (2016). Cardiovascular toxic effects of targeted cancer therapies. *New England Journal of Medicine*, 375(15), 1457–1467. <http://doi.org/10.1056/NEJMra1100265>
- Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., ... Turner, M. B. (2015). Heart disease and stroke statistics - 2016 update: A report from the American Heart Association. *Circulation*, 133(4), e38–e360. <http://doi.org/10.1161/CIR.0000000000000350>
- Pinder, M. C., Duan, Z., Goodwin, J. S., Hortobagyi, G. N., & Giordano, S. H. (2007). Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *Journal of Clinical Oncology*, 25(25), 3808–3815. <http://doi.org/10.1200/JCO.2006.10.4976>
- Roger, V. L., Weston, S. A., Redfield, M. M., Hellermann-Homan, J. P., Killian, J., Yawn, B. P.,

- & Jacobsen, S. J. (2004). Trends in heart failure incidence and survival in a community-based population. *JAMA*, *292*(3), 344–350. <http://doi.org/10.1001/jama.292.3.344>
- Schmitz, K. H., Prosnitz, R. G., Schwartz, A. L., & Carver, J. R. (2012). Prospective surveillance and management of cardiac toxicity and health in breast cancer survivors. *Cancer*, *118*(SUPPL.8), 2270–2276.
- Shelburne, N., Adhikari, B., Brell, J., Davis, M., Desvigne-Nickens, P., Freedman, A., ... Remick, S. C. (2014). Cancer treatment–related cardiotoxicity: Current state of knowledge and future research priorities. *Journal of the National Cancer Institute*, *106*(9). <http://doi.org/10.1093/jnci/dju232>
- StataCorp. (2015). *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.
- Zamorano, J. L., Lancellotti, P., Rodriguez Muñoz, D., Aboyans, V., Asteggiano, R., Galderisi, M., ... Suter, T. M. (2016). 2016 European Society of Cardiology position paper on cancer treatments and cardiovascular toxicity. *European Heart Journal*, *37*(36), 2768–2801. <http://doi.org/10.1093/eurheartj/ehw211>



## Chapter 5

### Synthesis and Conclusions

#### Summary of Major Research Findings

The purpose of this dissertation research was to characterize HRQOL, functional status, and long-term survival in a cohort of older women with breast cancer and heart failure, while examining the extent to which heart failure affects these outcomes. This research was undertaken to inform future development of patient-level and systems-level interventions to improve care of older adults with comorbid cancer and heart failure. The following are the key findings:

**Compared to women with later-stage cancer, women with early-stage breast cancer experienced greater physical and mental health burdens associated with heart failure.** The relative HRQOL burden of competing comorbidities (cancer and heart failure) appears to vary by cancer stage. We found that women with early-stage (I/II) breast cancer, who generally experience lower cancer-related morbidity and more favorable long-term health outcomes, experienced greater physical and mental health burdens compared with later-stage cancer patients. Heart failure was associated with poorer mental HRQOL in women with early-stage cancer, particularly in the domains of social functioning (i.e., the degree to which physical health or emotional problems interfere with social activities) and role-emotional (i.e., the degree to which emotional problems such as depression or anxiety interfere with normal work or activities). Interventions to improve HRQOL in this population may require a multifaceted approach to address both mental and physical health deficits.

**The most consistent HRQOL deficits associated with heart failure were physical deficits.** Heart failure was associated with a consistent pattern of physical impairment, fatigue, and general poor health. Across all cancer stages, heart failure was associated with clinically and statistically significant deficits in physical function, vitality (i.e., perceived energy level), general health, and overall physical HRQOL (physical component score). Even among women with advanced stage cancer who generally experience greater cancer-related morbidity, heart failure was associated with worse physical HRQOL. These findings are consistent with previous studies in which women with heart failure had poor perceived physical health status (Bennett, Baker, & Huster, 1998; Riedinger et al., 2001).

**Heart failure was associated with greater functional status impairment across all cancer stages.** We found that functional status impairment was common in women with breast cancer regardless of heart failure status, but heart failure was associated with more severe impairment in all six basic ADLs. Difficulty walking was the most common limitation. Nearly 70% of women with heart failure reported difficulty walking, including 10% who reported they were unable to walk. Further exploration is needed to determine the reasons for these impairments. Dyspnea and activity intolerance often contribute to walking difficulties in patients with heart failure, but the presence of cancer and other comorbidities such as arthritis may compound functional limitations. Tailored, evidence-based interventions to address individual risk factors for functional decline in older adults should be adapted to this population. Although physical activity interventions have been correlated with clinical endpoints such as improved physical functioning and cardiorespiratory fitness in breast cancer populations (McNeely et al., 2006), these interventions may not be feasible for women with chronic heart failure.

Functional impairment is common in heart failure patients, particularly women (Dunlay et al., 2015; Riedinger et al., 2001; Seo et al., 2008). Although we did not directly examine the interaction between heart failure and breast cancer, our findings were consistent with past studies in which clustering of chronic conditions resulted in far greater disability than individual chronic conditions (Fried et al., 1999; Jindai et al., 2016). Among older adults with multimorbidity, each additional chronic condition is associated with a greater number of functional limitations, on average (Jindai et al., 2016), and the type of impairment may vary based on the clustering of conditions (Fried et al., 1999). The association between multimorbidity and functional impairment is stronger for women than for men (Jindai et al., 2016). Our findings suggest that co-occurring cancer and heart failure in older women are associated with severe functional status impairment requiring clinical intervention.

**Heart failure was associated with significantly lower short- and long-term survival rates among older women with early-stage (I/II) breast cancer.** The contrast in survivorship we observed between participants with and without heart failure became apparent approximately three years post-cancer diagnosis and increased over time. Although early-stage breast cancer is generally associated with better prognosis, we found that the competing mortality risk of heart failure was greater for this group than for women with advanced stage (III/IV) cancer. Given the high prevalence of heart failure in breast cancer survivors, clinicians who manage such conditions need to be aware of this difference in prognosis. The European Society of Cardiology guidelines recommend that women undergoing breast cancer treatment with cardiotoxic agents such as anthracyclines or trastuzumab should see a cardiologist for assessment of baseline cardiac function and continued monitoring with echocardiography to detect subtle changes

(Zamorano et al., 2016). Prevention and management of cardiovascular comorbidities and other existing health issues among older women should remain a priority after cancer diagnosis.

