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Cardiovascular Disease Risk Among Breast Cancer Survivors

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CARDIOVASCULAR DISEASE RISK AMONG BREAST CANCER SURVIVORS

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A DISSERTATION

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ABSTRACT

Background: There are nearly 3.5 million breast cancer survivors in the U.S., and approximately 10% are diagnosed prior to age 45 and considered "young." The overall five-year survival rate for breast cancer survivors is approaching 90%. Living longer, many breast cancer survivors are at risk for developing cardiovascular disease due to cancer treatment, such as anthracyclines and/or trastuzumab. This study's purpose was to examine cardiovascular disease risk, measured using excess heart age, among young breast cancer survivors.

Methods: A retrospective, two-year longitudinal design was used to review electronic medical records of breast cancer survivors diagnosed between 30 and 44 years of age and treated at UAB Hospital. Heart age was calculated using chronological age, systolic blood pressure, antihypertensive medication use, body mass index, diabetes status, and smoking status. Excess heart age is the difference between heart age and chronological age. Excess heart age was examined at two time points: diagnosis and two-year follow-up. Statistical analyses included between-group and within-group mean comparison tests, linear regression modeling, and cluster analyses, conducted using R v3.2.2.

Results: Records were reviewed for 152 young breast cancer survivors; 95 were treated with anthracyclines and/or trastuzumab (Group A/T) and 57 were not (Group No-A/T). Overall excess heart age was 4.2 to 5.4 years from diagnosis to follow-up ($p = .08$).

Group A/T did not have a statistically significant difference in excess heart age from diagnosis to two-year follow-up (4.3 to 4.4 years, $p = .93$), whereas Group No-A/T had a significant increase (4 to 7.1 years, $p <. 01$). Factors that predicted excess heart age included hormone therapy and change in menopause status from premenopausal to postmenopausal.

Conclusions: Overall, excess heart age increased 1.2 years and may be clinically relevant. Records of young breast cancer survivors treated with anthracyclines and/or trastuzumab did not indicate increased excess heart age at follow-up. Group No-A/T had a significant increase of 3.1 years, which may be related to hormone therapy and/or treatment-induced menopause. Future research should evaluate cardiovascular disease risk over longer follow-up, consider incorporating cancer treatment risk factors into heart age, and develop a cancer-specific heart age measure.

Keywords: *breast cancer, cardiovascular disease, cardiotoxicity, cancer survivorship, cancer treatment, excess heart age*

DEDICATION

I dedicate this dissertation to my husband, Lam Jeffrey Hoang Vo, and my mother, Kimanh Thi Bui, who both never stopped believing in me, supporting me, and ensuring my success. They are the backbones to my life and my career.

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CHAPTER ONE

INTRODUCTION

Greater than 3.5 million breast cancer survivors live in the United States, comprising the largest group of cancer survivors in the nation (American Cancer Society, 2017). Approximately one in eight women will be diagnosed with breast cancer during her lifetime. However, advances in breast cancer treatment and early detection have contributed to a nearly 40% decline in mortality rates since 1975 (American Cancer Society, 2017; Berry et al., 2005). Women are living longer after breast cancer diagnoses, with five-year survival rates approaching 90% (American Cancer Society, 2017). Among breast cancer survivors, approximately 10% were diagnosed before 45 years of age and are considered "young" (Centers for Disease Control and Prevention, 2016). Despite the longer survival rates, many breast cancer treatments have potential side effects such as cardiotoxicity, constituting a continuing threat to the health of survivors.

Cardiotoxicity is defined by the National Cancer Institute (NCI) as "toxicity that affects the heart" (National Cancer Institute, 2015) and may occur as a result of various treatment regimens (Florescu, Cinteza, & Vinereanu, 2013). Anthracyclines and trastuzumab are two frequently used systemic cancer treatments associated with increased risk of cardiovascular disease (Appel et al., 2012; Bradshaw et al., 2016; Doyle, Neugut, Jacobson, Grann, & Hershman, 2005). Cardiovascular disease is defined by the American Heart Association as the development of coronary artery disease, cerebrovascular disease,

peripheral artery disease, and/or heart failure (D'Agostino, Wolf, Belanger, & Kannel, 1994). Anthracyclines and trastuzumab are most commonly associated with heart failure (Appel et al., 2012; Bowles et al., 2012; Feola et al., 2011; Narayan et al., 2017; Qin, Thompson, & Silverman, 2015; Rayson et al., 2012; Yood et al., 2012).

While anthracyclines and trastuzumab are the most common breast cancer treatments associated with heart failure, radiation to the breast and hormone therapy are associated with cardiovascular disease as well. Radiation to the left breast often leads to exposure of the heart and chest wall, increasing risk for coronary artery disease (Darby et al., 2013; Haque et al., 2011; Hooning et al., 2007). Hormone therapy including tamoxifen and aromatase inhibitors are associated with stroke (Amir et al., 2011; Mehta et al., 2018).

The risk for cardiovascular disease increases with age, and young breast cancer survivors are expected to be healthier, have longer survivorship periods, and less likely to have comorbidities compared with older women (Piccirillo et al., 2008). The lifetime risk for developing heart failure is 20% for Americans older than 40 years of age, and the highest prevalence of heart failure is in adults older than 65 years of age (Yancy et al., 2013). Young breast cancer survivors who are treated with anthracyclines and/or trastuzumab may be placed at higher risk for developing premature heart failure due to potential cardiotoxicity.

In addition to cancer treatment risk factors, modifiable and non-modifiable risk factors can also contribute to cardiovascular disease risk. Modifiable risk factors include smoking, obesity, physical inactivity, and poor diet. Non-modifiable risk factors include age, race, family history, and menopause status. Cardiovascular disease and breast cancer

have many similar contributing risk factors (Mehta et al., 2018), including these modifiable and non-modifiable risk factors.

Currently, there is no tool that incorporates cancer treatment risk factors to estimate cardiovascular disease risk. However, there are tools that incorporate modifiable and non-modifiable risk factors. Heart age is a tool that estimates the risk of developing cardiovascular disease, expressed as an age (D'Agostino et al., 2008). Heart age uses chronological age, systolic blood pressure, antihypertensive medication use, smoking status, diabetes status, and body mass index to estimate the risk of developing cardiovascular disease (D'Agostino et al., 2008).

The cardiotoxic side effects of anthracyclines and trastuzumab are well documented (Appel et al., 2012; Bowles et al., 2012; Feola et al., 2011; Narayan et al., 2017; Qin et al., 2015; Rayson et al., 2012; Yood et al., 2012). However, the cardiovascular disease risk of young breast cancer survivors is unknown. Research is needed to establish cardiovascular disease risk among young breast cancer survivors and understand how cancer treatment in addition to modifiable and non-modifiable factors contribute to increased cardiovascular disease risk. The purpose of this chapter is to describe the 1) background and significance of cardiovascular disease risk among young breast cancer survivors, 2) study purpose, 3) study aims and research questions, 4) theoretical framework, and 5) definitions of key terminology.

Background and Significance

The American Cancer Society estimates there will be greater than 250,000 new cases of breast cancer in 2018, and more than 40,000 women will die from breast cancer

(American Cancer Society, 2017). Approximately 23,000 women are diagnosed with breast cancer before 45 years of age each year (U.S. Cancer Statistics Working Group, 2017). The incidence of breast cancer is increasing, and the American Cancer Society expects the number of breast cancer survivors to increase from 3.5 to 4.5 million by 2026 (American Cancer Society, 2016). At the same time, survival rates increased nearly 15% over the past 40 years (American Cancer Society, 2017), contributing to longer life expectancies in breast cancer survivors.

The term "survivor" has evolved over the past decades. The NCI adopted the National Coalition for Cancer Survivorship definition and defines a cancer survivor "from the time of diagnosis, through the balance of his or her life" (Institute of Medicine and National Research Council, 2006; National Coalition for Cancer Survivorship, 1986). This dissertation adheres to this definition and defines breast cancer survivor as one diagnosed with breast cancer from the time of diagnosis forward.

Survivorship care is increasingly important with the great declines in mortality and longer life expectancies (American Cancer Society, 2017). Components of survivorship care include preventing and assessing for late physical effects (Institute of Medicine and National Research Council, 2006). Specifically, essential topics in survivorship care include cancer treatment-related cardiotoxicity and the risk for developing cardiovascular disease after breast cancer. Cancer treatments have contributed to declines in mortality rates, yet longer life expectancies have allowed time for negative consequences of cancer treatment, such as cardiotoxicity, to emerge (Berry et al., 2005; Patnaik, Byers, DiGuiseppi, Dabelea, & Denberg, 2011). The National Comprehensive Cancer Network (2018) reported the estimated incidence of anthracycline-induced heart

failure for survivors of adult cancers as less than 5%. The incidence of trastuzumab-related heart failure is estimated to be 2-7% (Curigliano et al., 2012; National Comprehensive Cancer Network, 2018). It is unknown what proportion of breast cancer survivors develop cardiovascular disease (Shelburne et al., 2014); however, cancer treatment-related cardiotoxicity is among the leading non-cancerous causes of death among pediatric cancer survivors (Mertens et al., 2001). Furthermore, cardiovascular disease is the leading cause of death among older breast cancer survivors (aged 65 years and older) (Patnaik et al., 2011).

In the emerging field of cardio-oncology, research institutions are targeting studies of cardiovascular disease among cancer survivors. In 2013, NCI joined forces with the National Heart, Lung, and Blood Institute (NHLBI) to gather experts in both cardiology and oncology to synthesize the state of the science in cardio-oncology and describe the need for future research (Shelburne et al., 2014). This workshop provided an opportunity for clinicians and researchers in both areas to describe the need for research to support clinical care of cancer survivors experiencing cardiotoxicity. Workshop recommendations suggested developing standards, exploring mechanisms of cardiotoxicity, preclinical and animal studies, early phase therapeutic studies, minimally invasive methods for diagnosis and monitoring, prevention, treatment of cardiotoxicity, and survivorship care (Shelburne et al., 2014).

As a result of the NCI and NHLBI collaboration, NCI developed the Community Oncology Cardiotoxicity Task Force to coordinate studies and programs and identify priorities within cardiotoxicity. This task force collaborates and coordinates with several academic and research institutions nationally within the NCI Community Oncology

Research Program. Moreover, cancer treatment-related cardiotoxicity is a focus within the Division of Cancer Control and Population Sciences at the NCI, which supports their goal to reduce the burden of cancer diagnoses and outcomes related to cancer treatment (National Cancer Institute, 2018). Finally, the NCI sponsors funding related to improving outcomes in cancer treatment-related cardiotoxicity (National Cancer Institute, 2018).

Both anthracyclines and trastuzumab can lead to permanent cardiac dysfunction (Florescu et al., 2013). The onset of cardiotoxicity may be acute, early chronic, or late chronic. Acute cardiotoxicity may occur during cancer treatment, early chronic occurs within one year after completion of cancer treatment, and late chronic occurs more than one year after completion of cancer treatment. Permanent, irreversible cardiac damage is most likely to occur in early or late chronic cardiotoxicity (Florescu et al., 2013). This dissertation does not look at the incidence of cardiotoxicity. Instead, the investigator examined the 10-year estimated risk of cardiovascular disease measured by heart age and subsequently estimated the risk for late chronic cardiotoxicity.

Cardiovascular risk predictor tools are used to estimate the probability of developing a cardiovascular disease (Wilson et al., 1998). It is recommended that patients with pre-existing cardiac risk factors do not receive cardiotoxic cancer treatment or that they use it with caution (Armenian et al., 2017; National Comprehensive Cancer Network, 2018; Runowicz et al., 2016). While anthracyclines and trastuzumab are most commonly associated with heart failure, there are no existing risk models that estimate the risk of developing heart failure. Several tools estimate mortality in patients once diagnosed with heart failure (Levy et al., 2006). Heart age is a valid tool that estimates the probability of developing cardiovascular disease inclusive of but not specific to heart

failure. Heart age is the cumulative probability of developing cardiovascular disease based on risk factors including chronological age, body mass index, smoking, diabetes, systolic blood pressure, and blood pressure medication use (D'Agostino et al., 2008). Excess heart age is the difference between heart age and chronological age and is used to describe one's cardiovascular disease risk (D'Agostino et al., 2008). This study used excess heart age to measure cardiovascular disease risk.

The link between cancer and heart disease, or "cardio-oncology," is increasingly important in survivorship care. Oncology organizations, such as American Cancer Society, American Society for Clinical Oncology, and the National Comprehensive Cancer Network, in addition to the American Heart Association, have developed guidelines for survivorship care that include treatment and management of cardiotoxicity (Armenian et al., 2017; Mehta et al., 2018; National Comprehensive Cancer Network, 2018; Runowicz et al., 2016). Clinical practice guidelines are evidence-based and provide recommendations to survey for recurrence, monitor and prevent secondary cancers, and manage side effects such as cardiotoxicity (Institute of Medicine and National Research Council, 2006). Application of these guidelines in clinical practice may lead to earlier diagnoses and better prognoses of cardiovascular disease among breast cancer survivors.

Young breast cancer survivors are living much longer, and their risk for developing subsequent cardiovascular disease heightens due to cancer treatment. Therefore, there is a need to examine cardiovascular disease risk in young breast cancer survivors. This study measured cardiovascular disease risk using excess heart age in young breast cancer survivors, compared heart age between young breast cancer survivors treated with anthracyclines and/or trastuzumab with young breast cancer

survivors not treated with anthracyclines and/or trastuzumab, and examined differences in excess heart age from diagnosis to two-year follow-up. Additionally, this study identified predictors of excess heart age in young breast cancer survivors. Understanding cardiovascular disease risk among young breast cancer survivors provided future implications for screening in women with excess heart age.

Statement of the Problem

Breast cancer survivors are living longer due to advances in cancer treatment and earlier diagnoses (American Cancer Society, 2017; Berry et al., 2005). However, cancer treatment sequelae are increasingly evident with longer life expectancy. Young women diagnosed with breast cancer may often live long after diagnosis. Cardiotoxicity is a life-threatening side effect of cancer treatment, particularly with anthracyclines and trastuzumab (Appel et al., 2012; Bowles et al., 2012; Feola et al., 2011; Narayan et al., 2017; Qin et al., 2015; Rayson et al., 2012; Yood et al., 2012). The overall cardiovascular disease risk of young breast cancer survivors is currently not established. Understanding cardiovascular disease risk, measured by excess heart age, among young breast cancer survivors is crucial to provide clinicians and researchers a better understanding of cardiovascular risk profiles (D'Agostino et al., 2008). Furthermore, it is unknown if heart age changes between diagnosis and two-year follow-up (expected end of cancer treatment). Cancer treatment may influence several factors within heart age, such as body mass index via weight gain (Demark-Wahnefried, Winer, & Rimer, 1993) or hypertension (Enright & Krzyzanowska, 2010). Screening for cardiovascular disease is recommended at six months and/or one-year post completion of anthracyclines and/or trastuzumab

treatment (Armenian et al., 2017; Mehta et al., 2018; National Comprehensive Cancer Network, 2018; Runowicz et al., 2016), but there are no current U.S.-based recommendations for long-term screening in breast cancer survivors. Therefore, research is needed to examine differences in excess heart age from breast cancer diagnosis to treatment completion and identify risk factors associated with increased cardiovascular disease risk among young breast cancer survivors.

Study Purpose

The purpose of this study was to examine excess heart age among young breast cancer survivors treated with and without anthracyclines and/or trastuzumab from diagnosis to two-year follow-up and to identify factors associated with increased excess heart age.

Specific Aims and Research Questions

The specific aims and corresponding research questions of this study are listed below defined by time period or type of specific aim.

<u>Time 1 (Breast Cancer Diagnosis)</u>

1. To characterize excess heart age among young breast cancer survivors at diagnosis.
    a. What is the excess heart age among young breast cancer survivors at diagnosis?

b. What is the difference in excess heart age between young breast cancer survivors treated with anthracyclines and/or trastuzumab and young breast cancer survivors who did not receive treatment with anthracyclines or trastuzumab at diagnosis?

Time 2 (24 ± 6 months Follow-up)

2. To characterize excess heart age among young breast cancer survivors at two-year follow-up.
    a. What is the excess heart age among young breast cancer survivors at two-year follow-up?
    b. What is the difference in excess heart age between young breast cancer survivors treated with anthracyclines and/or trastuzumab and young breast cancer survivors who did not receive treatment with anthracyclines or trastuzumab at two-year follow-up?

Comparison of Time 1 and Time 2

3. To examine differences in excess heart age among young breast cancer survivors from breast cancer diagnosis to two-year follow-up.
    a. What is the difference in excess heart age from breast cancer diagnosis to two-year follow-up in the total sample?
    b. What is the difference in excess heart age from diagnosis to two-year follow-up among young breast cancer survivors treated with anthracyclines and/or trastuzumab?

c. What is the difference in excess heart age from diagnosis to two-year follow-up among young breast cancer survivors who did not receive anthracyclines or trastuzumab?

4. To identify predictors of excess heart age among young breast cancer survivors.
    a. What are predictors of excess heart age at diagnosis?
    b. What are predictors of excess heart age at two-year follow-up?
    c. What are predictors of the difference in excess heart age at diagnosis and two-year follow-up?

Exploratory Aim

5. To explore characteristics of excess heart age within clusters of young breast cancer survivors.

Theoretical Framework

The web of causation theory developed by MacMahon and Pugh in 1970 was selected to adapt a theoretical framework for assessing cardiovascular disease risk among breast cancer survivors and guide this study. The web of causation is often used to explain chronic diseases and describe complex interactions (MacMahon, Pugh, & Ipsen, 1970). The web of causation supports the idea of multiple causation, in which one risk factor does not solely cause the disease (Krieger, 1994). Cardiovascular disease risk has multifactorial etiologies and is not a result of one risk factor; instead, multiple factors contribute to increased cardiovascular disease risk. Furthermore, interrelationships exist

between risk factors and other contributors of cardiovascular disease risk within the web. Thus, the web of causation theory was adapted using evidence-based literature (described further in Chapter 2) to depict the concept of cardiovascular disease risk among breast cancer survivors. Figure 1 is an adapted web of causation theoretical framework that was used to provide direction and context for the dissertation study.

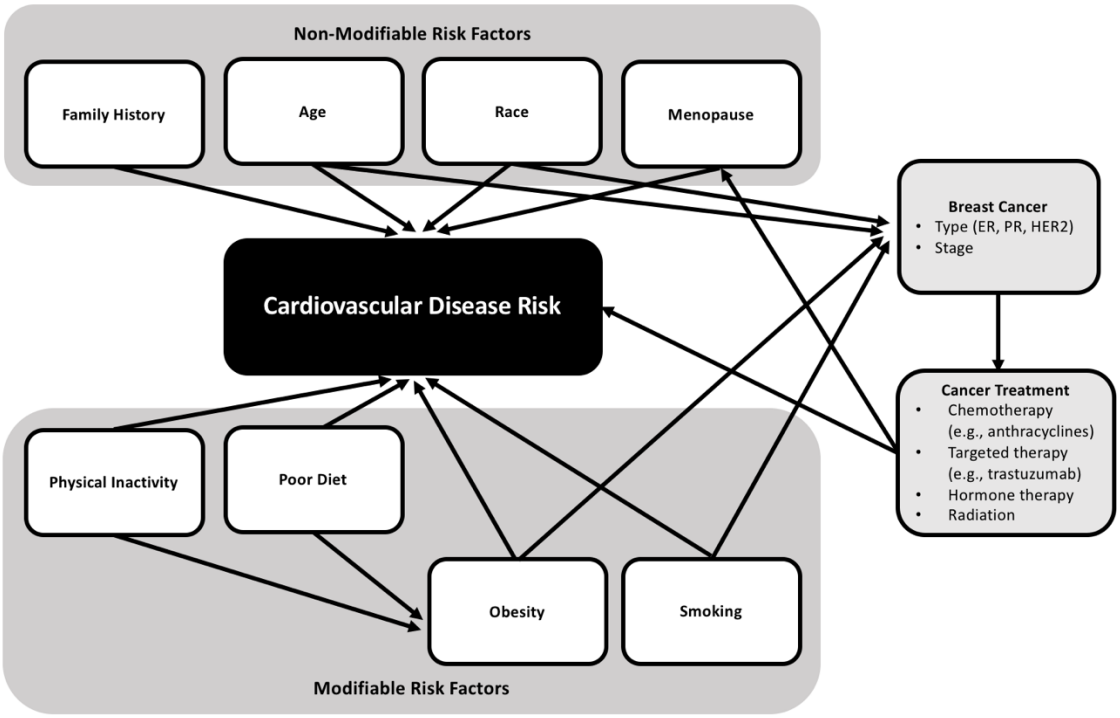


Figure 1. Adapted web of causation for cardiovascular disease risk among breast cancer survivors. © Vo, 2017

In this theoretical framework, modifiable and non-modifiable risk factors can contribute to both the development of breast cancer and cardiovascular disease. Specific factors contribute to increased risk of breast cancer such as age, race, menopause, and obesity. Once a patient is diagnosed with breast cancer, hormone status and cancer stage

will help determine cancer treatment type. Anthracyclines, trastuzumab, hormone therapy, and radiation are types of cancer treatment that lead to increased cardiovascular disease risk. Moreover, interrelationships exist, including the following: 1) physical inactivity and poor diet contribute to obesity and can subsequently contribute to increased risk of cardiovascular disease and breast cancer, and 2) type of breast cancer determines cancer treatment, which can contribute to early menopause, also associated with increased cardiovascular disease risk.

Several nursing studies have adapted the web of causation to develop interventions and/or strategies to address healthcare problems with multifactorial etiologies (Johnson, Giarelli, Lewis, & Rice, 2013; Matthews & Moore, 2013). Application of the web of causation in research on chronic diseases and beyond demonstrates the versatility of the theory and its appropriateness for explaining cardiovascular disease risk among breast cancer survivors. Furthermore, the web of causation may grow to include new risk factors or demonstrate novel interrelationships as newer research emerges. The adapted web of causation links different concepts derived from the literature to explain cardiovascular disease risk among breast cancer survivors and provides direction and context to the study.

Definitions of Terms

For the purpose of this dissertation, the following will define commonly used terms in this dissertation proposal:

Breast cancer is a malignant tumor developed in the breast (Harris, Lippman, Morrow, & Osborne, 2014).

Cancer survivor is a person who has lived through cancer "from the time of diagnosis until the end of life" (National Cancer Institute, 2015).

Cardiotoxicity is "toxicity that affects the heart" (National Cancer Institute, 2015) and damage to the cardiovascular system as a result of treatment (Harris et al., 2014).

Cardiovascular disease is defined as encompassing one or more of the following diagnoses: coronary heart disease (i.e., coronary death, myocardial infarction, coronary insufficiency, and angina), cerebrovascular disease (i.e., ischemic stroke, hemorrhagic stroke, transient ischemic attack), peripheral artery disease (i.e., intermittent claudication), and/or heart failure (asymptomatic left ventricular ejection fraction below 50% or symptomatic) (D'Agostino et al., 1994).

Heart age is an adapted Framingham Risk Score that estimates the probability of developing cardiovascular disease in the next 10 years, expressed as an age. Heart age is chosen based on a match between the individual's Framingham Risk Score and the age of an individual with a low to normal risk profile (D'Agostino et al., 2008). *Excess heart age* is the difference between heart age and the chronological age (D'Agostino et al., 2008).

Modifiable risk factors are risk factors that can be changed, including smoking, obesity, physical inactivity, and poor diet (Benjamin et al., 2018).

Non-modifiable risk factors are risk factors that cannot be changed, including age, race, family history, and menopause status (Benjamin et al., 2018).

Survivorship is the period after cancer diagnosis and focuses on "physical, psychosocial, and economic issues of cancer, beyond the diagnosis and treatment phases" (National Cancer Institute, 2015).

Young breast cancer survivors are women diagnosed with breast cancer prior to 45 years of age (Centers for Disease Control and Prevention, 2016).

Summary

There is a dearth of research in cardiovascular disease risk among young breast cancer survivors and a need to examine excess heart age to provide a greater understanding of risk factors that contribute to increased cardiovascular disease risk among the young breast cancer survivor population. This dissertation aimed to meet this need and propel the research toward the necessary step of understanding excess heart age among young breast cancer survivors. The study describes changes in excess heart age from breast cancer diagnosis to end of cancer treatment, the relationships between anthracyclines and/or trastuzumab use and excess heart age, and predictors of excess heart age in young breast cancer survivors. Chapter 2 will describe the current state of science of cardiovascular disease risk among young breast cancer survivors.

CHAPTER TWO

REVIEW OF LITERATURE

The purpose of this integrative review of literature was to synthesize the state of the science on cardiovascular disease risk among young breast cancer survivors. This review included studies retrieved from the following databases: PubMed, CINAHL, Scopus, and Embase. Search terms included: (cardiovascular disease, cardiovascular disease risk, or heart failure) and (breast cancer or breast neoplasm).

This search yielded 8,006 articles. The researcher then filtered the articles that were published within the last 10 years, which reduced the articles to 4,955. An age filter was placed to include articles with ages 18-44 included in the sample, yielding 1,188 articles. The investigator removed duplicates from the sample of articles (n = 190) and conducted a title review for 1,009 articles. Articles were included in the literature review if: 1) breast cancer survivors were in the sample, 2) cardiovascular disease and/or cardiovascular disease risk was the outcome, 3) breast cancer survivors were treated with anthracycline-based chemotherapy and/or trastuzumab, and 4) young survivors (< 45 years) were included in the sample. Exclusion criteria for the literature search consisted of: 1) sample did not include young survivors (specific to older breast cancer survivors) and 2) sample did not include breast cancer survivors.

Records were excluded if they did not meet inclusion/exclusion criteria. The investigator reviewed 108 articles, and 38 studies were included in this integrative

literature review. See Appendix A for the PRISMA diagram. In addition to the 38 studies, the investigator reviewed cancer practice guidelines, cancer survivorship guidelines, cardiac care guidelines, Federal Drug Administration medication guides, and other relevant non-journal articles. Furthermore, articles describing cardiotoxicity in pediatric cancer survivors were also included.

Breast Cancer

Epidemiology

Breast cancer is the most common non-cutaneous cancer in women worldwide (American Cancer Society, 2016). In the United States, approximately 250,000 new cases of breast cancer will be diagnosed in women, and approximately 40,000 women will die from breast cancer each year (American Cancer Society, 2017). Nearly 10% of women with breast cancer, or 23,000 women, are diagnosed with breast cancer at a young age (< 45 years) annually. Incidence rates of breast cancer at any age increased significantly between the 1980s and 1990s and have remained stagnant since 2005. However, in women under 50 years of age, incidence rates of breast cancer have steadily increased approximately 0.2% each year (American Cancer Society, 2017).

Trends in survival have increased and mortality rates have decreased tremendously since 1975. In 1975, 75% of women diagnosed with breast cancer survived at least five years. In more recent years, the overall five-year survival rate has reached nearly 90%. Between 1975 and 1989, death rates from breast cancer increased 0.4% annually. Between 1990 and 2015, the mortality rate dropped rapidly to an almost 40% decline (American Cancer Society, 2017). Still, breast cancer is the second leading cause

of cancer death in women, resulting in nearly 40,000 deaths annually (American Cancer Society, 2017). In young women under 45 years of age, cancer is the leading cause of death (Centers for Disease Control and Prevention, 2016).

Breast cancer commonly affects women who are older, with the average age of diagnosis at 62 years (Howlader et al., 2017). However, young breast cancer survivors are more likely to be diagnosed with aggressive cancers and have a 4.5-fold increased risk of breast cancer recurrence (American Cancer Society, 2017; Howlader et al., 2017). Further, women under 45 years of age are likely to be premenopausal at breast cancer diagnosis (The North American Menopause Society, 2017).

Pathology

Breast cancer is an abnormal growth of cells within breast tissue (American Cancer Society, 2017). Breast cancer may be localized to the breast (in situ) or spread to surrounding tissue (invasive). TNM staging is the most common staging system and classifies the disease based on distance of spread to adjacent tissue (T), extent to lymph nodes (N), and metastases spread (M) (Amin et al., 2017). The TNM then classifies diagnoses from Stage 0 – IV. Stage 0 is localized or in situ breast cancer. Stages I to IV are types of invasive breast cancer, and range from least invasive to advanced metastatic breast cancer (American Cancer Society, 2017; Amin et al., 2017). Breast cancer can further be classified as local, regional, or distant (Ruhl et al., 2018).

Breast cancer is also distinguished by biological markers including hormone receptors (HR) such as estrogen (ER), progesterone (PR), and the human epidermal growth factor receptor 2 (HER2). The four most common breast cancer subtypes are: 1)

Luminal A (HR+/HER2-), 2) Luminal B (HR+/HER2+), 3) triple negative (ER-/PR-/HER2-), and 4) HER2+enriched (HR-/HER2+) (American Cancer Society, 2017). Further, HR may be classified into ER+, ER-, PR+, and/or PR-.

Risk Factors

Risk factors for breast cancer include: obesity, physical inactivity, alcohol use, estrogen exposure, genetic predisposition, and reproductive factors (Tamimi et al., 2016). Many women who develop breast cancer at a young age may have mutations in BRCA1 or BRCA2 genes (American Cancer Society, 2017; Turnbull & Rahman, 2008). Risk factors associated with increased risk of developing breast cancer at a young age include family history of breast or ovarian cancer at a young age, dense breasts on mammogram, and Ashkenazi Jewish ancestry (American Cancer Society, 2017; Turnbull & Rahman, 2008).

Screening

Multiple organizations offer breast cancer screening guidelines, including the American Cancer Society and the U.S. Preventive Services Task Force. Mammography is the gold standard for screening for breast cancer. The American Cancer Society recommends screening annually with mammography beginning at age 45 years. Women between 40 to 45 years of age may start annual screening if they wish to do so (American Cancer Society, 2017). The U.S. Preventive Service Task Force recommends that decision-making for biennial mammography between the ages of 40 to 49 be done on a

risk-benefit individual basis and recommends biennial screening after age 50 (U.S. Preventive Services Task Force, 2016).

Treatment Types

Treatment of breast cancer varies and depends on breast cancer subtype and other clinical features. Options for breast cancer treatment include: 1) surgery, 2) radiation therapy, and 3) systemic therapy (i.e., chemotherapy, targeted therapy, and hormone therapy). Surgery removes the cancer from the breast and/or surrounding tissue and may be localized (partial mastectomy/lumpectomy) or remove the entire breast (total mastectomy). Women may opt to have reconstruction following breast surgery. Radiation therapy is the application of high energy beams to kill the cancerous cells. Radiation is often administered in combination with surgery for maximum anti-cancer effect. Radiation may be delivered internally or externally to the breast or chest area (American Cancer Society, 2017).

Systemic therapy travels through the bloodstream and includes chemotherapy, hormone therapy, and targeted therapy (American Cancer Society, 2017). Different combinations of chemotherapy can be used to treat breast cancer. Common chemotherapy regimens include: 1) doxorubicin and cyclophosphamide (AC), 2) AC followed by paclitaxel, and 3) docetaxel plus cyclophosphamide (TC) (National Comprehensive Cancer Network, 2017). Targeted therapy will target specific hormone receptors (i.e., HER2) to prevent uptake or increase uptake of specific hormones (American Cancer Society, 2017). Trastuzumab is the most common type of targeted therapy for women

who are HER2+ (Romond et al., 2005) and is administered over 52 weeks (Federal Drug Administration, 2010b).

Hormone therapy blocks the uptake of estrogen into the cells and is used to treat women who are HR+. Hormone therapy including tamoxifen and aromatase inhibitors may be used for five to 10 years (Burstein et al., 2014). Tamoxifen blocks the effects of estrogen in HR+ breast cancer survivors who are overexpressing estrogen and progesterone levels. Tamoxifen is used in both pre- and postmenopausal breast cancer survivors, but is the treatment of choice for premenopausal women. Aromatase inhibitors include letrozole, anastrozole, and exemestane, and are given primarily to postmenopausal women, but may be given to premenopausal women who cannot tolerate tamoxifen (American Cancer Society, 2017).