### **Significance**

Within the broader context of multimorbidity in aging cancer survivors, we sought to characterize the physical and mental health burden of heart failure among older women with breast cancer. The HRQOL deficits and functional status impairment we observed correlate with increased risk of hospitalization and mortality in heart failure patients (Dunlay et al., 2015; Konstam et al., 1996; Sehl, Lu, Silliman, & Ganz, 2013). The pattern of physical impairment, fatigue, and general poor health reported by breast cancer survivors with heart failure is consistent with the “frailty phenotype,” a weakened physiological state typically associated with advanced age (Fried et al., 2001). Frailty is defined as three or more of the following criteria: reduced muscle mass, exhaustion, low activity, slowness, and weakness. Prefrailty is defined as meeting one or two of these criteria. Based on our findings, the majority of breast cancer survivors with heart failure fit the criteria for frailty or prefrailty, putting them at risk for a cycle of increasing disability leading to hospitalization and death (Bennett, Winters-Stone, Dobek, & Nail, 2013). Although the concept of frailty in cancer survivors has not been studied extensively, both breast cancer and heart failure have been linked to accelerated development of frailty, resulting in “early-onset” frailty (Afilalo, 2011; Bennett et al., 2013). Frailty occurs prior to a measurable decline in ADL performance, and optimization of comorbid conditions in frail patients may reduce the development of disability (Afilalo, 2011). Because of the mortality risk associated with severe functional status impairment in heart failure patients, early intervention to prevent functional decline in this population should be a priority for clinicians. Although our

dataset did not include the measures to define frailty as Fried (2001) did, this area is worthy of further exploration.

Another notable finding was that the adverse sequelae associated with heart failure, including HRQOL burden and mortality risk, were greatest for women with early-stage cancer. Compared to women with later-stage cancer, women with early-stage breast cancer generally experience lower cancer-related morbidity and mortality. For this clinical subgroup, the relative burden and competing mortality risk of heart failure may be greater than cancer. These patients would likely benefit from behavioral interventions that have been successful in other heart failure populations, and they may gain the most improvement from interventions targeting functional status and HRQOL.

Given the adverse sequelae associated with heart failure in older women with early-stage breast cancer, providers need to carefully weigh the risks of cardiotoxic cancer therapies against the potential survival benefits. Overtreatment of early-stage breast cancer may cause more harm than benefit, particularly for older women with increased cardiovascular risk. Many low-risk tumors detected via mammography are treated with unnecessary mastectomies that can lead to complications from surgery (Alvarado, Ozanne, & Esserman, 2012). Based on molecular profiling, women over age 50 are more likely to have biologically low risk tumors that are responsive to endocrine therapy and do not require aggressive treatment (Esserman et al., 2011). In addition to molecular profiling of tumors, computerized clinical decision support tools to predict risk of breast cancer recurrence based on tumor characteristics can prevent overtreatment of early-stage disease (Esserman et al., 2011).

Although guidelines have been released for management of breast cancer in older women (Biganzoli et al., 2012), there is a need for clinician education regarding treatment guidelines for

early-stage breast cancer, especially for patients with multimorbidity (Jones et al., 2012). In some cases, breast cancer may not be the patient's primary illness if she has preexisting comorbidities that decrease her life expectancy and increase the risk of treatment complications (Jones, Leak, & Muss, 2012). Compared to younger individuals, older adults tend to emphasize quality of life over survival gains when making cancer treatment decisions (Wedding, Pientka, & Höffken, 2007). Adverse effects of breast cancer treatment can lead to cardiovascular complications, as well as functional loss and reduced quality of life. For this reason, patient-provider communication is important to help older adults make informed decisions regarding cancer treatment.

Management of the complex physical and mental health burdens we observed in women with cancer and heart failure will require an innovative, multifaceted approach. In addition to patient-level behavioral interventions, systems-level interventions are needed to improve quality of care for this population. These findings reinforce the need for interventions at the patient level, health system level, and health policy level for management of complex chronic conditions in older adults with cancer.

### **Strengths and Limitations**

To our knowledge, no prior study has examined HRQOL and functional status among a diverse sample of breast cancer survivors with heart failure. In addition, no prior study has examined the association between comorbid heart failure and overall survival at ten years among older women with breast cancer. Although we do not have sufficient clinical data to presume that women in this study developed heart failure as a result of breast cancer treatment, we have examined the collective burden of these two co-occurring conditions on patient-centered outcomes and mortality.

Several limitations of this study must be acknowledged. First, heart failure and other comorbid conditions were self-reported on the MHOS, and temporality of heart failure diagnosis in relation to breast cancer diagnosis was unknown. Our findings are biased toward the null, as some women in the control group may have had unreported heart disease. Self-reported heart failure on the MHOS has high specificity, i.e., patients without a heart failure diagnosis are unlikely to report it (Miller et al., 2008). Second, clinical data regarding heart failure type and stage and details of chemotherapy regimens and hormonal therapies were unavailable. Significant results from this analysis should be confirmed in prospective studies that include key clinical data, including chemotherapy regimens, tumor type, receipt of trastuzumab, heart failure type and stage, and duration of heart failure diagnosis. Third, our sample was limited to women aged 65 and older enrolled in Medicare managed care (Medicare Advantage) plans. Our results may not be generalizable to younger women, and Medicare managed care enrollees, on average, have better health but less education and lower income than fee-for-service enrollees (Shimada et al., 2009).

Despite these limitations, strengths of this study included a large national dataset with a diverse and representative sample of women in the US, validated measures, detailed cancer data from SEER registries, and survival data from the Medicare Enrollment Database. The Short Form-36 and activities of daily living performance are two of the universal patient outcome measures recommended by the National Institutes of Aging for assessment of health status in older adults with multiple chronic conditions (Adams et al., 2012). A propensity score matching approach minimized observed differences between women with heart failure and controls. Findings from this study can inform the rigorous design of future prospective studies and

development of interventions to address the HRQOL deficits and functional status impairment we observed in women with breast cancer and heart failure.

### **Directions for Future Research**

Our findings suggest that older women with comorbid cancer and heart failure require clinical intervention to reduce functional decline and address quality of life deficits. We found that the competing comorbidity burden of heart failure varied by cancer stage. Further research is needed to elucidate the reasons that women with early-stage cancer experienced greater physical and mental health deficits associated with heart failure. To fill the primary gap that our research did not address, future studies should incorporate clinical data regarding cancer treatment and heart failure diagnosis, while differentiating between women with preexisting heart failure and women who developed heart failure following cancer treatment. To build upon our findings, another priority for future research is to determine how the interaction between heart failure and cancer affects functional status and identify the cause of the severe ADL impairments we observed among breast cancer survivors with heart failure.

The conceptual framework guiding this research was adapted from the Wilson and Cleary model of HRQOL. In our adapted model, we accounted for the presence of additional patient-reported chronic conditions, classified as biological variables. We also included functional status as an additional outcome variable and added a bidirectional arrow to indicate interaction between functional status and HRQOL. A strength of the model is that it is not condition-specific and can be modified to account for multimorbidity. In future studies, the Ferrans revision of the Wilson and Cleary model (Ferrans, Zerwic, Wilbur, & Larson, 2005) may provide a more useful conceptual framework to examine health outcomes and guide clinical interventions in older adults with multimorbidity. The Ferrans revision is more parsimonious than the original model



and reflects that characteristics of the individual and his/her environment affect health outcomes at every level, including biological function, symptoms, functional status, health perceptions, and overall HRQOL (Bakas et al., 2012; Ferrans et al., 2005). The conceptual model should reflect that health outcomes are influenced by the social determinants of health such as socioeconomic status, access to care, and physical environment (Braveman & Gottlieb, 2014). By providing operational definitions of individual and environmental characteristics (i.e., social determinants of health), the Ferrans model explains HRQOL outcomes more accurately than the original model (Bakas et al., 2012). In addition, although HRQOL is the primary outcome variable of the Wilson and Cleary model, we found that functional status is an important clinical endpoint to evaluate in older adults with multimorbidity, whose degree of functional impairment may vary based on the clustering of chronic conditions.