Survivorship

Cancer survivorship is the period beginning at diagnosis of cancer to the end of life (Mullan, 1985; National Coalition for Cancer Survivorship, 1986). In 2006, the Institute of Medicine and the National Research Council published *From Cancer Patient to Cancer Survivor*, which focuses on cancer care after treatment completion. Survivorship care should be individualized and inclusive of physical and psychological effects as a result of cancer and/or cancer treatment (Institute of Medicine and National Research Council, 2006).

Cardiotoxicity

As survival has increased for breast cancer survivors, their risk for developing comorbidities has also increased, including secondary cancers and cardiovascular disease. Older breast cancer survivors are at higher risk of dying from cardiovascular disease than breast cancer (Patnaik et al., 2011). Several cancer treatments have associations with cardiovascular disease, including chemotherapy, targeted therapy, radiation therapy, and hormone therapy. This integrative review focuses on cardiotoxicity as a result of treatment with anthracyclines and trastuzumab.

Anthracyclines

The two common anthracyclines used to treat breast cancer are doxorubicin and epirubicin. The chemical structure of doxorubicin is: 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-lyxo- hexopyranosyl)oxy]-7,8,9,10-tetrahydro- 6,8,11-trihydroxy- 8-(hydroxylacetyl)-1- methoxy-, hydrochloride (8S-cis). It has a molecular weight of 579.99 (Federal Drug Administration, 2010a). The chemical structure of epirubicin is (8S- cis)-10-[(3-amino-2,3,6-trideoxy-α-L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione hydrochloride (Federal Drug Administration, 2006). Doxorubicin is indicated for treatment of breast cancer, ovarian cancer, blood-based cancers, thyroid cancer, stomach cancer, and many more (Federal Drug Administration, 2010a). Doxorubicin may be used in adult or pediatric cancer patients, whereas epirubicin is indicated in adult breast cancer patients. Anthracyclines are delivered via intravenous

administration (Federal Drug Administration, 2006; Federal Drug Administration, 2010a).

The World Health Organization (WHO) lists doxorubicin as an imperative drug in healthcare in the WHO Model List of Essential Medicines (World Health Organization, 2017). Despite their therapeutic benefit, anthracyclines may induce progressive cardiac complications. The Federal Drug Administration lists cardiotoxicity as a potential risk for the anthracyclines-based drugs (Federal Drug Administration, 2006; Federal Drug Administration, 2010a). The risk of cardiotoxicity increases with dose and pre-existing patient-level cardiac risk factors; however, cardiotoxicity may occur at the lowest dose even if no risk factors are present (Murtagh et al., 2016; Rayson et al., 2012).

Research indicates multiple possible mechanisms as to how anthracyclines affect the cardiac system, although the exact molecular pathway to cardiac damage is not known (Franco & Lipshultz, 2015). The most commonly accepted mechanism is the oxidative stress hypothesis (Franco & Lipshultz, 2015; Simunek et al., 2009). This hypothesis suggests that anthracyclines promote the development of reactive oxygen species, which subsequently damage cardiomyocytes (cardiac muscle cells). A loss of cardiomyocytes leads to decreased muscle contractility (Franco & Lipshultz, 2015; Simunek et al., 2009). Ejection fraction measures cardiac contractility, or the heart's ability to pump out blood. Lower ejection fraction indicates a poorer cardiac function. Decreased ejection fraction can lead to heart failure, which is a clinical diagnosis characterized by shortness of breath, fatigue, and edema (Hunt et al., 2009).

Other mechanistic theories for anthracycline-induced cardiotoxicity include damage to the cardiac microvasculature, proteins, cardiac progenitor cells, and fibroblasts

(Sadurska, 2015). Damage to cardiac progenitor cells that produce cardiomyocytes may weaken the heart's ability to recover from cardiac injury caused by anthracyclines and/or patient-level comorbidities. The multiple mechanistic actions of anthracyclines may not be mutually exclusive, as a combination of pathways may damage the cardiac system (Simunek et al., 2009).

Anthracycline-induced cardiotoxicity may appear at any dose range but begins to increase rapidly after reaching the dose of 400 mg/m^2 (Federal Drug Administration, 2010a). Recommendations to limit dose may help mitigate cardiotoxicity. The recommended lifetime dose is no more than 450 to 550 mg/m^2 for doxorubicin (Federal Drug Administration, 2010a) and 900 mg/m^2 for epirubicin (Federal Drug Administration, 2006). Increasing doses of anthracycline-based chemotherapy are associated with higher risk of cardiovascular disease (Murtagh et al., 2016; Rayson et al., 2012).

Investigators reported incidence of heart failure from breast cancer survivors treated with anthracycline-based chemotherapy ranging from 3 to 24.5% (Appel et al., 2012; Feola et al., 2011; Qin et al., 2015; Rayson et al., 2012; Yood et al., 2012). Numerous studies demonstrate that chemotherapy regimens that included anthracycline-based chemotherapy were associated with decreases in left ventricular ejection fraction (Boerman et al., 2017; de Azambuja et al., 2015; Drafts et al., 2013; Feola et al., 2011; Gallucci et al., 2010; Jones et al., 2007; Murtagh et al., 2016; Narayan et al., 2017; Sulpher et al., 2015).

Women treated with anthracycline-based chemotherapy were often younger than the average age of breast cancer survivors receiving treatment (Boerman et al., 2017). Anthracyclines (doxorubicin and/or epirubicin) were associated with abnormal resting

heart rate, peak oxygen consumption and workload, high triglycerides, increased high density protein, hypertension, aortic stiffness, increased pulse wave velocity, increased troponin and hyaluronan levels, poor mitral E/A ratios, decreased aortic expandability, higher heart rate, abnormal echocardiogram, and lower left ventricular ejection fraction (Chaosuwannakit et al., 2010; de Azambuja et al., 2015; Inanc et al., 2016; Jones et al., 2007). Breast cancer survivors more commonly experience chronic cardiotoxicity than acute onset. Developing heart failure more than one year after treatment was associated with increased mortality (Qin et al., 2015).

Anthracyclines are used in pediatric cancer patients and have contributed to the increase in the five-year survival rate from 58% in the 1970s to 80% in 2012 (Siegel, Miller, & Jemal, 2018). The extensive survivorship period experienced by pediatric cancer survivors has provided the opportunity for research to understand the late effects of cancer treatment. The Children's Oncology Group is a worldwide consortium of institutions that conducts trials for pediatric cancer patients, supported by the National Cancer Institute (Children's Oncology Group, 2018). Cardiovascular complications are among the leading causes of non-cancer-related deaths in pediatric cancer survivors (Reulen et al., 2010), and the risk is nearly 10-fold higher than in children who do not have cancer (Mertens et al., 2001; Shankar et al., 2008). Factors that increase risk of developing anthracycline-induced cardiotoxicity among pediatric cancer survivors include total cumulative dose of anthracyclines, time of survivorship (longer survivorship is associated with higher cardiovascular disease risk), female gender, black race, use in conjunction with radiation therapy, use in conjunction with other cardiotoxic therapies, and pre-existing cardiovascular risk factors (Sadurska, 2015).

Moreover, there is potential for a lifelong, anthracycline-induced cardiotoxicity risk. Researchers have documented cardiovascular events occurring 45 years after completion of cancer treatment; greater than 7% of pediatric cancer survivors will experience heart failure if they received more than 250 mg/m^2 of anthracyclines treatment (Mulrooney et al., 2009). As a result, the Children's Oncology Group developed survivorship guidelines to mitigate cardiotoxic effects in pediatric cancer survivors, recommending interval screening at one, two, or five years depending on the anthracyclines dose, age at treatment, and chest radiation (Children's Oncology Group, 2013; Landier et al., 2004). A cost-effectiveness analysis showed that screening frequency extended life expectancy by at least six months and led to an 18% reduction in risk of developing late chronic onset heart failure (Wong et al., 2014).

Trastuzumab

Trastuzumab is a form of targeted therapy also known as Herceptin. Trastuzumab is a humanized IgG1 kappa monoclonal antibody that binds to the HER2 hormone and is administered intravenously (Federal Drug Administration, 2010b). Trastuzumab is a standard treatment for breast cancer patients with overexpressed HER2 (Amerian Cancer Society, 2017; Romond et al., 2005) and for high-risk breast cancer patients who are ER-/PR- (Federal Drug Administration, 2010b; Romond et al., 2005). Trastuzumab is also indicated for metastatic breast and gastric cancers. When trastuzumab is used in combination with anthracyclines, the recommended dose schedule is 8 mg/kg for the first dose, and 6 mg/kg every three weeks for a total of 52 weeks (Federal Drug Administration, 2010b).

Trastuzumab is associated with arrhythmias, hypertension, left ventricular dysfunction, cardiomyopathy, and heart failure (Bowles et al., 2012; Federal Drug Administration, 2010b; Narayan et al., 2017; Obi et al., 2014; Slamon et al., 2001). The incidence of trastuzumab-induced cardiotoxicity is approximately 2-7% and is often reversible. The incidence of heart failure may rise to 27% when used concurrently with anthracyclines (Curigliano et al., 2012). When trastuzumab is used with anthracyclines, breast cancer patients have an increased risk of developing heart failure or cardiomyopathy (Bowles et al., 2012; Narayan et al., 2017; Slamon et al., 2001). Breast cancer survivors treated with both drugs were at a seven-fold increased risk compared to those who did not receive chemotherapy (Bowles et al., 2012). This risk also increases as breast cancer survivors age. Women diagnosed with breast cancer prior to 55 years of age and treated with both anthracyclines and trastuzumab had a significant risk of developing cardiovascular disease (Bowles et al., 2012). In survivors who had a normal left ventricular ejection fraction after treatment with anthracycline-based chemotherapy and trastuzumab, cardiac adrenergic function decreased by 50%, compared to no change in survivors treated with anthracyclines only (Guimaraes et al., 2015).

Symptoms of Cardiotoxicity

The most commonly reported symptom of cardiotoxicity is a decrease in left ventricular ejection fraction (Boerman et al., 2017; Chaosuwannakit et al., 2010; de Azambuja et al., 2015; Drafts et al., 2013; Feola et al., 2011; Gallucci et al., 2010; Guimaraes et al., 2015; Ho et al., 2010; Inanc et al., 2016; Jones et al., 2007; Koelwyn et al. 2016; Murtagh et al., 2016; Narayan et al., 2017; Sulpher et al., 2015). Burnett,

Kluding, Porter, Fabian, and Klemp (2013) examined the left ventricular ejection fraction of breast cancer survivors during cardiorespiratory testing. Breast cancer survivors with at least two cardiovascular disease risk factors and at least one cancer treatment-related risk factor were likely to score below the 20th percentile of low cardiorespiratory fitness (Burnett et al., 2013). Additionally, studies demonstrated that breast cancer survivors had increased heart rate variability and reduced mitral E/A ratio (determinant of mitral valve dysfunction) than healthy controls (Caro-Moran et al., 2016; Ho et al., 2010; Inanc et al., 2016).

Measures of Cardiotoxicity

Cardiac arrhythmias were measured using electrocardiograms (Ho et al., 2010; Inanc et al., 2016; Jones et al., 2007). Left ventricular ejection fraction was measured in the studies using echocardiograms (Appel et al., 2012; Boerman et al. 2017; de Azambuja et al., 2015; Feola et al., 2011; Gallucci et al., 2010; Guimaraes et al., 2015; Ho et al., 2010; Inanc et al., 2016; Jones et al., 2007; Murtagh et al., 2016; Narayan et al., 2017; Rayson et al., 2012; Sulpher et al., 2015), multi-gated acquisition testing (Appel et al., 2012; Feola et al., 2011; Jones et al., 2007; Rayson et al., 2012; Sulpher et al., 2015), and/or magnetic resonance imaging (Chaosuwannakit et al., 2010; Chotenimitkhun et al., 2015; de Azambuja et al., 2015; Drafts et al., 2013).

Heart failure may be asymptomatic with subclinical changes in left ventricular ejection fraction or may have symptoms such as fatigue and shortness of breath (Benjamin et al., 2018; Hunt et al., 2001). The American Heart Association and American College of Cardiology Foundation diagnose heart failure using Stage A (no structural

damage to the heart, but at risk for heart failure), Stage B (structural damage to the heart but no signs and symptoms of heart failure, Stage C (signs and symptoms of heart failure), and Stage D (advanced structural damage requiring end stage heart failure treatment) (Hunt et al., 2001; Yancy et al., 2013). Asymptomatic breast cancer survivors treated with anthracyclines who have no structural damage to the heart are classified under Stage A heart failure (Hunt et al., 2001; National Comprehensive Cancer Network, 2018; Yancy et al., 2013).

Treatment and Management of Cardiotoxicity

Two studies examined statin therapy to combat cardiovascular disease risk (Chotenimitkhun et al., 2015; Shum et al., 2016). Statins were associated with increases in left ventricular ejection fraction post administration of anthracycline-based chemotherapy, suggesting potential mitigation of cardiac dysfunction (Chotenimitkhun et al., 2015; Shum et al., 2016). Despite many survivors reporting having cardiovascular risk factors, healthcare providers did not always educate patients on cardiovascular screening or teach methods to reduce cardiovascular disease risk (Christian et al., 2017; Enright & Krzyzanowska, 2010; Weaver et al., 2013). Additionally, many survivors did not have concerns regarding cardiovascular disease risk (Christian et al., 2017).

Risk Factors for Cardiovascular Disease Among Breast Cancer Survivors

Cancer Treatment

Sixteen studies reported cardiovascular disease risk among breast cancer survivors, but the research was not specific to anthracyclines and/or trastuzumab. Overall, breast cancer survivors had a higher risk for developing cardiovascular disease risk compared to controls (Armenian et al., 2016; Boekel et al., 2016; Boerman et al., 2014; Bradshaw et al., 2016; Shum et al., 2016). Breast cancer survivors treated with chemotherapy had an increased risk of cardiovascular disease compared to non-cancer controls (Boekel et al., 2016; Boerman et al., 2014; Hooning et al., 2007). Among postmenopausal breast cancer survivors, the risk for cardiovascular disease was higher than breast cancer recurrence risk. This sample had an excess heart age of seven years, indicating that predicted age of the heart was similar to that of an individual seven years their senior (Bardia et al., 2012). Furthermore, cardiovascular disease mortality rates were greatest at seven years follow-up (Bradshaw et al., 2016). Approximately 15 to 21% of breast cancer survivors (older than 45 years) reported diagnosis of cardiovascular disease prior to beginning cancer treatment (Bhatia, Lenihan, Sawyer, & Lenneman, 2016; Enright & Krzyzanowska, 2010; Obi et al., 2014).

Left-sided radiation therapy following mastectomy was associated with increased cardiovascular disease risk, which rose even higher among participants under age 50 (Boekel et al., 2016). Radiation therapy was associated with myocardial infarction and heart failure (Hooning et al., 2007). Radiation to the left breast increases radiation exposure to the heart and is associated with increased risk of cardiovascular disease (Darby et al., 2013; Haque et al., 2011; Hooning et al., 2007). Both tamoxifen and

aromatase inhibitors (types of hormone therapy) are associated with increased risk of stroke. Due to their anti-estrogen properties, both tamoxifen and aromatase inhibitors can lead to clots in the blood and subsequently stroke (Amir et al., 2011; Mehta et al., 2018).

Non-Modifiable Risk Factors

Age, race, and family history are common non-modifiable risk factors for both breast cancer and cardiovascular disease. As one ages, the risk for developing cancer and/or cardiovascular disease increases (American Cancer Society, 2017; Benjamin et al., 2018; Haque et al., 2014). In one study, older breast cancer survivors were at high risk for developing early onset heart failure (Patnaik et al., 2011). Further, breast cancer survivors diagnosed prior to 55 years, who were treated with cytotoxic chemotherapy and/or combination therapy, were more likely to develop cardiovascular disease than survivors who received surgery only. Specifically, cardiovascular disease risk was three-fold when survivors were treated with chemotherapy and four-fold when survivors were treated with combination therapy in comparison to those treated with surgery only (Tan et al., 2016).

African Americans have increased risk of developing both cancer and cardiovascular disease and often have multiple cardiovascular disease risk factors (American Cancer Society, 2017; Benjamin et al., 2018). Before the age of 45, black women are at higher risk for developing breast cancer and more likely to die from breast cancer at any age compared to white women (American Cancer Society, 2017). Family history corresponding to the disease increases risk of developing cancer and cardiovascular disease. In breast cancer, women with BRCA1 and BRCA2 gene mutations have a markedly increased risk of developing breast cancer (American Cancer

Society, 2017). Likewise, family history of coronary history or heart disease is associated with individual development of the disease (Benjamin et al., 2018).

Menopause is also a non-modifiable risk factor that is specific to women and plays a role in both breast cancer and cardiovascular disease. Menopause is the cessation of menstrual periods for 12 consecutive months (The North American Menopause Society, 2017). Nearly 95% of women experience menopause between 45 and 55 years of age, with the average age of 51 years (The North American Menopause Society, 2017). Women who experience menopause at a later age are often at increased risk for developing breast cancer (American Cancer Society, 2017). However, women who are diagnosed with breast cancer prior to menopause are likely to enter premature menopause if treated with chemotherapy or hormone therapy (Goodwin, Ennis, Pritchard, Trudeau, & Hood, 1999). Approximately 33-73% of premenopausal breast cancer survivors will become menopausal after cancer treatment (National Comprehensive Cancer Network, 2018). Menopause is also a risk factor for developing cardiovascular disease (Benjamin et al., 2018). Research examining the effects of premature or treatment-induced menopause on cardiovascular disease risk is lacking.

Modifiable Risk Factors

Smoking, obesity, physical inactivity, and poor diet are modifiable risk factors for both breast cancer and cardiovascular disease. Breast cancer survivors often reported having multiple cardiovascular risk factors (Christian et al., 2017; Enright & Krzyzanowska, 2010; Ho et al., 2010; Weaver et al., 2013). Cancer survivors were more likely to be smokers (Enright & Krzyzanowska, 2010). Limited evidence suggests that

smoking is associated with increasing risk of developing breast cancer (American Cancer Society, 2017). However, smoking is a known risk factor for cardiovascular disease. Overall, smoking contributes to greater than 480,000 premature deaths related to all causes annually (Benjamin et al., 2018).

Obesity increases the risk of developing breast cancer among postmenopausal women (American Cancer Society, 2017). Increasing body mass index heightens the risk of developing breast cancer and cardiovascular disease. Weight gain is often a side effect of cancer treatment (Demark-Wahnefried et al., 1993), and uncontrolled weight gain may lead to overweight or obese body mass indexes. Obesity is also a risk factor for Type II diabetes and cardiovascular disease. Subsequently, Type II diabetes is a risk factor for both breast cancer and cardiovascular disease (American Cancer Society, 2017; Benjamin et al., 2018). In contrast, obesity is protective of breast cancer in premenopausal women (American Cancer Society, 2017), although obesity is associated with more aggressive breast cancer types in young women (Bandera et al., 2015). Obese breast cancer survivors had a 1.65 times increased risk of dying from cardiovascular disease. Each 5-kg weight gain was associated with 19% increased mortality from cardiovascular disease. Additionally, survivors who were obese prior to breast cancer diagnosis have a two-fold increased risk of cardiovascular disease mortality (Nichols et al., 2009).

Poor diet increases the risk of developing breast cancer by 7-10% for every 10 grams of alcohol consumed per day (American Cancer Society, 2017; Liu, Nguyen, & Colditz, 2015). Poor diet can influence multiple cardiovascular disease risk factors such as blood pressure, cholesterol, glucose levels, and obesity/weight gain (Benjamin et al.,

2018). A combination of poor diet with other risk factors may increase the risk of breast cancer and cardiovascular disease.

While physical inactivity does not directly impact breast cancer, in combination with poor diet, it may lead to weight gain and obesity and subsequently lead to breast cancer. Physical inactivity increases the risk for developing cardiovascular disease (Artinian et al., 2010; Benjamin et al., 2018). Women who are physically active have lower risk of developing both breast cancer and cardiovascular disease than women who are not physically active (American Cancer Society, 2017; Benjamin et al., 2018; Obi et al., 2014).

Measures of Cardiovascular Disease Risk

Commonly used tools to predict an individual's risk for developing cardiovascular disease are the Framingham Risk Score, heart age, Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator, and Life's Simple 7. The Framingham Risk Score is a widely-used tool that estimates the probability of developing a cardiovascular disease within a 10-year time frame. The tool was developed from a large cohort study, the Framingham Heart Study (Dawber, Meadors, & Moore, 1951). Investigators have revised the Framingham Risk Score several times (D'Agostino et al., 1994; D'Agostino et al., 2008; Dawber et al., 1951; Lloyd-Jones et al., 2004). One adaptation estimates the risk of developing coronary artery disease (Lloyd-Jones et al., 2004), and another estimates risk of stroke (D'Agostino et al., 1994). The most recent adaptation of the Framingham Risk Score is heart age (D'Agostino et al., 2008).

Heart age is interpreted by calculating the Framingham Risk Score and matching the 10-year cardiovascular disease probability with the age of the same gender with the same probability but with a low to normal risk factor profile (i.e., body mass index = 22.5, systolic blood pressure = 125 mmHg, no diabetes, no smoking in the last year, no hypertensive medication use). Heart age may also be calculated with and without available cholesterol levels. Heart age is gender-specific and limited to ages 30 to 74 years of age (D'Agostino et al., 2008).

The ASCVD Risk Estimator is similar to the Framingham Risk Score and estimates 10-year and lifetime risks of developing an atherosclerotic or cardiovascular event. The ASCVD Risk Estimator was established by the American College of Cardiology and the American Heart Association. Subscales of ASCVD include race and cholesterol (Goff et al., 2014). Life's Simple 7 is another tool to estimate cardiovascular disease risk, established by the American Heart Association. The tool accounts for personal history of cardiovascular disease, systolic and diastolic blood pressure, and dietary patterns. The maximum score for Life's Simple 7 is 10, indicating ideal health. The tool also has an online interactive platform that provides patient education on areas of improvement (Lloyd-Jones et al., 2010).

Heart Age Using Framingham Risk Score

The cardiovascular disease risk estimator of interest for this study is heart age because of its applicability to retrospective data and its focus on increasing understanding of cardiovascular disease risk. Heart age predicts the risk of developing a cardiovascular disease. Furthermore, heart age has an adapted model that estimates the probability of

developing a cardiovascular disease that is based on the body mass index and does not require cholesterol levels (D'Agostino et al., 2008). Increasing understanding of cardiovascular disease risk can lead to positive changes in modifiable risk factors including physical activity, smoking cessation, healthier diet, and improved body mass index (D'Agostino et al., 2008). For example, if a 35-year-old patient was told her heart age was 45, she may understand more clearly the risk of developing cardiovascular disease than if she was told she has a 15% increased risk of developing cardiovascular disease over the next 10 years.

Clinical Practice Guidelines

The American Heart Association provides recommendations for echocardiographic screening for breast cancer survivors who receive anthracyclines and/or trastuzumab treatment (Mehta et al., 2018). A baseline echocardiogram is recommended for any breast cancer survivor who receives either drug. For breast cancer survivors who receive a cumulative dose of anthracyclines of 240 mg/m^2, additional echocardiograms are recommended prior to additional doses, at completion of therapy, and at six months post completion of treatment. For breast cancer survivors who receive HER2 targeted therapy (i.e., trastuzumab), echocardiograms are recommended every three months during treatment but not warranted after completion of treatment if the patient remains asymptomatic. For breast cancer survivors who receive anthracyclines therapy followed by HER2 targeted therapy, echocardiograms are recommended every three months during treatment and six months post treatment (Mehta et al, 2018). In addition to the recommended screenings, the American Heart Association recommends

that breast cancer survivors should be referred to a cardiologist if an ejection fraction drops below 53%.

The American Cancer Society and American Society of Clinical Oncology collaboratively developed breast cancer survivorship care guidelines (Runowicz et al., 2016). Recommendations for assessing/reducing cardiovascular disease risk among breast cancer survivors include: 1) monitoring serum lipid levels and providing cardiovascular monitoring as needed similarly to other high-risk populations, 2) encouraging lifestyle changes in regard to physical activity, nutrition, and smoking, and 3) educating patients on symptoms of cardiotoxicities such as shortness of breath or fatigue. The guidelines do not recommend routine cardiovascular screening for asymptomatic breast cancer survivors and are not specific to cancer treatment types (Runowicz et al., 2016).

The American Society of Clinical Oncology released cardiac-specific survivorship guidelines for adult cancer survivors in 2017 (Armenian et al., 2017). The guidelines describe in detail the effects of anthracycline-based chemotherapy on the heart. Further, the guidelines suggest that cancer survivors who are at increased risk for cardiovascular disease include survivors treated with high-dose anthracycline, high-dose radiation, or low-dose anthracyclines in combination with low-dose radiation. Recommendations for monitoring and screening of high-risk patients for cardiovascular disease include: 1) routine imaging during treatment for asymptomatic, high-risk patients, and 2) screening using cardiac imaging (e.g., echocardiogram) between six and 12 months after completion of treatment in asymptomatic patients who are considered at high risk. The American Society of Clinical Oncology states that there are no recommendations on

long-term monitoring or screening for cardiovascular disease if there is no presence of cardiac dysfunction during the six- to 12-month follow-up screening (Armenian et al., 2017).

The National Comprehensive Cancer Network includes specific guidelines for anthracycline-induced cardiac toxicity (2018). These guidelines state that cardiac toxicity after anthracycline-based chemotherapy may manifest years or decades after the treatment cessation. The National Comprehensive Cancer Network describes the American Heart Association/American College of Cardiology Guidelines for the Evaluation and Management of Heart Failure and discusses anthracycline-based chemotherapy use as a risk factor for heart failure (Hunt et al., 2001). Cancer survivors who were treated with anthracycline-based chemotherapy, but have not yet developed heart failure symptoms or structural damage to the heart, are classified as Stage A heart failure. Treatment of Stage A heart failure includes addressing underlying risk factors, recommending lifestyle changes (i.e., physical activity and healthy diet), and referring to a cardiologist for management. Stage B heart failure consists of patients who have structural damage to the heart but have not yet developed symptoms. Stages C and D both have signs and symptoms of heart failure. Further, the guidelines recommend monitoring and screening for heart failure within one year of completing anthracycline-based chemotherapy (National Comprehensive Cancer Network, 2018); however, these guidelines do not yet have recommendations for long-term screening.

The Children's Oncology Group developed guidelines for survivors of pediatric cancers. The guidelines recommend that frequency of cardiac imaging (i.e., echocardiogram or equivalent) for cardiovascular disease screening depends on the

patient's age at the time of first administration of cardiotoxic treatment, use with radiation, and cumulative anthracyclines dosage. Recommendations include screening for cardiovascular disease every one, two, or five years depending on the cumulative risk factors (Children's Oncology Group, 2013; Landier et al., 2004). The Children's Oncology Group used clinical expertise to recommend interval screening since research examining cardiovascular disease risk for pediatric cancer survivors is limited (National Comprehensive Cancer Network, 2017).

The European Society for Medical Oncology has specific cardiotoxicity guidelines for cancer survivors (Curigliano et al., 2012). These guidelines recommend monitoring and screening for cardiovascular disease four and 10 years after completion of anthracycline-based chemotherapy if a specified cumulative dose limit is reached (240 mg/m^2 for doxorubicin; 360 mg/m^2 for epirubicin). For both anthracyclines and trastuzumab, echocardiograms should be given at before treatment; at three, six, and nine months during treatment; and at 12 and 18 months after treatment initiation. The guidelines also discuss other cancer treatment-related risk factors including radiation (Curigliano et al., 2012).

Both the Children's Oncology Group and the European Society for Medical Oncology recommend long-term screening dependent on additional risk factors. The applicable guidelines for breast cancer survivors in the United States have no recommendations on long-term screening, despite existing data that breast cancer survivors may develop anthracycline-induced cardiotoxicity years after treatment ends. See Table 1 for comparison of guidelines.

Table 1

Comparison of Clinical Guidelines' Recommendations

Institution	Recommendation	Short-term Screening	Long-term Screening
American Heart Association (2018)	• Echocardiogram (echo) at baseline • If anthracyclines dose > 240 mg/m^2, then echo prior to each additional dose of 50 mg/m^2, at completion of therapy, and 6 months later • HER2 targeted therapy, echo every 3 months during treatment • Anthracyclines, followed by HER2 targeted therapy, echo every 3 months during treatment, and 6 months post treatment	x	
American Society for Clinical Oncology (2017)	• Routine imaging during treatment • Screening using cardiac imaging between 6-12 months after completion of treatment	x	
American Society for Clinical Oncology/American Cancer Society (2016)	• Monitoring lipid levels • Cardiac monitoring as needed • Cardiac education		
European Society for Medical Oncology (2012)	• Screening for cardiovascular disease 4 and 10 years after completion of anthracycline-based chemotherapy if a specified cumulative dose limit is reached (> 240 mg/m^2 for doxorubicin; > 360 mg/m^2 for epirubicin) • For anthracyclines and trastuzumab: echocardiogram before treatment; 3, 6, 9 months after treatment; 12 and 18 months after treatment initiation	x	x
Children's Oncology Group (2013)	• Screening for cardiovascular disease every 1, 2, or 5 years depending on the cumulative risk factors	x	x
National Comprehensive Cancer Network (2018)	• Screening within 1 year of completing anthracyclines treatment	x	

Gaps in the Literature

This literature review revealed several gaps in current knowledge. First, no identified studies examined cardiovascular disease risk among young breast cancer

survivors only. The studies included in this analysis included young women diagnosed before 45 years of age but not solely young breast cancer survivors.

Second, United States-based clinical practice guidelines do not have recommendations for long-term cardiovascular screening and monitoring for breast cancer survivors. In comparison, the European Society for Medical Oncology and the Children's Oncology Group recommend screening at specific intervals depending on cancer treatment risk factors. The National Comprehensive Cancer Network acknowledges the difference and reports the absence of data regarding cardiovascular disease risk for cancer survivors that essentially would be used to inform guidelines.

Third, there was a paucity in published behavioral interventions aimed to reduce cardiovascular disease among breast cancer survivors. Two studies examined medication as preventive measures for cardiovascular disease. The current state of the science for cardiovascular disease risk among breast cancer survivors would benefit from pharmacological and behavioral interventional studies. Increasingly, research is examining the effectiveness of cardiac medications as a preventive for high-risk patients. Particularly, studies examine statin medications as a potential option to mitigate cardiovascular disease risk.

Non-pharmacological interventions that target behavioral risk factors may also be beneficial for breast cancer survivors. It is also very important for healthcare providers to heighten awareness of cardiovascular disease risk among breast cancer survivors. Many breast cancer survivors are not discussing with their healthcare providers (either oncologist or primary care) their risk of developing or methods to prevent cardiovascular

disease. As such, many breast cancer survivors are simply unaware of their risk of developing cardiovascular disease.

Fourth, there were insufficient prospective studies. The prospective studies included in this analysis had small sample sizes, which limited generalizability and statistical inferences. Prospective studies will allow investigators to select variables to be examined. Thus, a detailed history, left ventricular ejection fraction testing, and risk factor assessment may provide further detail on which subsamples of breast cancer survivors are at increasing cardiovascular disease risk. However, prospective studies may be time consuming and costly. This area of research will benefit from additional retrospective studies examining the influence of cardiotoxic cancer treatment among young breast cancer survivors. This integrative review of literature identified the need for additional studies that use retrospective and prospective designs to further expand the knowledge of cardiovascular disease risk among breast cancer survivors.