To expand upon the results of this dissertation in a broader context, the following priorities for future research can advance the objective of improving health outcomes and quality of life among older adults with cancer and complex chronic conditions.

**Determine the trajectory of cardiovascular disease development in cancer survivors.**

Additional comorbidities often occur after an “incident chronic condition” such as cancer (Parekh, Goodman, Gordon, & Koh, 2011). Prospective longitudinal studies are needed to examine the trajectory of cardiovascular disease development in aging cancer survivors, particularly women, while examining the effects of preexisting comorbidities and cancer treatment variables. In addition to sex differences in cardiovascular aging and heart failure pathophysiology, women also have greater susceptibility to anthracycline cardiotoxicity (Scardovi, Petruzzi, Rosano, Lucia, & De Maria, 2012; Strait & Lakatta, 2012; Volkova & Russell, 2011). Patients who develop heart failure during or soon after cancer treatment may be

classified as a different population than long-term survivors who develop heart failure. Similarly, patients with preexisting heart failure that occurred before cancer diagnosis would be classified as a separate population. A greater understanding of the disease trajectories that occur after a cancer diagnosis can inform strategies for risk-adapted surveillance to prevent cardiovascular complications, as well as strategies to better manage preexisting cardiovascular disease in older adults with cancer. Leveraging population-level data to examine these outcomes in cancer survivors is a major research priority identified by the National Cancer Institute (Shelburne et al., 2014).

**Adapt effective interventions from the broader chronic disease community to address specific needs for patients with cancer and heart failure.** To improve health outcomes and quality of life among women with comorbid cancer and heart failure, effective interventions from the broader chronic disease community can be adapted to this patient population. Many behavioral interventions targeting older adults with multimorbidity have improved functional outcomes and physical and mental HRQOL (Smith, Soubhi, Fortin, Hudon, & O'Dowd, 2012). Evidence-based interventions to address individual risk factors for functional decline can reduce ADL impairment in community-dwelling older adults (Phelan, Williams, Penninx, LoGerfo, & Leveille, 2004). In addition, tailored interventions to promote patient engagement in self-management and health behavior change can be effective for older adults with multimorbidity (Hibbard & Greene, 2013).

Motivational interviewing, a technique to identify and address individual barriers to health behavior change, has been shown to improve outcomes in heart failure patients with multimorbidity (Riegel et al., 2016). Motivational interviewing interventions for heart failure patients have increased physical activity, improved physical and mental HRQOL, and reduced

hospital readmissions (Brodie & Inoue, 2005; Brodie, Inoue, & Shaw, 2008; Riegel et al., 2016). This approach may be helpful to address individual barriers to self-management for women with cancer and heart failure, while helping patients identify personal goals related to symptom management, functional status, and role functioning.

Another promising avenue for older adults with multimorbidity is the use of mobile health technology (mHealth) to improve chronic disease self-management and quality of life. Extensive evidence supports the effectiveness of technology-mediated interventions to facilitate symptom management and promote adherence to self-care behaviors for patients with cardiovascular disease and other chronic illness (Burke et al., 2015; Hamine, Gerth-Guyette, Faulx, Green, & Sarah Ginsburg, 2015; Widmer et al., 2015). Telehealth interventions have improved self-efficacy and clinical endpoints in patients with multiple chronic conditions (Blasco et al., 2012; Pratt et al., 2013; Wakefield et al., 2011; Widmer et al., 2015). An important area for future study is adaptation of mobile technologies using features such as interactive voice response to fit the needs of older adults with visual impairment and other age-related changes. mHealth interventions may benefit patients with cancer and heart failure, particularly underserved populations with limited access to health care providers.

**Develop new models of care to improve quality and continuity of care for older adults with cancer and complex chronic conditions.** Models of care for management of high-cost, high-needs patients are essential to improve patient outcomes in a cost-efficient manner. Health care spending for cancer survivors remains elevated even after treatment is finished. For older adults diagnosed with cancer in 2004, the estimated aggregate 5-year costs to Medicare were \$21.1 billion (Yabroff et al., 2008). Multimorbidity in older adults with cancer complicates coordination of cancer treatment as well as primary care. However, most existing models of care

for management of chronic conditions do not include cancer (Sarfati, Koczwara, & Jackson, 2016).

The emerging field of cardio-oncology is described as “encompassing a continuum of cardiovascular risk stratification, prevention, and treatment that spans the timeline from cancer diagnosis into survivorship” (Barac et al., 2015). Thus far, the primary emphasis of cardio-oncology has been attenuation of cardiotoxicity from cancer treatment. However, the survivorship aspect of cardio-oncology is equally important. The skills and expertise of this field should be integrated into primary care for the long-term prevention and management of cardiovascular disease in aging cancer survivors. Many primary care providers have limited training in cancer survivorship issues and are unaware of the long-term cardiac risks of anthracyclines and other agents commonly used to treat breast cancer (Nekhlyudov, Aziz, Lerro, & Virgo, 2012). As survivors transition from oncology to primary care, communication between oncologists and primary care providers regarding potential long-term effects of cancer treatment is important to promote early recognition and treatment of cardiovascular complications (Dossett et al., 2017; Nekhlyudov et al., 2012). Survivorship care planning may facilitate communication between disciplines (Dossett et al., 2017).

Innovative models of care may promote better integration of health care services for cancer patients and survivors with multimorbidity. For example, patient-centered medical homes for management of patients with complex chronic conditions, including cancer, have shown potential for reducing hospital admissions and improving survival (Sweeney, Halpert, & Waranoff, 2007). Reports from the Institute of Medicine have emphasized the need for survivorship care planning to improve interdisciplinary care coordination for cancer survivors (Institute of Medicine, 2005). Proposed models of care for cancer survivors include a “shared-

care” model to promote collaboration between primary care providers and specialists, a nurse-led model of survivorship care, and specialized survivorship clinics to provide integrated health care. It is unclear which of these models is feasible, efficacious, and acceptable to patients and providers (Institute of Medicine, 2005). Large-scale health policy analyses can examine the effectiveness of different health service delivery models for cancer survivorship outcomes.

### **Conclusions**

In summary, the co-occurrence of cancer and cardiovascular disease is a major public health issue that will become more prevalent as the population of older adults in the US rapidly increases over the next several decades (Hung, Ross, Boockvar, & Siu, 2011, 2012; Smith, Smith, Hurria, Hortobagyi, & Buchholz, 2009). Clinical intervention is necessary to address the adverse sequelae of comorbid cancer and heart failure among older women. We found that chronic heart failure in older women with breast cancer is associated with clinically significant deficits in physical and mental HRQOL, substantial functional status impairment, and increased five- and ten-year mortality risk for women with early-stage cancer. To address the observed deficits in functional status and quality of life, successful behavioral interventions from other chronic illness populations may be adapted to this patient population. Further prospective research is needed to determine the trajectory of cardiovascular disease development in aging cancer survivors, particularly women. Continued development of tailored, goal-oriented strategies for chronic disease self-management may improve health outcomes for patients with cancer and heart failure. In addition, new models of care can improve care coordination for cancer survivors with multimorbidity. Although the burden of comorbid cancer and heart failure can be overwhelming for patients as well as the healthcare system, evidence-based interventions

and innovative health care delivery models have potential to reduce the burden of chronic illness and improve quality of life for these patients.

## References

- Adams, K., Bayliss, E., Blumenthal, D., Boyd, C., Guralnik, J., Krist, A. H., ... Working Group on Health Outcomes for Older Persons with Multiple Chronic Conditions. (2012). Universal health outcome measures for older persons with multiple chronic conditions. *Journal of the American Geriatrics Society*, *60*(12), 2333–2341. <http://doi.org/10.1111/j.1532-5415.2012.04240.x>
- Afilalo, J. (2011). Frailty in patients with cardiovascular disease: Why, when, and how to measure. *Current Cardiovascular Risk Reports*. <http://doi.org/10.1007/s12170-011-0186-0>
- Alvarado, M., Ozanne, E., & Esserman, L. (2012). Overdiagnosis and overtreatment of breast cancer. *American Society of Clinical Oncology Educational Book / ASCO. American Society of Clinical Oncology. Meeting*, e40-5. [http://doi.org/10.14694/EdBook\\_AM.2012.32.e40](http://doi.org/10.14694/EdBook_AM.2012.32.e40)
- Bakas, T., McLennon, S. M., Carpenter, J. S., Buelow, J. M., Otte, J. L., Hanna, K. M., ... Welch, J. L. (2012). Systematic review of health-related quality of life models. *Health & Quality of Life Outcomes*, *10*(1), 134–145. <http://doi.org/10.1186/1477-7525-10-134>
- Barac, A., Murtagh, G., Carver, J. R., Chen, M. H., Freeman, A. M., Herrmann, J., ... Douglas, P. S. (2015). Cardiovascular health of patients with cancer and cancer survivors: A roadmap to the next level. *Journal of the American College of Cardiology*, *65*(25), 2739–2746. <http://doi.org/10.1016/j.jacc.2015.04.059>
- Bennett, J. A., Winters-Stone, K. M., Dobek, J., & Nail, L. M. (2013). Frailty in older breast cancer survivors: Age, prevalence, and associated factors. *Oncology Nursing Forum*, E126–34 1p. <http://doi.org/10.1188/13.ONF.E126-E134>
- Bennett, S. J., Baker, S. L., & Huster, G. A. (1998). Quality of life in women with heart failure.

*Health Care for Women International*, 19(3), 217–29.

<http://doi.org/10.1080/073993398246386>

Biganzoli, L., Wildiers, H., Oakman, C., Marotti, L., Loibl, S., Kunkler, I., ... Audisio, R. (2012). Management of elderly patients with breast cancer: Updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncology*, 13(4), e148-60.

[http://doi.org/http://dx.doi.org/10.1016/S1470-2045\(11\)70383-7](http://doi.org/http://dx.doi.org/10.1016/S1470-2045(11)70383-7)

Blasco, A., Carmona, M., Fernandez-Lozano, I., Salvador, C. H., Pascual, M., Sagredo, P. G., ... Alonso-Pulpon, L. (2012). Evaluation of a telemedicine service for the secondary prevention of coronary artery disease. *Journal of Cardiopulmonary Rehabilitation and Prevention*, 32(1), 25–31. <http://doi.org/10.1097/HCR.0b013e3182343aa7> [doi]

Braveman, P., & Gottlieb, L. (2014). The social determinants of health: It's time to consider the causes of the causes. *Public Health Reports (Washington, D.C. : 1974)*, (Suppl 2), 19–31. <http://doi.org/10.1177/00333549141291S206>

Brodie, D. A., & Inoue, A. (2005). Motivational interviewing to promote physical activity for people with chronic heart failure. *Journal of Advanced Nursing*, 50(5), 518–527. <http://doi.org/10.1111/j.1365-2648.2005.03422.x>

Brodie, D. A., Inoue, A., & Shaw, D. G. (2008). Motivational interviewing to change quality of life for people with chronic heart failure: A randomised controlled trial. *International Journal of Nursing Studies*, 45(4), 489–500. <http://doi.org/10.1016/j.ijnurstu.2006.11.009>

Burke, L. E., Ma, J., Azar, K. M. J., Bennett, G. G., Peterson, E. D., Zheng, Y., ... Quinn, C. C. (2015). Current science on consumer use of mobile health for cardiovascular disease prevention. *Circulation*, 132(12), 1157–1213.



<http://doi.org/10.1161/CIR.0000000000000232>

- Dossett, L. A., Hudson, J. N., Morris, A. M., Lee, M. C., Roetzheim, R. G., Feters, M. D., & Quinn, G. P. (2017). The primary care provider (PCP)-cancer specialist relationship: A systematic review and mixed-methods meta-synthesis. *CA: A Cancer Journal for Clinicians*, *67*(2), 156–169. <http://doi.org/10.3322/caac.21385>
- Dunlay, S. M., Manemann, S. M., Chamberlain, A. M., Cheville, A. L., Jiang, R., Weston, S. A., & Roger, V. L. (2015). Activities of daily living and outcomes in heart failure. *Circulation: Heart Failure*, *8*(2), 261–7. <http://doi.org/10.1161/CIRCHEARTFAILURE.114.001542>
- Esserman, L. J., Shieh, Y., Rutgers, E. J. T., Knauer, M., Retèl, V. P., Mook, S., ... Van 'T Veer, L. J. (2011). Impact of mammographic screening on the detection of good and poor prognosis breast cancers. *Breast Cancer Research and Treatment*, *130*(3), 725–734. <http://doi.org/10.1007/s10549-011-1748-z>
- 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*(4), 336–342. <http://doi.org/http://dx.doi.org/10.1111/j.1547-5069.2005.00058.x>
- Fried, L. P., Bandeen-Roche, K., Kasper, J. D., & Guralnik, J. M. (1999). Association of comorbidity with disability in older women: The Women's Health and Aging Study. *Journal of Clinical Epidemiology*, *52*(1), 27–37. [http://doi.org/10.1016/S0895-4356\(98\)00124-3](http://doi.org/10.1016/S0895-4356(98)00124-3)
- Fried, L., Tangen, C., Walston, J., Newman, A., Hirsch, C., Gottdiener, J., ... McBurnie, M. (2001). Frailty in older adults: Evidence for a phenotype. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *56*(3), M146–M157. <http://doi.org/10.1093/gerona/56.3.M146>