Fifth, limited studies used cardiovascular risk estimator tools to examine cardiovascular disease risk among breast cancer survivors. Predictive risk modeling is an easy, inexpensive, and effective way to identify individuals at increased risk for cardiovascular disease. This literature review identified models used to predict cardiovascular disease among cancer survivors: heart age and the Atherosclerotic Cardiovascular Disease Risk Estimator. Both of the tools are valid in estimating cardiovascular disease risk by incorporating modifiable and non-modifiable cardiovascular risk factors. While these models are sufficient for predicting risk in the general population, they may not be sufficient to predict risk for cancer survivors. Neither tool includes cancer treatment risk factors. Current data are not sufficient to inform such

models; however, future consideration should include adapting valid cardiovascular disease risk estimators and tailoring the tools to cancer survivors.

Summary

Research regarding cardiovascular disease risk among breast cancer survivors is a growing body of literature. Data demonstrate the link between breast cancer and cardiovascular disease. As a result, national guidelines have recommendations for screening of cardiovascular disease in breast cancer survivors at one year after completion of cancer treatment. Heart failure secondary to anthracyclines and trastuzumab has been shown to appear well after the one-year mark, and therefore, there may be implications for long-term screening among high-risk breast cancer survivors.

The integrative literature review identified a lack of studies focused on young breast cancer survivors. Therefore, there is a need to examine cardiovascular disease risk among young breast cancer survivors at breast cancer diagnosis and after treatment completion. Studies in this integrative literature review included women under 45 years of age in the samples but were not limited to only young breast cancer survivors due to lack of data. Young breast cancer survivors have longer life survivorship periods and, as they age, will be at risk for cardiovascular disease, which may be potentiated if the cancer is treated with anthracyclines and/or trastuzumab. Chapter 3 describes the methodology of this study to fill a gap in the literature regarding cardiovascular disease risk among young breast cancer survivors.

CHAPTER THREE

METHODOLOGY

This chapter describes the methodology of the dissertation proposal, examining excess heart age among young breast cancer survivors treated with and without anthracyclines and/or trastuzumab from diagnosis to two-year follow-up and identifying factors associated with increased excess heart age. This chapter describes the study design, access to data, sampling, data variables, data abstraction, sample selection, data analysis plan, validity, and ethical considerations. The specific aims and corresponding research questions are as follows:

Time 1 (Breast Cancer Diagnosis)

1. To characterize excess heart age among young breast cancer survivors at diagnosis.
    a. What is the excess heart age among young breast cancer survivors at diagnosis?
    b. What is the difference in excess heart age between young breast cancer survivors treated with anthracyclines and/or trastuzumab and young breast cancer survivors who did not receive treatment with anthracyclines or trastuzumab at diagnosis?

Time 2 (24 ± 6 months Follow-up)

2. To characterize excess heart age among young breast cancer survivors at two-year follow-up.
    a. What is the excess heart age among young breast cancer survivors at two-year follow-up?
    b. What is the difference in excess heart age between young breast cancer survivors treated with anthracyclines and/or trastuzumab and young breast cancer survivors who did not receive treatment with anthracyclines or trastuzumab at two-year follow-up?

Comparison of Time 1 and Time 2

3. To examine differences in excess heart age among young breast cancer survivors from diagnosis to two-year follow-up.
    a. What is the difference in excess heart age from breast cancer diagnosis to two-year follow-up in the total sample?
    b. What is the difference in excess heart age from diagnosis to two-year follow-up among young breast cancer survivors treated with anthracyclines and/or trastuzumab?
    c. What is the difference in excess heart age from diagnosis to two-year follow-up among young breast cancer survivors who did not receive anthracyclines or trastuzumab?

4. To identify predictors of excess heart age among young breast cancer survivors.
    a. What are predictors of excess heart age at diagnosis?
    b. What are predictors of excess heart age at two-year follow-up?
    c. What are predictors of the difference in excess heart age at diagnosis and two-year follow-up?

Exploratory Aim

5. To explore characteristics of excess heart age within clusters of young breast cancer survivors.

Design

This study used a retrospective, two-year longitudinal design. The investigator used electronic medical records to review records of breast cancer patients who were treated at UAB Hospital and examine excess heart age among young breast cancer survivors who were 30 to 44 years of age at diagnosis. Two time points were examined: diagnosis (Time 1) and two-year follow-up (Time 2).

Access to Data

Approval from the UAB Institutional Review Board was required to conduct this study. The data for this study include patient identifiers derived from electronic medical records at the UAB Hospital. The investigator submitted an expedited Human Subjects Protocol Form 200, review level 5. Prior to submitting the Human Subjects Protocol Form, the research underwent three levels of review: Department of Cardiology,

Comprehensive Cancer Center, and School of Nursing. First, the investigator sought review from the Department of Cardiology and received approval from the Kirklin Institute for Research in Surgical Outcomes.

Next, the Comprehensive Cancer Center review board required a review process that includes: 1) UAB Comprehensive Cancer Center, Cancer Control and Population Sciences, New Protocol Submission Form, 2) Institutional Review Board materials (i.e., Human Subjects Protocol, Waiver of Authorization and Informed Consent), and 3) Planned Enrollment Table form. The investigator scheduled time to present the proposed study to the Cancer Control and Population Sciences committee, a subcommittee of the Comprehensive Cancer Center. The committee reviewed and forwarded the protocol to the primary Comprehensive Cancer Center committee for final review and approval.

After both the Department of Cardiology and Comprehensive Cancer Center reviewed and approved the protocol, the forms were forwarded to the School of Nursing for review. The investigator submitted the Protocol Oversight Review Form required for PhD students to the committee chair, program coordinator, and senior associate dean for academic affairs. Approvals from all three departments were sent to the UAB Institutional Review Board for final review. Since this study does not directly interact with patients and utilizes previously collected data, this study did not require an informed consent. The investigator submitted a waiver for authorization and informed consent. This study received expedited approval from the UAB Institutional Review Board (Protocol IRB-170328008). See Appendix B.

To access UAB data, the investigator: 1) was listed as an investigator on the dissertation's Institutional Review Board protocol, 2) obtained a UAB-MC account, 3)

installed Impact software on a UAB-secured computer, 4) installed RSA Token App on mobile device, and 5) attended Impact software training. To gain access to the specific data for the dissertation, the investigator obtained approval from the UAB Institutional Review Board.

Sampling

The study sample included records of women who were diagnosed with breast cancer between January 1, 2012, and December 31, 2015. The inclusion criteria for the study sample were: 1) female diagnosed with Stage I-III breast cancer between January 1, 2012, and December 31, 2015, 2) diagnosed between 30 to 44 years of age, and 3) treated for breast cancer at UAB Health System.

The exclusion criteria for the study sample included: 1) charted diagnosis of cardiovascular disease at time of breast cancer diagnosis, 2) diagnosis of stage 0 breast cancer, 3) diagnosis of Stage IV or metastatic breast cancer, 4) diagnosed with breast cancer outside of the time range (before January 1, 2012, or after December 31, 2015, and 5) potential out-migration (no record of treatment at UAB Health System).

A consecutive sampling approach was used to select the study sample from the electronic medical records. This approach selected all participants who met the eligibility criteria over a time interval (Polit & Beck, 2017). For this study, all records of breast cancer survivors who met the inclusion and exclusion criteria were included in the sample. Given use of the consecutive sampling technique, a power calculation was not conducted.

Variables

The variables collected included demographic variables, survivorship characteristics, and heart age variables. The data from two time points were described as Time 1 and Time 2. Time 1 was described as the visit closest to diagnosis. Time 2 was the two-year follow-up at an estimated 24 ± 6 months post diagnosis.

The demographic variables included gender, race, ethnicity, marital status, and employment. The survivorship variables included date of diagnosis (distinguished by affected breast), stage of initial diagnosis, type of breast cancer (ER, PR, HER2), genetics (BRCA1, BRCA2), first-degree family history of breast cancer or cardiovascular disease, cancer treatment types (chemotherapy, radiation, hormone therapy, and/or surgery), and cancer treatment data (e.g., dose, field, date initiated/completed).

The heart age variables include chronological age, systolic blood pressure, diabetes status, smoking status, antihypertensive medication use, and body mass index. The variables collected at each time point include: date of clinic visit, age at the time of visit, heart rate, blood pressure (systolic and diastolic), antihypertensive medication use (if yes, list type), body metrics (height, weight, and body mass index), smoking history (current, former, last date of smoking, or never), diabetes history (yes/no, Type I/II, medication), exercise (yes/no, type, duration, times per week), menopause status (premenopausal, postmenopausal, date of last menstrual period, or unknown), birth control (yes/no, type), other medication history, past medical history. Menopause was defined as not having a menstrual period for more than 12 months (The North American Menopause Society, 2017). At Time 2, the investigator recorded new medication and medical history since Time 1.

Data Abstraction

The data derived from UAB Health System medical records through Tumor Registry data and electronic medical records. To access the data, the investigator collaborated with a UAB Health System Data Manager from the Informational Technology (IT) department to obtain Tumor Registry data. The Tumor Registry consists of patients who were diagnosed with cancer and includes limited treatment and diagnosis data. The investigator queried the Tumor Registry to select records of patients diagnosed with Stage I-III breast cancer between January 1, 2012, and December 31, 2015. The investigator then reviewed the electronic medical records for the selected sample and filtered the sample based on inclusion/exclusion criteria. The investigator used the data collection form to manually collect the data. Each medical record took approximately 30 minutes to review, abstract data, and print on the form.

The investigator obtained records of breast cancer patients who visited UAB Hospital at any time and were identified via the UAB Hospital Tumor Registry. The investigator first limited the records to patients diagnosed with Stage I through III breast cancer during 2012 through 2015. Further, the investigator filtered the records to identify breast cancer patients who were between the ages of 30 and 44 at the time of diagnosis. Then, the investigator reviewed the sample of records to identify breast cancer patients who were treated at UAB Hospital with records of before and after breast cancer treatment. The first breast cancer-related visit was defined as "Time 1." The investigator defined "Time 2" as the clinic visit documented approximately 24 months (± 6 months) from the corresponding diagnosis. The investigator confirmed that the subsequent record occurred after conclusion of primary breast cancer treatment (i.e., radiation, surgery,

chemotherapy). If a record had multiple visits during the two-year follow-up time frame, the investigator selected the record closest to the 24-month date. If there were two dates equally close to the 24-month follow-up, the investigator used the latter record.

For data abstraction, the investigator created a data abstraction form to ensure consistent data collection. The data abstraction form was created based on the variables of interest. See Appendix C for Form 101: Data Collection Form. The form was reviewed by the dissertation committee. The investigator collected the data on the form manually. Once data collection was complete, the investigator entered the data from the data abstraction forms into an Excel file. The investigator entered the data two times on two separate dates to ensure accuracy. If there were discrepencies in the data, the investigator returned to the electronic medical records to confirm data.

Sample Selection

There were 1,857 records of breast cancer survivors diagnosed between January 1, 2012, and December 31, 2015. The investigator restricted records to include breast cancer survivors diagnosed between the age of 30 and 44 years and excluded 1,544 records to a remaining 313. Finally, inclusion of records diagnosed at Stage I, II, or III resulted in 186 electronic medical records, excluding 127 who were diagnosed at Stage 0 or Stage IV.

The investigator reviewed 186 records over three weeks over an approximate 95 hours (~32 hours per week). Through the medical record review, the investigator identified 34 records that did not meet the inclusion and exclusion criteria for a final sample size of 152 records. For the purpose of this dissertation, the term “record” was

used to describe a breast cancer survivor, as this was a retrospective review of electronic medical records and breast cancer survivors were not directly involved.

Data Analysis Plan

The investigator worked with a methodologist and a statistician (dissertation committee members) to complete data cleaning and manage potential missing data. Prior to conducting the analysis of each aim, the investigator calculated heart age of the sample. To calculate heart age, the investigator first calculated the Framingham Risk Score based on chronological age, systolic blood pressure, antihypertensive medication use, diabetes status, smoking status, and body mass index. The Framingham Risk Score is an estimated probability of developing cardiovascular disease over the next 10 years. Heart age was interpreted based on the 10-year cardiovascular disease probability corresponding with that of another individual of the same gender with the same probability but with a low to normal risk factor profile (i.e., body mass index = 22.5, systolic blood pressure = 125 mmHg, no diabetes, no smoking in the last year, no hypertensive medication use). The equation to calculate the 10-year probability of developing a cardiovascular disease for women on antihypertensive medication is as follows:

$$1 - 0.94833^{e^{2.72107*\ln(Age)+0.51125*\ln(BMI)+0.77763*DIAB+0.61868*SMK+2.88267\ln(SBP)-26.0145}}$$

The equation to calculate the 10-year probability of developing a cardiovascular disease for women not on antihypertensive medication is as follows:

$$1 - 0.94833^{e^{2.72107*\ln(Age)+0.51125*\ln(BMI)+0.77763*DIAB+0.61868*SMK+2.81291\ln(SBP)-26.0145}}$$

To determine the heart age, the results from the previous equations were placed into the following equation (in "CVDRisk"):

$$e^{\frac{1}{2.72107}\ln\left(\frac{\log_{0.94833}(1-CVDRisk)}{e^{0.51125*\ln(22.5)+2.81291*\ln(125)-26.0145}}\right)} = HeartAge$$

Once the heart age was calculated, the excess heart age variable was created by subtracting the chronological age from the heart age (D'Agostino et al., 2008).

Statistical Analysis Plan

Preliminary Statistics

Excess heart age was calculated for the entire sample by subtracting chronological age from heart age. Records were categorized into Group A/T (received anthracyclines and/or trastuzumab) and Group No-A/T (did not receive anthracyclines or trastuzumab). Parametric assumptions were tested. The investigator assessed for normality via Shapiro-Wilk's test and homogeneity of variance via Levene's test for quantitative variables.

The investigator assessed relationships (e.g., positive, negative, or none) between variables using Pearson's and Spearman's Rho correlations techniques and examined the correlation coefficient and *p*-values between Time 1 variables, Time 2 variables, and cross-correlations of Time 1 x Time 2 variables. For categorical variables, relationships were assessed using chi-squared test of independence (categories > 5) or Fisher's exact test (categories ≤ 5) when appropriate.

The investigator conducted descriptive statistics for the entire sample, and compared differences between Group A/T and Group No-A/T characteristics using chi-squared test of independence or Fisher's exact test for categorical variables and *t*-tests

and Mann-Whitney tests for quantitative variables. In addition, Time 1 and Time 2 were compared between-groups (at each time point), and within-group (from Time 1 to Time 2 in Group A/T and Group No-A/T separately).

Analyses Related to Specific Aims and Research Questions

Specific Aim 1. To characterize excess heart age among young breast cancer survivors at diagnosis. Specific Aim 2. To characterize excess heart age among young breast cancer survivors at two-year follow-up. For Specific Aims 1 and 2 and their corresponding questions, the investigator examined excess heart age at diagnosis and two-year follow-up, respectively. The investigator conducted descriptive statistics including means, range, and standard deviations for quantitative variables, and frequencies and percent for categorical variables. The investigator also used frequency distributions to organize the numerical data to seek the distribution using histograms and understand the variability in the excess heart age.

Research Question 1A. What is the excess heart age among young breast cancer survivors at diagnosis? Research Question 2A. What is the excess heart age among young breast cancer survivors at two-year follow-up? The investigator conducted descriptive statistics to examine excess heart age for the overall sample for Research Question 1A and 2A at diagnosis and two-year follow-up, respectively.

Research Question 1B. What is the difference in excess heart age between young breast cancer survivors treated with anthracyclines and/or trastuzumab and young breast cancer survivors who did not receive treatment with anthracyclines or trastuzumab at diagnosis? Research Question 2B. What is the difference in excess heart age between

young breast cancer survivors treated with anthracyclines and/or trastuzumab and young breast cancer survivors who did not receive treatment with anthracyclines or trastuzumab at two-year follow-up? Research Questions 1B and 2B examined group differences by comparing the excess heart age between Group A/T and Group No-A/T. The investigator assessed assumptions (i.e., normality and homogeneity of variance) to determine appropriate tests. Appropriate tests were reported; however, the investigator conducted both parametric and nonparametric tests to ensure accurate estimates of *p*-values.