- Hamine, S., Gerth-Guyette, E., Faulx, D., Green, B. B., & Sarah Ginsburg, A. (2015). Impact of mHealth chronic disease management on treatment adherence and patient outcomes: A systematic review. *J Med Internet Res*. <http://doi.org/10.2196/jmir.3951>
- Hibbard, J. H., & Greene, J. (2013). What the evidence shows about patient activation: Better health outcomes and care experiences; fewer data on costs. *Health Affairs*, *32*(2), 207–214. <http://doi.org/10.1377/hlthaff.2012.1061>
- Hung, W. W., Ross, J. S., Boockvar, K. S., & Siu, A. L. (2011). Recent trends in chronic disease, impairment and disability among older adults in the United States. *BMC Geriatrics*, *11*, 47. <http://doi.org/10.1186/1471-2318-11-47>
- Hung, W. W., Ross, J. S., Boockvar, K. S., & Siu, A. L. (2012). Association of chronic diseases and impairments with disability in older adults: A decade of change? *Medical Care*, *50*(6), 501–7. <http://doi.org/10.1097/MLR.0b013e318245a0e0>
- Institute of Medicine. (2005). From Cancer Patient to Cancer Survivor: Lost in Transition - Institute of Medicine. <http://doi.org/10.17226/11468>
- Jindai, K., Nielson, C. M., Vorderstrasse, B. A., & Quinones, A. R. (2016). Multimorbidity and functional limitations among adults 65 or older, NHANES 2005-2012. *Preventing Chronic Disease*, *13*, E151. <http://doi.org/10.5888/pcd13.160174>
- Jones, E. L., Leak, A., & Muss, H. B. (2012). Adjuvant therapy of breast cancer in women 70 years of age and older: Tough decisions, high stakes. *Oncology (Williston Park, N.Y.)*, *26*(9), 793–801.
- Konstam, V., Salem, D., Pouleur, H., Kostis, J., Gorkin, L., Shumaker, S., ... Yusuf, S. (1996). Baseline quality of life as a predictor of mortality and hospitalization in 5,025 patients with congestive heart failure. SOLVD Investigations. Studies of Left Ventricular Dysfunction

Investigators. *American Journal of Cardiology*, 78(8), 890–895.

<http://doi.org/S0002914996004638>

McNeely, M. L., Campbell, K. L., Rowe, B. H., Klassen, T. P., Mackey, J. R., & Courneya, K. S. (2006). Effects of exercise on breast cancer patients and survivors: A systematic review and meta-analysis. *Canadian Medical Association Journal*, 175(1), 34–41.

<http://doi.org/10.1503/cmaj.051073>

Miller, D. R., Rogers, W. H., Kazis, L. E., Spiro, A., Ren, X. S., & Haffer, S. C. (2008). Patients' self-report of diseases in the Medicare Health Outcomes Survey based on comparisons with linked survey and medical data from the Veterans Health Administration. *The Journal of Ambulatory Care Management*, 31(2), 161–77.

<http://doi.org/10.1097/01.JAC.0000314707.88160.9c>

Nekhlyudov, L., Aziz, N., Lerro, C. C., & Virgo, K. S. (2012). Oncologists' and primary care providers' awareness of late effects of cancer treatment: Implications for survivorship care. *Journal of Clinical Oncology*, 30(15).

Parekh, A. K., Goodman, R. a, Gordon, C., & Koh, H. K. (2011). Managing multiple chronic conditions: A strategic framework for improving health outcomes and quality of life. *Public Health Reports*, 126(4), 460–71. <http://doi.org/10.2307/41639389>

Phelan, E. A., Williams, B., Penninx, B. W., LoGerfo, J. P., & Leveille, S. G. (2004). Activities of daily living function and disability in older adults in a randomized trial of the Health Enhancement Program. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, 59(8), 838–843.

Pratt, S. I., Bartels, S. J., Mueser, K. T., Naslund, J. A., Wolfe, R., Pixley, H. S., & Josephson, L. (2013). Feasibility and effectiveness of an automated telehealth intervention to improve

illness self-management in people with serious psychiatric and medical disorders.

*Psychiatric Rehabilitation Journal*, 36(4), 297–305. <http://doi.org/10.1037/prj0000022>

Riedinger, M. S., Dracup, K. a., Brecht, M.-L., Padilla, G., Sarna, L., & Ganz, P. a. (2001).

Quality of life in patients with heart failure: Do gender differences exist? *Heart & Lung:*

*The Journal of Acute and Critical Care*, 30(2), 105–116.

<http://doi.org/10.1067/mhl.2001.114140>

Riegel, B., Masterson Creber, R., Hill, J., Chittams, J., Hoke, L., & Clemmer Steinbright

Professor, E. (2016). Effectiveness of motivational interviewing in decreasing hospital

readmission in adults with heart failure and multimorbidity. *Clinical Nursing Research*,

25(4), 362–377. <http://doi.org/10.1177/1054773815623252>

Sarfati, D., Koczwara, B., & Jackson, C. (2016). The impact of comorbidity on cancer and its

treatment. *CA: A Cancer Journal for Clinicians*. <http://doi.org/10.3322/caac.21342>

Scardovi, A. B., Petruzzi, M., Rosano, A., Lucia, A. R., & De Maria, R. (2012). Heart failure

phenotype in women. *Giornale Italiano Di Cardiologia*, 13(5 Suppl 1), 6S–11S. Retrieved

from <http://www.ncbi.nlm.nih.gov/pubmed/23678528>

Sehl, M., Lu, X., Silliman, R., & Ganz, P. A. (2013). Decline in physical functioning in first 2

years after breast cancer diagnosis predicts 10-year survival in older women. *Journal of*

*Cancer Survivorship*, 7(1), 20–31. <http://doi.org/10.1007/s11764-012-0239-5>

Seo, Y., Roberts, B. L., Piña, I., Dolansky, M., Seo Y, Roberts BL, ... Dolansky M. (2008).

Predictors of motor tasks essential for daily activities among persons with heart failure.

*Journal of Cardiac Failure*, 14(4), 296–302. <http://doi.org/10.1016/j.cardfail.2008.01.005>

Shelburne, N., Adhikari, B., Brell, J., Davis, M., Desvigne-Nickens, P., Freedman, A., ...

Remick, S. C. (2014). Cancer treatment–related cardiotoxicity: Current state of knowledge

and future research priorities. *Journal of the National Cancer Institute*, 106(9).

<http://doi.org/10.1093/jnci/dju232>

Shimada, S., Zaslavsky, A., Zaborski, L., O'Malley, J., Heller, A., & Cleary, P. (2009). Market and beneficiary characteristics associated with enrollment in Medicare managed care plans and fee-for-service. *Medical Care*, 47(5), 517–523.

<http://doi.org/10.1097/MLR.0b013e318195f86e>

Smith, B. D., Smith, G. L., Hurria, A., Hortobagyi, G. N., & Buchholz, T. A. (2009). Future of cancer incidence in the united states: Burdens upon an aging, changing nation. *Journal of Clinical Oncology*, 27(17), 2758–2765. <http://doi.org/10.1200/JCO.2008.20.8983>

Smith, S. M., Soubhi, H., Fortin, M., Hudon, C., & O'Dowd, T. (2012). Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *The Cochrane Database of Systematic Reviews*, 4(4), CD006560.

<http://doi.org/10.1002/14651858.CD006560.pub2>

Strait, J. B., & Lakatta, E. G. (2012). Aging-associated cardiovascular changes and their relationship to heart failure. *Heart Failure Clinics*. <http://doi.org/10.1016/j.hfc.2011.08.011>

Sweeney, L., Halpert, A., & Waranoff, J. (2007). Patient-centered management of complex patients can reduce costs without shortening life. *American Journal of Managed Care*, 13(2), 84–92.

Volkova, M., & Russell, R. (2011). Anthracycline cardiotoxicity: Prevalence, pathogenesis and treatment. *Current Cardiology Reviews*, 7(4), 214–220.

<http://doi.org/10.2174/157340311799960645>

Wakefield, B. J., Holman, J. E., Ray, A., Scherubel, M., Adams, M. R., Hillis, S. L., & Rosenthal, G. E. (2011). Effectiveness of home telehealth in comorbid diabetes and

hypertension: A randomized, controlled trial. *Telemedicine and E-Health*, 17(4), 254–261.

<http://doi.org/10.1089/tmj.2010.0176>

Wedding, U., Pientka, L., & Höffken, K. (2007). Quality-of-life in elderly patients with cancer:

A short review. *European Journal of Cancer*, 43(15), 2203–10.

<http://doi.org/10.1016/j.ejca.2007.06.001>

Widmer, R. J., Collins, N. M., Collins, C. S., West, C. P., Lerman, L. O., & Lerman, A. (2015).

Digital health interventions for the prevention of cardiovascular disease: A systematic review and meta-analysis. *Mayo Clinic Proceedings*, 90(4), 469–480.

<http://doi.org/10.1016/j.mayocp.2014.12.026>

Yabroff, K. R., Lamont, E. B., Mariotto, A., Warren, J. L., Topor, M., Meekins, A., & Brown,

M. L. (2008). Cost of care for elderly cancer patients in the United States. *Journal of the National Cancer Institute*, 100(9), 630–641. <http://doi.org/10.1093/jnci/djn103>

Zamorano, J. L., Lancellotti, P., Rodriguez Muñoz, D., Aboyans, V., Asteggiano, R., Galderisi,

M., ... Suter, T. M. (2016). 2016 European Society of Cardiology position paper on cancer treatments and cardiovascular toxicity. *European Heart Journal*, 37(36), 2768–2801.

<http://doi.org/10.1093/eurheartj/ehw211>

## Appendix

### Reliability and Validity of the Short Form-36 in Breast Cancer Survivors

Psychometric property	Studies that assessed
Internal consistency reliability	<p>Overall assessment (Treanor &amp; Donnelly, 2015):</p> <ul style="list-style-type: none"> <li>• Acceptable to good internal consistency reliability across multiple ethnic and language subgroups (Ashing-Giwa, Padilla, Tejero, &amp; Kim, 2004; Ashing-Giwa, Lam, &amp; Xie, 2013; Ashing-Giwa &amp; Rosales, 2013)</li> </ul> <p>[1] Ashing-Giwa et al., 2004:</p> <ul style="list-style-type: none"> <li>• Measures tested               <ul style="list-style-type: none"> <li>○ SF-36 Spanish, Korean, Chinese and English language versions</li> </ul> </li> <li>• Cronbach's alpha ranged from acceptable to good for the entire sample (n=703, <math>\alpha = 0.76</math> to <math>\alpha = 0.91</math>) and across ethnic and language subgroups: African-American (n=135, <math>\alpha = 0.64</math> to <math>\alpha = 0.93</math>), European-American (n=179, <math>\alpha = 0.76</math> to <math>\alpha = 0.90</math>), Latina-American (n=183, <math>\alpha = 0.71</math> to <math>\alpha = 0.94</math>), Asian-American (n=206, <math>\alpha = 0.79</math> to <math>\alpha = 0.89</math>).</li> </ul> <p>[2] Ashing-Giwa &amp; Rosales, 2013:</p> <ul style="list-style-type: none"> <li>• Measures tested               <ul style="list-style-type: none"> <li>○ SF-36 English language version, four subscales only (general health, pain, physical role limitations, and social functioning)</li> </ul> </li> <li>• Cronbach's alpha ranged from acceptable to good for the entire sample (n=320, <math>\alpha = 0.72</math> to <math>\alpha = 0.90</math>) and across ethnic and language subgroups: African-American (n=88, <math>\alpha = 0.68</math> to <math>\alpha = 0.87</math>), English language proficient (EP) Latina-American (n=95, <math>\alpha = 0.74</math> to <math>\alpha = 0.89</math>) and limited English language proficient (LEP) Latina-American (n=137, <math>\alpha = 0.73</math> to <math>\alpha = 0.93</math>).</li> </ul>

	<p>[3] Ashing-Giwa et al., 2013:</p> <ul style="list-style-type: none"> <li>• Measures tested <ul style="list-style-type: none"> <li>○ SF-12 Chinese language Version</li> </ul> </li> <li>• Among Chines-American breast cancer survivors (n=74), Cronbach's alpha was acceptable (<math>\alpha &gt; 0.70</math>) at baseline and one-year follow-up. Baseline SF-12 physical component summary (PCS) score <math>\alpha = 0.82</math>, SF-12 mental component summary score (MCS) <math>\alpha = 0.80</math>; One-year follow-up: SF-12 PCS <math>\alpha = 0.81</math>, SF-12 MCS <math>\alpha = 0.79</math>.</li> </ul>
Construct validity	<p>Overall assessment (Treanor &amp; Donnelly, 2014):</p> <ul style="list-style-type: none"> <li>• Moderately good construct validity among multiple ethnic and language subgroups (Ashing-Giwa et al., 2004; Ashing-Giwa et al., 2013; Ashing-Giwa &amp; Rosales, 2013)</li> </ul> <p>[1] Ashing-Giwa et al., 2004:</p> <ul style="list-style-type: none"> <li>• Exploratory factor analysis with varimax rotation conducted for entire sample and for each ethnic/language subgroup (African-American, European-American, Latina-American, Asian-American)</li> <li>• Measures tested <ul style="list-style-type: none"> <li>○ SF-36 Spanish, Korean, Chinese and English language versions</li> </ul> </li> <li>• Factor structure was consistent for the total sample, except for SF-36 Social Functioning subscale. The European-, Asian-, and African-American groups had generally consistent factor structure, except for the General Health and Physical Functioning subscales. The Latina-American group had inconsistent factor structure in all subscales except Emotional Role Limitations.</li> </ul> <p>[2] Ashing-Giwa &amp; Rosales, 2013:</p> <ul style="list-style-type: none"> <li>• Confirmatory factor analysis based on original factor structure of the SF-36 conducted for entire sample and for each ethnic/language subgroup (African-American, English language proficient (EP) Latina-American, and limited English language proficient (LEP) Latina-American)</li> <li>• Measures tested <ul style="list-style-type: none"> <li>○ SF-36 English language version, four subscales only (general health, pain, physical role limitations, and social functioning)</li> </ul> </li> </ul>