In addition to *p*-values resulting from the tests, the investigator assessed effect sizes. Cohen's *d* and Cramer's *v* determined effect size. The investigator used Cohen's recommendations of small ~0.2, medium ~0.5, and large ~0.8 effect sizes (Cohen, 1988). Finally, the investigator used multiple testing to adjust *p*-values for significance with false discovery rate tests. The letter "*e"* was used to describe effect sizes using appropriate tests (Cohen's *d* for quantitative variables and Cramer's *v* for categorical variables).

Specific Aim 3. To examine differences in excess heart age among young breast cancer survivors from diagnosis to two-year follow-up. Research Question 3A. What is the difference in excess heart age from breast cancer diagnosis to two-year follow-up in the total sample? Research Question 3B. What is the difference in excess heart age from breast cancer diagnosis to two-year follow-up among young breast cancer survivors treated with anthracyclines and/or trastuzumab? Research Question 3C. What is the difference in excess heart age from breast cancer diagnosis to two-year follow-up among young breast cancer survivors who did not receive anthracyclines or trastuzumab? For

Research Questions 3A, 3B, and 3C, the investigator conducted two sample *t*-tests and nonparametric Mann-Whitney tests examining within-group differences for the overall sample, Group No-A/T, and Group A/T, respectively. The investigator reported *p*-values and effect sizes and used multiple testing to adjust *p*-values.

Specific Aim 4. To identify predictors of excess heart age among young breast cancer survivors. Research Question 4A. What are predictors of excess heart age at diagnosis? Research Question 4B. What are predictors of excess heart age at two-year follow-up? Research Question 4C. What are predictors of the difference between excess heart age at diagnosis and two-year follow-up? In preparation for Research Questions 4A, 4B, and 4C, the investigator reviewed associations between all variables. Further, the investigator conducted univariate analysis for all variables to predict: 1) excess heart age at Time 1, 2) excess heart age at Time 2, and 3) the difference between excess heart age from Time 1 to Time 2. Preliminary univariate regression models for the variables determined their correlation with the outcome and determined positive and negative relationships of the variables with the outcome. The investigator set alpha at 0.2, and all variables that had a $p \leq 0.2$ when tested in the univariate model were used in the multivariable linear regression model.

The investigator conducted three multivariable linear regression models. In the linear regression models, the outcomes were: 1) excess heart age at Time 1, 2) excess heart age at Time 2, and 3) the difference between excess heart age from Time 1 to Time 2. The model examined the effects of selected variables based on the univariate analyses, correlations, and clinical relevance of each model. If two variables were highly correlated, the investigator determined which of the highly correlated variables was more

appropriate to place in the model. In addition to these variables, stage of breast cancer and Group A/T (yes/no) were forced into the model: Group A/T was the primary predictor, and stage was included in order to adjust for differences in severity of breast cancer. Further, heart age variables were grouped together (i.e., age, systolic blood pressure, anti-hypertensive medication use, body mass index, diabetes status, smoking status) and kept in the model.

In order to determine which potential model was the best fit, the investigator conducted multiple models based on the potential variables, and compared model fit using coefficient of determination (r^2). The closer the r^2 is to 1, the better the model fits the data..

Specific Aim 5. To explore characteristics of excess heart age within clusters of young breast cancer survivors. The investigator used exploratory analysis to explore characteristics of excess heart age among young breast cancer survivors. Specifically, the investigator employed cluster analyses to group clusters of records based on similar quantitative variables (e.g., excess heart age, body mass index). The investigator used *k*-means cluster analysis techniques. First, the data were plotted on a graph based on the similar quantitative variables. Then, the elbow technique determined the appropriate number of clusters based on the "elbow" of the graph. Once the appropriate number of clusters was determined, the investigator examined the excess heart age, demographic data, and breast cancer treatment characteristics of each cluster.

Validity

This quantitative study attempted to ensure rigor and credibility of findings via the following strategies. First, the investigator attempted to identify the appropriate measurements of identified constructs (such as cardiovascular disease). A review of literature described in Chapter 2 identified common operational definitions of cardiovascular disease risk. Excess heart age was selected to operationalize cardiovascular disease risk in this proposed study. Application of heart age and the Framingham Risk Score provided a unique perspective to understanding cardiovascular disease risk among young breast cancer survivors.

Second, the investigator attempted to increase external validity by excluding Stages 0 and IV breast cancer survivors. Stage 0 breast cancer survivors are not likely to receive systemic cancer treatment and may skew the results of the study. As mentioned in Chapter 2, the survival rate for Stage IV breast cancer was significantly lower than for Stage I, II, or III breast cancer. Thus, excluding Stage IV increased generalizability to breast cancer survivors, as Stage IV survivors are more likely to die of breast cancer-related causes. Further, the investigator carefully generated inferences from the study results to ensure that the data were not inaccurately generalized.

Finally, the investigator attempted to ensure precision of results. The investigator worked closely with a methodologist and statistician to ensure that adequate methods and statistical analysis techniques were appropriately used and findings were appropriately interpreted. The investigator worked closely with the content experts to ensure that statistically significant results were clinically relevant. Further, to strengthen the results, effect sizes in addition to *p*-values were reported. *P*-values were adjusted for multiple

comparisons using the false discovery rate in order to strengthen the results and interpretation. Because healthcare professionals input data, the electronic medical records are subject to human error.

Ethical Considerations

According to the Belmont Report, a basic ethical principle is respect for persons (U.S. Department of Health & Human Service, 1979). Although participants did not provide consent to participate in the research process, respect for persons is important and was implemented by protecting participant privacy and confidentiality. The investigator attempted to protect patient privacy and confidentiality.

The investigator took multiple steps to protect from breaches in privacy and confidentiality. Once all necessary data were collected, personal identifiers were removed and destroyed from the dataset, and future analyses cannot link back to the participants. Data remained confidential. Data were stored on a password-protected, encrypted, UAB-secured computer. Further, the study has approval from the University of Alabama at Birmingham Institutional Review Board. At the completion of the study, all data will be destroyed.

Summary

This study aimed to explore excess heart age among young breast cancer survivors and compared excess heart age between survivors treated with anthracyclines and/or trastuzumab and survivors who did not receive anthracyclines or trastuzumab. By researching this issue, this study provided a better understanding of cardiovascular

disease risk among breast cancer survivors. Chapter 4 will describe the results of the dissertation.

CHAPTER FOUR

RESULTS

This chapter describes the results of the dissertation study. There were 1,857 records of breast cancer survivors treated between January 1, 2012, and December 31, 2015. Among records of breast cancer survivors treated at UAB Hospital, 152 met the inclusion and exclusion criteria. Time 1 was the breast cancer diagnosis, and the two-year follow-up was referred to as Time 2.

Description of the Sample

Table 2 describes the sample characteristics. The mean age at diagnosis was 39.1 ± 3.7 years. Of these records, 73% were Non-Hispanic White, 21.1% were Non-Hispanic Black, and 5.9% were other race/ethnicity. Most were married (73.7%) and employed (71.7%).

The majority of the sample had diagnoses of Stage I (41%) or Stage II (41%) breast cancer, with only 17% Stage III. Of the entire sample, 83% received chemotherapy, 75.7% had a mastectomy and 23% had a lumpectomy, 65% received radiation, and 68.4% received hormone therapy.

The 95 records of breast cancer survivors who received anthracyclines and/or trastuzumab were categorized to “Group A/T.” The remaining 57 records consisted of

breast cancer survivors who did not receive anthracyclines or trastuzumab but were also treated at UAB Hospital. This group was categorized as "Group No-A/T."

Table 2

Sample Characteristics (N = 152)

Variable	Total Sample (N = 152)	Group A/T (n = 95)	Group No-A/T (n = 57)	*p*	fdr	*e*
Age at diagnosis	39.1 ± 3.7 years (range 30-44)	38.4 ± 4 years (range 30-44)	40.3 ± 3 years (range 33-44)	**<.01**	**<.01**	.53
Race				.80	.84	.05
NH White	111 (73%)	71 (74.7%)	40 (70.2%)			
NH Black	32 (21.1%)	19 (20%)	13 (22.8%)			
Other	9 (5.9%)	5 (5.3%)	4 (7.1%)			
Marital Status				.59	.67	.09
Single	29 (19.1%)	16 (16.8%)	13 (22.8%)			
Married	112 (73.7%)	71 (74.7%)	41 (71.9%)			
Divorced/Widowed	11 (7.2%)	8 (8.5%)	3 (5.3%)			
Employment				.60	.67	.09
Employed	109 (71.7%)	70 (73.7%)	39 (68.4%)			
Unemployed/Homemaker	33 (21.6%)	21 (22.1%)	12 (21.1%)			
Disabled/Retired	7 (4.6%)	3 (3.2%)	4 (7%)			
Missing	3 (2%)	1 (1%)	2 (3.5%)			
Stage				**<.01**	**<.01**	.40
I	63 (41%)	27 (28.4%)	36 (63.2%)			
II	63 (41%)	43 (45.3%)	20 (35.1%)			
III	26 (17%)	25 (26.3%)	1 (1.8%)			
Breast Cancer Type						
ER+	108 (71%)	58 (61.1%)	50 (87.7%)	**<.01**	**<.01**	.27
PR+	101 (66%)	51 (53.7%)	50 (87.7%)	**<.01**	**<.01**	.33
HER2+	37 (24%)	35 (36.8%)	2 (3.5%)	**<.01**	**<.01**	.36
ER-/PR-/HER2-	29 (19%)	23 (24.2%)	6 (10.5%)	**.04**	.08	.17
Treatment						
Chemotherapy	126 (83%)	95 (100%)	32 (56.1%)	**<.01**	**<.01**	.57
Anthracyclines	65 (42.8%)	65 (68.4%)	0 (0.0%)			
Trastuzumab	40 (26.3%)	40 (42.1%)	0 (0.0%)			
Mastectomy	115 (75.7%)	76 (80%)	39 (68.4%)	.08	.13	.11
Reconstruction	100 (65.8%)	66 (69.5%)	34 (59.6%)	.22	.30	.15
Lumpectomy	35 (23%)	17 (17.9%)	18 (31.6%)	.05	**.05**	.16
Radiation	99 (65%)	67 (70.5%)	32 (56.1%)	.07	.12	.15
Hormone Therapy	104 (68.4%)	56 (58.9%)	48 (84.2%)	**<.01**	**<.01**	.26
Genetic Testing						
BRCA1 positive	8 (5.3%)	5 (5.3%)	3 (5.3%)	.99	.99	.00
BRCA2 positive	7 (4.6%)	7 (4.6%)	0 (0.0%)	**.04**	.08	.18
First Degree Family History						
Breast cancer	21 (13.8%)	11 (11.6%)	10 (17.5%)	.30	.38	.08
Cardiovascular disease	25 (16.4%)	12 (12.6%)	13 (22.8%)	.10	.15	.13

*Bold indicative of significance set at 0.05.
**e* = effect size, Cohen's *D* or Cramer's *V* where appropriate

Group A/T and Group No-A/T Comparison

The records in Group A/T were younger than those in Group No-A/T (38.4 years vs. 40.3 years, $p < .01$, $e = .53$). There were no differences in race, marital status, or employment status (all $p \geq .05$). Group A/T had a higher proportion of Stage III diagnoses (26.3% vs. 10.5%, $p = .04$, $e = .40$). Records of Group A/T were more likely to have triple negative breast cancer ($p = .04$) and HER2+ ($p < .01$), while those in Group No-A/T were more likely to have ER+ or PR+ breast cancer ($p < .01$). In regards to cancer treatment, Group A/T had higher proportions of records who received chemotherapy (100% vs. 56.1%, $p < .01$, $e = .57$) and fewer who received hormone therapy (58.9% vs. 84.2%, $p < .01$, $e = .26$). There were no significant differences in receipt of mastectomy, reconstruction, lumpectomy, and/or radiation ($p \geq .05$). Adjusting for *p*-values using false discovery rate (fdr) did not change statistical significance for any comparison between Group A/T and Group No-A/T except for lumpectomy, which changed from > .05 to < .05.

Most of the records showed a history of genetic testing ($n = 137$, 90%). There was no difference in BRCA1 mutations ($p = .99$) between the groups; however, Group No-A/T had more records with BRCA2 mutations (4.6% vs. 0%, $p < .01$, $e = .18$). Although not statistically significant, there was a higher proportion of first-degree family history of breast cancer (17.5% vs. 11.6%, $p = .38$, $e = .08$) and cardiovascular disease (22.8% vs. 12.6%, $p = .10$, $e = .13$) in Group No-A/T compared to Group A/T.

After adjusting for *p*-values post false discovery tests, *p*-values < .05 remained significant except for triple negative breast cancer (ER-, PR-, HER2-) and BRCA2 positive, in which values became not statistically significant ($p \geq .05$).

Heart Age Analysis

The heart age of the overall sample was 43.6 years at Time 1 and 46.7 years at Time 2. Further, there was an average excess heart age of 4.2 ± 9.2 years at Time 1, which had a non-statistically significant increase to an average of 5.4 ± 10.4 years at Time 2 (p = .08, e = .12).

Preliminary Analyses

Assumptions

Normality and homogeneity testing were conducted on 20 quantitative variables. Only heart rate at Time 1 met parametric assumptions. The remaining variables met assumptions for homogeneity of variance between Time 1 and Time 2, but variables were not normally distributed. Both parametric and nonparametric were conducted, and results of appropriate tests were reported.

Associations of Quantitative Variables

Table 3 examines the correlations among Time 1 variables, while Table 4 shows the correlations among Time 2 variables. Table 5 displays the cross relationships between Time 1 and Time 2 variables. Correlation coefficients and Spearman's Rho tests were reported.

Age at diagnosis was associated with systolic blood pressure at both Time 1 and Time 2. Specifically, older age at diagnosis was associated with an increase in systolic blood pressure (p < .01). In addition to being associated with systolic blood pressure, age at diagnosis was also associated with diastolic blood pressure and excess heart age at

Time 2. Stage of breast cancer was associated with heart rate and decrease in systolic blood pressure. Body mass index at Time 2 was associated with increase in heart rate and weight gain at Time 2. Additionally, excess heart age at Time 1 was associated with Time 2 heart age variables (i.e., systolic blood pressure, weight, body mass index, and excess heart age at Time 2). Excess heart age was significantly associated with systolic and diastolic blood pressure and body mass index at both time points.

Table 3

Spearman's Rho Correlation for Time 1 x Time 1 Variables

Variable		**Time 1**								
		Age	Stage	Heart Rate	SYS BP	DIA BP	Height	Weight	BMI	Excess HA
Time 1	Age at DX	**<.01**	0.21	0.89	**<.01**	0.19	0.65	0.33	0.32	0.1
		1	-0.1	-0.01	0.21	0.11	0.04	0.08	0.08	0.13
	Stage	0.21	**<.01**	0.95	0.45	0.53	0.06	0.3	0.09	0.6
		-0.1	1	0.01	-0.06	-0.05	-0.15	0.08	0.14	-0.04
	Heart Rate	0.89	0.95	**<.01**	0.36	0.36	0.47	0.33	0.25	0.73
		-0.01	0.01	1	0.07	0.07	0.06	0.08	0.09	0.03
	SYS BP	**<.01**	0.45	0.36	**<.01**	**<.01**	0.55	0.26	0.2	**<.01**
		0.21	-0.06	0.07	1	0.72	-0.05	0.09	0.11	0.69
	DIA BP	0.19	0.53	0.36	**<.01**	**<.01**	0.24	0.23	0.08	**<.01**
		0.11	-0.05	0.07	0.72	1	-0.1	0.1	0.14	0.51
	Height	0.65	0.06	0.47	0.55	0.24	**<.01**	0.08	**0.04**	0.22
		0.04	-0.15	0.06	-0.05	-0.1	1	0.14	-0.16	-0.1
	Weight	0.33	0.3	0.33	0.26	0.23	0.08	**<.01**	**<.01**	**<.01**
		0.08	0.08	0.08	0.09	0.1	0.14	1	0.92	0.32
	BMI	0.32	0.09	0.25	0.2	0.08	**0.04**	**<.01**	**<.01**	**<.01**
		0.08	0.14	0.09	0.11	0.14	-0.16	0.92	1	0.34
	Excess HA	0.1	0.6	0.73	**<.01**	**<.01**	0.22	**<.01**	**<.01**	**<.01**
		0.13	-0.04	0.03	0.69	0.51	-0.1	0.32	0.34	1

*Upper is *p*-value; lower is correlation coefficient.
Abbreviations: DX = diagnosis, SYS BP = systolic blood pressure, DIA BP = diastolic blood pressure, BMI = body mass index, HA = heart age

Table 4

Spearman's Rho Correlation for Time 2 x Time 2 Variables

Variable		Time 2								
		Age	Heart Rate	SYS BP	DIA BP	Height	Weight	Weight Gain	BMI	Excess HA
Time 2	Age	**<.01** 1	0.33 0.08	**<.01** 0.23	**0.05** 0.16	14 0	0.3 0.08	0.75 -0.03	0.24 0.1	**<.01** 0.22
	Heart Rate	0.33 0.08	**<.01** 1	0.73 0.03	0.79 0.02	0.27 -0.09	0.13 0.12	0.78 0.02	**0.03** 0.17	0.06 0.15
	SYS BP	**<.01** 0.23	0.73 0.03	**<.01** 1	**<.01** 0.74	0.24 0.1	0.13 0.12	0.42 0.07	0.35 0.08	**<.01** 0.74
	DIA BP	**0.05** 0.16	0.79 0.02	**<.01** 0.74	**<.01** 1	0.6 -0.04	0.14 0.12	**0.04** 0.16	0.22 0.1	**<.01** 0.61
	Height	1 0	0.27 -0.09	0.24 0.1	0.6 -0.04	**<.01** 1	0.07 0.15	0.8 0.02	**0.04** -0.17	0.47 -0.06
	Weight	0.3 0.08	0.13 0.12	0.13 0.12	0.14 0.12	0.07 0.15	**<.01** 1	**0.01** 0.21	**<.01** 0.24	0.07 0.15
	Weight Gain	0.75 -0.03	0.78 0.02	0.42 0.07	0.04 0.16	0.8 0.02	**0.01** 0.21	**<.01** 1	**<.01** 0.92	**<.01** 0.41
	BMI	0.24 0.1	**0.03** 0.17	0.35 0.08	0.22 0.1	0.04 -0.17	<.01 0.24	**<.01** 0.92	**<.01** 1	**<.01** 0.4
	Excess HA	**<.01** 0.22	0.06 0.15	**<.01** 0.74	**<.01** 0.61	0.47 -0.06	0.07 0.15	**<.01** 0.41	**<.01** 0.4	**<.01** 1

*Upper is *p*-value; lower is correlation coefficient.
Abbreviations: SYS BP = systolic blood pressure, DIA BP = diastolic blood pressure, BMI = body mass index, HA = heart age

Table 5

Spearman's Rho Correlation for Time 1 x Time 2 Variables

Variable		Time 2							
		Heart Rate	SYS BP	DIA BP	Height	Weight	Weight Gain	BMI	Excess HA
Time 1	Stage	**0.01**	**0.03**	0.19	**0.03**	0.64	0.11	0.29	0.18
		0.2	-0.17	-0.11	-0.18	0.04	-0.13	0.09	-0.11
	Heart Rate	**<.01**	0.95	0.35	0.35	0.19	0.2	0.12	0.98
		0.35	0	-0.08	0.08	0.11	0.11	0.13	0
	SYS BP	0.42	**<.01**	**<.01**	0.4	0.41	0.53	0.2	**<.01**
		0.07	0.41	0.42	-0.07	0.07	-0.05	0.1	0.34
	DIA BP	0.42	**0.01**	**<.01**	0.25	0.12	0.41	**0.03**	**<.01**
		0.07	0.23	0.3	-0.09	0.13	0.07	0.18	0.3
	Height	0.31	0.19	0.5	**<.01**	0.2	0.85	**0.03**	0.52
		-0.08	0.11	-0.05	1	0.1	-0.02	-0.18	-0.05
	Weight	0.11	0.26	0.39	**0.03**	**<.01**	0.16	**<.01**	**<.01**
		0.13	0.09	0.07	0.18	0.93	-0.11	0.84	0.35
	BMI	**0.03**	0.71	0.68	0.08	**<.01**	0.49	**<.01**	**<.01**
		0.18	0.03	0.04	-0.14	0.88	-0.06	0.93	0.36
	Excess HA	**0.01**	**<.01**	**<.01**	0.12	**<.01**	0.25	**<.01**	**<.01**
		0.2	0.29	0.3	-0.13	0.27	-0.09	0.3	0.57

*Upper is *p*-value; lower is correlation coefficient.
Abbreviations: SYS BP = systolic blood pressure, DIA BP = diastolic blood pressure, BMI = body mass index, HA = heart age

Associations of Categorical Variables

Table 6 demonstrates the associations among categorical variables. This table was used to identify relationships between variables prior to creating a multivariable model.

Table 6

Associations of Categorical Variables

	Race	Mar	Emp	Stage	Side	Lt. Side	Rt. Side	ER+	PR+	HER 2+	Chem	Chem-A	Chem-T	Chem-C	Mast	Lump	Rad	HT	BRC A1	BRC A2	BC FHx	CVD Fhx	Meno Δ
Race	**<.01**	**<.01**	0.18	0.1	0.82	0.68	0.6	0.07	0.1	0.84	1	0.96	0.64	0.26	**0.02**	**<.01**	0.06	**0.04**	0.18	0.31	0.71	0.5	0.13
Mar	**<.01**	**<.01**	0.19	0.1	0.38	0.33	0.46	0.29	0.73	0.61	0.64	0.72	0.39	0.61	0.85	0.79	0.43	0.35	1	0.23	0.36	0.15	0.28
Emp	0.18	0.19	**<.01**	0.11	0.81	0.57	0.72	0.09	0.29	0.34	0.29	1	0.28	0.73	0.23	0.15	0.66	0.32	0.18	0.74	0.17	0.35	0.19
Stage	0.1	0.1	0.11	**<.01**	**0.02**	0.02	0.03	1	1	0.25	**<.01**	**<.01**	**0.02**	0.12	0.59	0.58	**<.01**	0.97	0.45	0.87	0.49	0.38	0.05
Side	0.82	0.38	0.81	**0.02**	**<.01**	<.01	<.01	0.68	0.5	0.26	0.77	0.87	0.49	0.82	0.69	0.67	0.21	0.82	0.08	1	1	**0.01**	0.2
Lt. Side	0.68	0.33	0.57	0.02	<.01	**<.01**	<.01	0.72	0.49	0.13	0.83	0.74	0.36	1	0.57	0.56	1	0.73	0.28	1	1	**0.01**	0.2
Rt. Side	0.6	0.46	0.72	0.03	<.01	<.01	**<.01**	0.86	0.5	0.19	0.66	0.75	0.46	1	0.45	0.44	0.87	0.86	0.72	1	1	**0.03**	0.14
ER+	0.07	0.29	0.09	1	0.68	0.72	0.86	**<.01**	**<.01**	0.21	**<.01**	**0.03**	0.22	0.85	0.84	1	0.71	**<.01**	**<.01**	1	0.19	1	0.07
PR+	0.1	0.73	0.29	1	0.5	0.49	0.5	**<.01**	**<.01**	0.07	**<.01**	**<.01**	0.08	0.72	0.42	0.54	0.37	**<.01**	**0.02**	1	0.63	1	**0.03**
HER2	0.84	0.61	0.34	0.25	0.26	0.13	0.19	0.21	0.07	**<.01**	**0.04**	**<.01**	**<.01**	**<.01**	0.83	0.37	0.55	0.22	0.11	1	0.41	0.8	0.52
Chem	1	0.64	0.29	**<.01**	0.77	0.83	0.66	**<.01**	**<.01**	**0.04**	**<.01**	**<.01**	**<.01**	**<.01**	0.62	0.6	**<.01**	**0.02**	0.35	0.6	1	0.57	0.62
Chem-A	0.96	0.72	1	**<.01**	0.87	0.74	0.75	**0.03**	**<.01**	**<.01**	**<.01**	**<.01**	**0.01**	**<.01**	0.09	0.17	0.06	**0.03**	0.72	0.13	0.48	0.83	0.46
Chem-T	0.64	0.39	0.28	**0.02**	0.49	0.36	0.46	0.22	0.08	**<.01**	**<.01**	**0.01**	**<.01**	**<.01**	0.83	0.39	0.57	0.23	0.44	1	0.59	0.32	0.68
Chem-C	0.26	0.61	0.73	0.12	0.82	1	1	0.85	0.72	**<.01**	**<.01**	**<.01**	**<.01**	**<.01**	0.43	0.32	0.48	1	0.26	0.42	0.62	0.82	**0.05**
Mast	**0.02**	0.85	0.23	0.59	0.69	0.57	0.45	0.84	0.42	0.83	0.62	0.09	0.83	0.43	**<.01**	**<.01**	**<.01**	0.84	0.2	1	0.29	0.8	0.13
Lump	**<.01**	0.79	0.15	0.58	0.67	0.56	0.44	1	0.54	0.37	0.6	0.17	0.39	0.32	**<.01**	**<.01**	**<.01**	1	0.2	0.2	0.58	0.8	0.08
Rad	0.06	0.43	0.66	**<.01**	0.21	1	0.87	0.71	0.37	0.55	**<.01**	0.06	0.57	0.48	**<.01**	**<.01**	**<.01**	0.86	0.13	0.24	0.81	0.36	0.25
HT	**0.04**	0.35	0.32	0.97	0.82	0.73	0.86	**<.01**	**<.01**	0.22	**0.02**	**0.03**	0.23	1	0.84	1	0.86	**<.01**	**0.02**	0.68	0.31	1	**0.03**
BRCA1	0.18	1	0.18	0.45	0.08	0.28	0.72	**<.01**	**0.02**	0.11	0.35	0.72	0.44	0.26	0.2	0.2	0.13	**0.02**	**<.01**	1	**<.01**	0.35	0.41
BRCA2	0.31	0.23	0.74	0.87	1	1	1	1	1	1	0.6	0.13	1	0.42	1	0.2	0.24	0.68	1	**<.01**	**<.01**	0.35	0.37
BC FHx	0.71	0.36	0.17	0.49	1	1	1	0.19	0.63	0.41	1	0.48	0.59	0.62	0.29	0.58	0.81	0.31	<.01	<.01	<.01	0.34	0.59
CVD FHx	0.5	0.15	0.35	0.38	**0.01**	**0.01**	**0.03**	1	1	0.8	0.57	0.83	0.32	0.82	0.8	0.8	0.36	.03	0.35	0.35	0.34	**<.01**	0.8
Meno Δ	0.13	0.28	0.19	**0.05**	0.2	0.2	0.14	0.07	**0.03**	0.52	0.62	0.46	0.68	**0.05**	0.13	0.08	0.25	**0.03**	0.41	0.37	0.59	0.8	**<.01**

Note. *P-values* in bold indicative of significance at .05. Abbreviations: Mar = marital, Emp = employment, Lt. = left, Rt. = Right, Chem = chemotherapy, Chem-A= anthracyclines, Chem-T = trastuzumab, Chem-C = cyclophosphamide, Mast = mastectomy, Lump = lumpectomy, Rad = radiation, HT = hormone therapy, BC FHx = first-degree breast cancer family history, CVD FHx = first-degree cardiovascular disease family history, Meno Δ = menopause change.

Time 1 to Time 2 Comparisons

Table 7 demonstrates within-group differences. Heart rate, blood pressure (systolic and diastolic), smoking rates, and diabetes rates did not have a statistically significant change from Time 1 to Time 2 (all $p \geq .05$) for the total sample, Group A/T, or Group No-A/T. Although blood pressure was similar, rates of blood pressure medication use increased significantly for both Group A/T (9.5% to 20%, $p < .01$, $e = .60$) and Group No-A/T (17.5% to 29.8%, $p = .02$, $e = .66$).

Both groups increased in weight from Time 1 to Time 2 ($p < .01$). Average body mass index remained within the overweight category (25 – 29 kg/m^2) at both time points. However, there were statistically significant increases in body mass index among both groups, with 33.6% classified as obese (≥30 kg/m^2) at Time 1 and 43.4% obese at Time 2.

At Time 1, 86.2% of the overall sample were premenopausal. At Time 2, only 59.2% were premenopausal. This difference was also statistically significant among records of both Group A/T and Group No-A/T ($p < .01$). In Group A/T, many of those who were using hormonal birth control at Time 1 were not at Time 2 (14.7% vs. 5.3%, $p = .02$, $e = .37$). Yet, in Group No-A/T, two records were using hormonal birth control at both time points.

Overall, at each time point, no statistically significant between-group differences were found between Group A/T and Group No-A/T, except for percentage of records with a medication history of hormonal birth control at Time 1. Group A/T had higher rates of hormonal birth control use than Group No-A/T (14.7% vs. 3.5%, $p = .05$, $e = .15$) at Time 1, but rates were similar at Time 2 ($p = .71$).

Table 7

Within-Group Differences from Time 1 to Time 2

Variable	Total Sample (N = 152)		p	e	Group A/T (n = 95)		p	e	Group No-A/T (n = 57)		p	e
	Time 1	Time 2			Time 1	Time 2			Time 1	Time 2		
Excess Heart Age (years)	4.2 ± 9.2	5.4 ± 10.4	0.08	0.12	4.3 ± 9.6	4.4 ± 9.7	0.93	0.01	4 ± 8.6	7.1 ± 11.3	**<.01**	0.31
Heart Rate (beats per minute)	84.1 ± 11.9	81.8 ± 14.4	0.07	0.17	84.7 ± 12.4	81.8 ± 14.1	0.07	0.22	83 ± 11.1	81.8 ± 15	0.58	0.08
Blood Pressure (mmHg)												
Systolic	124.1 ± 15.5	125 ± 15.6	0.56	0.05	123.3 ± 15.9	123.3 ± 14.3	0.98	0	125.6 ± 14.8	127.7 ± 17.4	0.33	0.13
Diastolic	80.6 ± 9.9	80.5 ± 10.8	0.92	0.01	79.6 ± 10.1	79.6 ± 10.1	0.74	0	82.1 ± 9.6	81.9 ± 11.9	0.89	0.02
BP Medication	19 (12.5%)	36 (23.7%)	**<.01**	0.66	9 (9.5%)	19 (20%)	**<.01**	0.60	10 (17.5%)	17 (29.8%)	**0.02**	0.66
Height (inches)	64.9 ± 2.7	64.9 ± 2.7	1	0	64.8 ± 2.8)	64.8 ± 2.8	1	0	65 ± 2.8)	65 ± 2.8	1	0
Weight (lbs)	166 ± 41.5	173.2 ± 39.6	**<.01**	0.16	165.9 ± 40.1	171.3 ± 38.6	**<.01**	0.14	167.8 ± 41.1	176.4 ± 41.3	**<.01**	0.21
10% Weight Gain		33 (21.7%)				17 (17.9%)				16 (28.1%)		
BMI (kg/m^2)	27.9 ± 6.8	29.1 ± 7	**<.01**	0.18	27.8 ± 6.9	29 ± 7.2	**<.01**	0.17	28 ± 6.6)	29.4 ± 6.6	**<.01**	0.22
BMI Categories												
Underweight	5 (3.3%)	3 (2%)			4 (4.2%)	2 (2.1%)			1 (1.8%)	1 (1.8%)		
Normal	48 (31.6%)	42 (27.6%)			33 (34.7%)	28 (29.5%)			15 (26.3%)	14 (24.6%)		
Overweight	48 (31.6%)	41 (27%)			25 (26.3%)	23 (24.2%)			23 (40.4%)	18 (31.6%)		
Obese	51 (33.6%)	66 (43.4%)			33 (34.7%)	42 (44.2%)			18 (31.6%)	24 (42.1%)		
Smoking			0.39	.06			0.39	.08			1	0
Current	16 (10.5%)	14 (9.2%)			13 (13.7%)	11 (11.6%)			3 (5.3%)	3 (5.3%)		
Former	17 (11.2%)	19 (12.5%)			13 (13.7%)	15 (15.8%)			4 (7%)	4 (7%)		
Never	119 (78.3%)	119 (78.3%)			69 (72.6%)	69 (72.6%)			50 (87.7%)	50 (87.7%)		
Diabetes	7 (4.6%)	10 (6.6%)	0.37	0.64	5 (5.3%)	5 (5.3%)	1	0	2 (3.5%)	5 (8.8%)	0.25	0.46
Menopause			**<.01**	0.47			**<.01**	0.42			**<.01**	0.49
Pre	131 (86.2%)	90 (59.2%)			84 (88.4%)	57 (60%)			47 (82.5%)	33 (57.9%)		
Post	21 (13.8%)	61 (40.1%)			11 (11.6%)	37 (39%)			10 (17.5%)	24 (42.1%)		
Missing		1 (<1%)										
Hormonal Birth Control	16 (10.5%)	7 (4.6%)	**0.04**	0.28	14 (14.7%)	5 (5.3%)	**0.02**	0.37	2 (3.5%)	2 (3.5%)	1	0

*Bold indicative of significance set at 0.05.
BMI = body mass index

Results Related to Specific Aims and Research Questions

Specific Aim 1

The first specific aim was to characterize excess heart age among young breast cancer survivors at diagnosis, which consisted of two parts. The first part was to evaluate whether there was a difference in excess heart age among the records of young breast cancer survivors at diagnosis. Results showed that at Time 1, the overall sample had a mean excess heart age of 4.2 ± 9.2 years (range -8 to 40).