	<ul style="list-style-type: none"> <li>• For the total sample, four distinct factors for each SF-36 subscale explained 72% of the variance and were consistent with the structure of the SF-36. The four factors of the SF-36 explained 73-75% of the variance in HRQOL scores within each language and ethnic subgroup, but the factor structure of the subscales were inconsistent across groups.</li> </ul> <p>[3] Ashing-Giwa et al., 2013:</p> <ul style="list-style-type: none"> <li>• Exploratory factor analysis with promax rotation conducted for sample of Chinese-American breast cancer survivors at baseline; confirmatory factor analysis conducted one year later in same population</li> <li>• Measures tested <ul style="list-style-type: none"> <li>○ SF-12 Chinese language version</li> </ul> </li> <li>• Construct validity was excellent at baseline. Two factors emerged in the exploratory factor analysis: all MCS items loaded on Factor 1, and the PCS items loaded highly on Factor 2. However, the confirmatory factor analysis at one-year follow-up showed inconsistent factor loadings, and only 58.1% of the common variance was explained.</li> <li>• Baseline: SF-12 PCS <math>\alpha = 0.82</math>; SF-12 MCS <math>\alpha = 0.80</math></li> <li>• One-year follow-up: SF-12 PCS <math>\alpha = 0.81</math>; SF-12 MCS <math>\alpha = 0.79</math></li> </ul>
<p>Convergent validity with cancer-specific HRQOL measures</p>	<p>Overall assessment (Treanor &amp; Donnelly, 2014):</p> <ul style="list-style-type: none"> <li>• Good convergent validity with cancer-specific HRQOL measures, the FACT-B (Ashing-Giwa et al., 2013) and FACT-G (Ashing-Giwa &amp; Rosales, 2013)</li> </ul> <p>[1] Ashing-Giwa et al., 2004:</p> <ul style="list-style-type: none"> <li>• Measures tested <ul style="list-style-type: none"> <li>○ SF-36 Spanish, Korean, Chinese and English language versions</li> <li>○ Functional Assessment of Cancer Therapy-Breast (FACT-B)</li> </ul> </li> <li>• Sample included African-American, European-American, Latina-American, and Asian-American breast cancer survivors</li> <li>• Respective subscales of the FACT-B and SF-36 were significantly correlated, with similar strength and direction of correlations across the total sample and ethnic and language subgroups</li> </ul>

- Total sample: SF-36 general health and FACT-B functional well-being ( $\rho = 0.62$ ); SF-36 physical functioning and FACT-G physical well-being ( $\rho = 0.60$ ); SF-36 physical role limitations and FACT-G physical well-being ( $\rho = 0.61$ ); SF-36 emotional role limitations and FACT-G functional well-being ( $\rho = 0.51$ ); SF-36 vitality and FACT-G functional well-being ( $\rho = 0.64$ ) and physical wellbeing ( $\rho = 0.64$ ); SF-36 mental health and FACT-G emotional well-being ( $\rho = 0.65$ ); SF-36 social functioning and FACT-G functional well-being ( $\rho = 0.62$ ); SF-36 bodily pain and FACT-G physical well-being ( $\rho = 0.68$ ).

[2] Ashing-Giwa & Rosales, 2013:

- Measures tested
  - SF-36 English language version, four subscales only (general health, pain, physical role limitations, and social functioning)
  - Functional Assessment of Cancer Therapy-General (FACT-G)
- Sample included African-American, English language proficient (EP) Latina-American, and limited English language proficient (LEP) Latina-American breast cancer survivors
- Respective subscales of the FACT-G and SF-36 were significantly correlated across groups.
- African-Americans: FACT-G physical well-being subscale strongly correlated with the SF-36 general health ( $\rho = 0.60$ ), role limitations due to physical health ( $\rho = 0.56$ ), and pain ( $\rho = 0.69$ ) subscales; FACT-G social/family well-being not significantly correlated with SF-36 social functioning subscale. FACT-G functional well-being was highly correlated with SF-36 social functioning limitations ( $\rho = 0.59$ ).
- EP and LEP Latina-Americans, respectively: FACT-G physical well-being correlated with SF-36 general health subscale ( $\rho = 0.50$ ;  $\rho = 0.54$ ), role limitations due to physical health subscale ( $\rho = 0.50$ ;  $\rho = 0.51$ ), and pain subscale ( $\rho = 0.71$ ;  $\rho = 0.62$ ). For LEP Latina-Americans, FACT-G functional well-being was highly correlated with SF-36 social functioning limitations ( $\rho = 0.61$ ). For EP Latina-Americans, FACT-G functional well-being was highly correlated with SF-36 social functioning limitations ( $\rho = 0.62$ ) and pain ( $\rho = 0.63$ ).

<p>Convergent validity with lymphedema-specific symptom measures</p>	<p>Overall assessment (Treanor &amp; Donnelly, 2014):</p> <ul style="list-style-type: none"> <li>• Good convergent validity with lymphedema-specific measures (Devoogdt, Van Kampen, Geraerts, Coremans, &amp; Christiaens, 2011; Viehoff, van Genderen, &amp; Wittink, 2008)</li> </ul> <p>[1] Devoogdt et al., 2011:</p> <ul style="list-style-type: none"> <li>• Measures tested <ul style="list-style-type: none"> <li>○ SF-36 Dutch language version</li> <li>○ Lymphedema Functioning, Disability, and Health Questionnaire (Lymph-ICF) Dutch language version</li> </ul> </li> <li>• Sample included n=90 breast cancer survivors at least 12 months post-axillary dissection <ul style="list-style-type: none"> <li>○ n=30 with objective lymphedema, mean(SD) age 61.2(10) years</li> <li>○ n=30 with subjective lymphedema, mean(SD) age 56.7(9.3) years</li> <li>○ n=30 with no reported lymphedema, mean(SD) age 58.3(11) years</li> </ul> </li> <li>• The SF-36 demonstrated good convergent validity with subscales of the Lymph-ICF, supporting 5/5 convergent validity hypotheses: <ul style="list-style-type: none"> <li>○ (1) Lymph-ICF physical function and SF-36 bodily pain (<math>\rho = -0.52</math>)</li> <li>○ (2) Lymph-ICF mental function and SF-36 mental health (<math>\rho = -0.70</math>)</li> <li>○ (3) Lymph-ICF household activities and SF-36 physical functioning (<math>\rho = -0.51</math>)</li> <li>○ (4) Lymph-ICF mobility activities and SF-36 physical functioning (<math>\rho = -0.62</math>)</li> <li>○ (5) Lymph-ICF life and social activities and SF-36 social functioning (<math>\rho = -0.33</math>)</li> </ul> </li> <li>• Three of the five divergent validity hypotheses were supported: <ul style="list-style-type: none"> <li>○ (1) Lymph-ICF physical function and SF-36 role-emotional (<math>\rho = 0.03</math>) and mental health (<math>\rho = -0.14</math>)</li> <li>○ (2) Lymph-ICF mental health and SF-36 physical function (<math>\rho = -0.24</math>) and physical role limitations (<math>\rho = -0.25</math>)</li> <li>○ (3) Lymph-ICF household activities and SF-36 emotional role limitations (<math>\rho = -0.22</math>) and mental health (<math>\rho = -0.27</math>)</li> </ul> </li> </ul>
--	---

	<ul style="list-style-type: none"> <li>○ (4) Support for emotional role limitations but not mental health-Lymph-ICF mobility activities and SF-36 emotional role limitations: (<math>\rho = -0.15</math>) and mental health: (<math>\rho = -0.42</math>)</li> <li>○ (5) Unsupported-Lymph-ICF life and social activities and SF-36 physical functioning (<math>\rho = -0.25</math>); (role limitations-emotional had lowest correlation <math>\rho = -0.19</math>)</li> </ul> <p>[2] Viehoff et al., 2008:</p> <ul style="list-style-type: none"> <li>● Measures tested <ul style="list-style-type: none"> <li>○ SF-36 Dutch language version</li> <li>○ Upper limb lymphedema 27-item questionnaire (ULL27) Dutch language version</li> </ul> </li> <li>● Sample included breast cancer patients with unilateral lymphedema of the upper limb</li> <li>● ULL27 physical domain correlated highly with SF-36 bodily pain (<math>\rho = 0.69</math>), general health (<math>\rho = 0.60</math>) and social functioning (<math>\rho = 0.55</math>) domains, but not physical role limitations (<math>\rho = 0.38</math>) or vitality (<math>\rho = 0.47</math>) domains.</li> <li>● ULL27 psychological domain correlated highly with SF-36 general health (<math>\rho = 0.54</math>), vitality (<math>\rho = 0.55</math>), mental health (<math>\rho = 0.66</math>) and social functioning (<math>\rho = 0.51</math>) domains as expected, but not the emotional role limitations (<math>\rho = 0.42</math>) domain.</li> <li>● The ULL27 social domain correlated highly with SF-36 physical functioning (<math>\rho = 0.64</math>), general health (<math>\rho = 0.56</math>) and social functioning (<math>\rho = 0.45</math>) domains.</li> <li>● Overall: good convergent validity between ULL27 psychological and social domains and SF-36 subscales; lower convergent validity of ULL27 physical domains with SF-36 subscales may be related to focus on lower limb functioning in SF-36 versus focus on upper limb functioning in ULL27.</li> </ul>
<p>Convergent validity with fatigue-specific symptom measures</p>	<p>Overall assessment:</p> <ul style="list-style-type: none"> <li>○ The eight SF-36 subscales are sensitive to fatigue in breast cancer survivors (Meeske et al., 2007), and the SF-36 vitality subscale has a high degree of correlation with the validated with the Piper Fatigue Scale-Revised (PFS-R) (Stover et al., 2013).</li> </ul> <p>[1] Meeske et al. (2007):</p> <ul style="list-style-type: none"> <li>● Measures tested</li> </ul>

	<ul style="list-style-type: none"> <li>○ SF-36 English language version</li> <li>○ Piper Fatigue Scale-Revised</li> <li>● Multi-center prospective study of women with in-situ to Stage IIIA breast cancer; n=800 women completed PFS-R and SF-36 at two to five years post-diagnosis</li> <li>● 41% of participants had clinically significant fatigue, as determined by a score of 4 or greater on the validated PFS-R. All eight subscale scores on the SF-36 were significantly lower (<math>p &lt; 0.0001</math>) for participants with fatigue than for those without fatigue. The domains with the greatest difference between participants with and without fatigue were role functioning physical (mean difference <math>33 \pm 36.5</math>), role functioning emotional (mean difference <math>30.1 \pm 36.1</math>), and social functioning (mean difference <math>25.1 \pm 22.2</math>). Mean differences between participants with and without fatigue were greater for mental health (mean difference <math>10.7 \pm 9.6</math>) than for physical health (mean difference <math>7.9 \pm 10.7</math>).</li> </ul> <p>[2] Stover et al. (2013):</p> <ul style="list-style-type: none"> <li>● Measures tested <ul style="list-style-type: none"> <li>○ SF-36 English language version</li> <li>○ Piper Fatigue Scale-Revised</li> </ul> </li> <li>● Severity of fatigue in breast cancer survivors, as measured by a model of clinically significant threshold scores derived from the PFS-R, explained approximately 40% of the variance in the SF-36 physical component score and 30% of the variance in the mental component score (Stover et al., 2013). The SF-36 vitality subscale showed a high degree of correlation with scores on the PFS-R (<math>\rho = -0.73</math>, <math>p &lt; 0.0001</math>) (Stover et al., 2013).</li> </ul>
--	---

## References

- Ashing-Giwa, K., Lam, C. N., & Xie, B. (2013). Assessing health-related quality of life of Chinese-American breast cancer survivors: A measurement validation study. *Psycho-Oncology*, 22(3), 704–707. <http://doi.org/10.1002/pon.3030>
- Ashing-Giwa, K., Padilla, G., Tejero, J., & Kim, J. (2004). Breast cancer survivorship in a multiethnic sample - challenges in recruitment and measurement. *Cancer*, 101, 450–465. <http://doi.org/10.1002/cncr.20370>
- Ashing-Giwa, K., & Rosales, M. (2013). A cross-cultural validation of patient-reported outcomes measures: A study of breast cancers survivors. *Quality of Life Research*, 22(2), 295–308. <http://doi.org/10.1007/s11136-012-0140-8>
- Devoogdt, N., Van Kampen, M., Geraerts, I., Coremans, T., & Christiaens, M.-R. (2011). Lymphoedema Functioning, Disability and Health Questionnaire (Lymph-ICF): Reliability and validity. *Physical Therapy*, 91(6), 944–57. <http://doi.org/10.2522/ptj.20100087>
- Meeske, K., Smith, A. W., Alfano, C. M., McGregor, B. a., McTiernan, A., Baumgartner, K. B., ... Bernstein, L. (2007). Fatigue in breast cancer survivors two to five years post diagnosis: A HEAL Study report. *Quality of Life Research*, 16(6), 947–960. <http://doi.org/10.1007/s11136-007-9215-3>
- Stover, A. M., Reeve, B. B., Piper, B. F., Alfano, C. M., Smith, A. W., Mitchell, S. A., ... Ballard-Barbash, R. (2013). Deriving clinically meaningful cut-scores for fatigue in a cohort of breast cancer survivors: a Health, Eating, Activity, and Lifestyle (HEAL) Study. *Quality of Life Research*, 22(9), 2279–92. <http://doi.org/10.1007/s11136-013-0360-6>
- Treanor, C., & Donnelly, M. (2015). A methodological review of the Short Form Health Survey 36 (SF-36) and its derivatives among breast cancer survivors. *Quality of Life Research*,

24(2), 339–62. <http://doi.org/10.1007/s11136-014-0785-6>

Viehoff, P. B., van Genderen, F. R., & Wittink, H. (2008). Upper limb lymphedema 27 (ULL27): Dutch translation and validation of an illness-specific health-related quality of life questionnaire for patients with upper limb lymphedema. *Lymphology*, *41*(3), 131–8.