The second part of this specific aim was to compare excess heart age at diagnosis between Group A/T and Group No-A/T. The results showed that Group A/T had a mean excess heart age of 4.3 ± 9.6 years (range -8 to 40) and Group No-A/T had a mean excess heart age of 4 ± 8.6 years (range -8 to 36) at diagnosis. There was no statistically significant between-group difference and very small effect size (p = .85, e = .03).

Specific Aim 2

The second specific aim was to characterize excess heart age among young breast cancer survivors at two-year follow-up. The first part of this aim was to examine the excess heart age among young breast cancer survivors at two-year follow-up. The results showed that at Time 2, the overall sample had a mean excess heart age of 5.4 ± 10.4 years (range -9 to 43).

The second part of this aim was to compare excess heart age between Group A/T and Group No-A/T at two-year follow-up. At Time 2, the results showed the mean excess heart age of Group A/T was 4.4 ± 9.7 years (range -9 to 38), and the mean excess heart

age of Group No-A/T was 7.1 ± 11.3 years (range -9 to 43). The difference was statistically insignificant with a small effect size (p = .13, e = .27).

Specific Aim 3

The third specific aim was to examine within-group differences in excess heart age among young breast cancer survivors from diagnosis to two-year follow-up. Table 7 describes the within-group difference from Time 1 to Time 2, by total sample, Group A/T, and Group No-A/T. This specific aim has three parts. The first part of this aim was to evaluate the difference in excess heart age from diagnosis to two-year follow-up in the total sample. From Time 1 to Time 2, the overall sample had a non-statistically significant increase in excess heart age of 1.2 ± 8.4 years (p = .08, e = .12).

The second part of this specific aim was to examine the difference in excess heart age from diagnosis to two-year follow-up among records of Group A/T. From Time 1 to Time 2, the results showed that Group A/T had a 0.1 ± 8.3 years increase of excess heart age (p = .93, e = .01).

The third part of this specific aim was to examine the difference in excess heart age from diagnosis to two-year follow-up among the records of Group No-A/T. From Time 1 to Time 2, the results showed Group No-A/T had an increase of excess heart age of 3.1 ± 8.2 years with a small to medium effect size (p < .01, e = .31).

Specific Aim 4

The fourth specific aim of this study was to identify predictors of excess heart age among young breast cancer survivors. The results of multivariable models were reported based on stepwise selection using univariate analyses ≤ .2.

The first part of Specific Aim 4 was to identify predictors of excess heart age at Time 1. Univariate linear regression was conducted on 37 predictor variables. Based on associations and variables with *p*-values ≤ .2, the multivariable linear regression analyses included group, stage, Time 1 heart age variables (age, systolic blood pressure, antihypertensive medication use, smoking status, diabetes status, and body mass index), menopause (premenopausal/postmenopausal), mastectomy (yes/no), and lumpectomy (yes/no). The final multivariable model consisted of group, stage, and Time 1 heart age variables. The r^2 was .9798. Stage of breast cancer was significant ($p < .05$); advancing stage was associated with higher excess heart age. Group A/T or No-A/T was statistically insignificant ($p = .92$). Heart age variables (except for age) were significant. See Table 8. Because stage was significant and correlated with treatment with anthracyclines and trastuzumab, variance inflation factor was checked to test for multicollinearity between stage and group to predict excess heart age. The variance inflation factor between stage and Group A/T was 1.19; therefore, the factor was low, and stage was left in the final model to predict excess heart age at Time 1.

Table 8

Multivariable Linear Regression Model of Predicting Excess Heart Age at Breast Cancer Diagnosis

Variable	Estimate	Standard Error	*p*
Group	-0.03	0.25	0.92
Stage	0.32	0.16	**0.05**
Time 1 – Age	0.01	0.02	0.64
Time 1 – Systolic blood pressure	0.39	0.01	**<.01**
Time 1 – Antihypertension medication	6.1	0.35	**<.01**
Time 1 – Body mass index	0.29	0.02	**<.01**
Time 1 – Smoking	10.96	0.29	**<.01**
Time 1 – Diabetes	12.73	0.53	**<.01**

*Bold indicative of significance at *p*-value <.05

The second part of Specific Aim 4 was to identify predictors of excess heart age at Time 2. Univariate linear regression was conducted on 52 predictor variables (including Time 1 predictors). Variables found with *p*-values ≤ .2 included group status, Time 1 heart age variables, Time 2 heart age variables, race (white/black/other), breast cancer side (left/right/both), ER+ status (yes/no), PR+ status (yes/no), HER2+ status (yes/no), hormone therapy (yes/no), menopause change (yes/no), and weight gain (yes/no).

The final multivariable linear regression model to predict excess heart age at Time 2 after stepwise elimination consisted of group, stage, Time 1 menopause status, Time 2 heart age variables, hormone therapy, and menopause change. The r^2 was .9803. See Table 9. Group A/T or No-A/T did not predict excess heart age at Time 2 (p = .38). Stage of breast cancer was also not a predictor (p = .97). All heart age variables predicted excess heart age at Time 2. Premenopausal status at diagnosis was associated with higher excess heart age at Time 2 (p =.04) compared to those who had already reached menopause at Time 1. Additionally, change in menopause status (from premenopausal at

diagnosis to menopausal at two-year follow-up) was a significant predictor of increased excess heart age. Finally, hormone therapy use was associated with higher excess heart age ($p < .01$).

Table 9

Multivariable Linear Regression Model of Predicting Excess Heart Age at Two-Year Follow-Up

Variable	Estimate	Standard Error	*p*
Group	0.25	0.29	0.38
Stage	0.01	0.19	0.97
Time 1 Menopause	-0.81	0.39	**0.04**
Time 2 – Age	0.18	0.03	**<.01**
Time 2 – Systolic blood pressure	0.39	0.01	**<.01**
Time 2 – Antihypertension medication	6.32	0.3	**<.01**
Time 2 – Body mass index	0.33	0.02	**<.01**
Time 2 – Smoking	11.25	0.39	**<.01**
Time 2 – Diabetes	15.87	0.49	**<.01**
Hormone Therapy	0.83	0.28	**<.01**
Menopause Change	0.77	0.28	**<.01**

*Bold is indicative of significance at *p*-value <.05

The third part of Specific Aim 4 was to identify predictors of the difference between Time 1 and Time 2 excess heart age. Univariate linear regression was conducted on 52 variables (including Time 1 predictors). Variables included in the multivariable analyses were group, Time 1 heart age variables, Time 2 heart age variables, race, breast cancer side, ER+ status, PR+ status, triple negative breast cancer status, hormone therapy, menopause change, weight gain, and breast cancer family history.

The final model consisted of group, stage, Time 1 heart age variables, Time 2 heart age variables, PR+ status, hormone therapy, menopause change, and weight gain. The r^2 was .9706. Group, stage of breast cancer, PR+ status, hormone therapy, and weight

gain were not statistically significant predictors ($p \geq .05$). See Table 10. Statistically significant predictors included Time 1 and Time 2 heart age variables, and menopause change ($p = .04$).

Table 10

Multivariable Linear Regression Model of Predicting the Difference in Excess Heart Age at Breast Cancer Diagnosis and Two-Year Follow-Up

Variable	Estimate	Standard Error	*p*
Group	0.002	0.3	0.99
Stage	-0.13	0.19	0.49
Time 1 – Age	-0.06	0.03	**0.03**
Time 1 – Systolic blood pressure	-0.37	0.01	**<.01**
Time 1 – Antihypertension medication	-5.73	0.55	**<.01**
Time 1 – Body mass index	-0.27	0.07	**<.01**
Time 1 – Smoking	-10.35	0.44	**<.01**
Time 1 – Diabetes	-16.57	0.85	**<.01**
Time 2 – Age	0.14	0.03	**<.01**
Time 2 – Systolic blood pressure	0.39	0.01	**<.01**
Time 2 – Antihypertension medication	5.65	0.4	**<.01**
Time 2 – Body mass index	0.28	0.08	**<.01**
Time 2 – Smoking	10.6	0.54	**<.01**
Time 2 – Diabetes	18.2	0.75	**<.01**
PR Positive	0.86	0.44	0.05
Hormone Therapy	-0.8	0.44	0.07
Menopause Change	0.59	0.29	**0.04**
Weight Gain	0.54	0.36	0.14

*Bold is indicative of significance at *p*-value <.05

Specific Aim 5

The fifth specific aim was to use cluster analyses to explore characteristics of excess heart age of young breast cancer survivors. Three clusters were identified at Time 1, and three clusters were identified separately at Time 2. Table 11 depicts the characteristics of clusters at each time point.

Table 11

Description of Clusters

Variable	Time 1			Time 2		
	Cluster 1	**Cluster 2**	**Cluster 3**	**Cluster 1**	**Cluster 2**	**Cluster 3**
Age at Diagnosis (years)	39.7 ± 3.8	38.8 ± 3.6	39 ± 3.8	39 ± 4	40.1 ± 3.1	38.7 ± 3.8
Race						
White/Caucasian	24 (77.4%)	25 (67.6%)	62 (73.8%)	43 (78.2%)	20 (69%)	48 (70.6%)
Black/African American	4 (12.9%)	8 (21.6%)	20 (23.8%)	8 (14.5%)	7 (24.1%)	17 (25%)
Other	3 (9.7%)	4 (10.8%)	2 (2.4%)	4 (7.3%)	2 (6.9%)	3 (4.4%)
Stage at Diagnosis						
I	15 (48.4%)	15 (40.5%)	33 (39.3%)	21 (28.2%)	8 (27.6%)	34 (50%)
II	12 (38.7%)	15 (40.5%)	36 (42.9%)	23 (41.8%)	15 (51.7%)	25 (36.8%)
III	4 (12.9)	7 (18.9%)	15 (17.9%)	11 (20%)	6 (20.7%)	9 (13.2%)
Type of Breast Cancer						
ER+	20 (64.5%)	25 (67.6%)	63 (75%)	44 (80%)	16 (55.2%)	48 (70.6%)
PR+	17 (54.8%)	25 (67.6%)	59 (70.2%)	44 (80%)	16 (55.2%)	41 (60.3%)
HER2+	6 (19.4%)	4 (10.8%)	27 (32.1%)	16 (29.1%)	4 (13.8%)	17 (25%)
(ER-/PR-/HER2-)	8 (25.8%)	9 (24.3%)	12 (14.3%)	5 (9.1%)	10 (34.5%)	14 (20.6%)
Cancer Treatment						
Radiation	20 (64.5%)	25 (67.6%)	54 (64.3%)	40 (72.7%)	22 (75.9%)	37 (54.4%)
Surgery – Lumpectomy	6 (19.4%)	11 (29.7%)	18 (21.4%)	14 (25.5%)	9 (31%)	12 (17.6%)
Surgery – Mastectomy	25 (80.6%)	26 (70.3%)	64 (76.2%)	41 (74.5%)	20 (69%)	54 (79.4%)
Chemotherapy	26 (83.9%)	31 (83.8%)	70 (83.3%)	43 (78.2%)	26 (89.7%)	58 (85.3%)
Chemotherapy – A/T	22 (71%)	18 (48.6%)	55 (65.5%)	31 (56.4%)	19 (65.5%)	45 (66.2%)
Hormone Therapy	17 (54.8%)	25 (67.6%)	62 (73.8%)	43 (78.2%)	15 (51.7%)	46 (67.6%)
Change in Menopause Status	9 (29%)	8 (21.6%)	23 (27.4%)	10 (18.2%)	8 (27.6%)	22 (32.4%)
Heart Age Characteristics						
Time 1 Body Mass Index (kg/m^2)	29.7 ± 5.9	27.8 ± 6.3	27.2 ± 7.2	28 ± 6.6	28.9 ± 6.6	27.3 ± 7
Time 1 Heart Age (years)	45.9 ± 11.6	41.7 ± 8.2	43.7 ± 11.5	43.4 ± 10.1	44.2 ± 10.3	43.6 ± 11.8
Time 1 Excess Heart Age (years)	6.1 ± 11	2.8 ± 6.6	4.1 ± 9.3	4.3 ± 8.5	3.9 ± 9.6	4.2 ± 9.7
Time 2 Body Mass Index (kg/m^2)	31.1 ± 6.4	29.2 ± 6.6	28.4 ± 7.4	29.6 ± 6.9	29.9 ± 6.4	28.5 ± 7.4
Time 2 Heart Age (years)	48.7 ± 13.9	45.4 ± 8.5	46.6 ± 13	46.9 ± 11.8	46.7 ± 8.2	46.6 ± 14
Time 2 Excess Heart Age (years)	6.1 ± 11	4.4 ± 7.2	5.6 ± 11.4	5.8 ± 10.1	4.6 ± 7.3	5.4 ± 11.7
Excess Heart Age Difference (years)	0 ± 11.7	1.7 ± 7.4	1.5 ± 7.3	1.5 ± 5.9	0.7 ± 9.5	1.2 ± 9.6

Time 1 clusters. Time 1 had three clusters based on selected Time 1 variables. Time 1 Cluster 1 comprised 31 records of young breast cancer survivors. The mean age was 39.7 ± 3.8 years. The average body mass index was 29.7 ± 5.9 years. The excess heart age was 6.1 years at Time 1 and Time 2, with no excess heart age change from time point to time point. Records indicated that 71% received anthracyclines and/or trastuzumab treatment.

Time 1 Cluster 2 comprised 37 records of young breast cancer survivors. The mean age was 38.8 ± 3.6 years. The average body mass index was 27.8 ± 6.3 kg/m^2. The excess heart age was 2.8 years at Time 1 and 4.4 years at Time 2, with an excess heart age difference of +1.6 years between time points. Records showed that 48.6% received anthracyclines and/or trastuzumab treatment.

Time 1 Cluster 3 comprised 84 records of young breast cancer survivors. The mean age was 39 ± 3.8 years. The average body mass index was 27.2 ± 7.2 kg/m^2. The excess heart age was 4.1 years at Time 1 and 5.6 years at Time 2, with an excess heart age difference of +1.5 years between time points. Records showed that 65.6% received anthracyclines and/or trastuzumab treatment.

Time 2 clusters. Time 2 had three clusters based on selected Time 2 variables. Time 2 Cluster 1 comprised 55 records of young breast cancer survivors. The mean age at diagnosis was 39 ± 3.9 years. The average body mass index was 28 ± 6.6 kg/m^2. The excess heart age was 4.3 years at Time 1 and 5.8 years at Time 2, with an excess heart age difference of +1.5 years between time points. Records documented that 56.4% received anthracyclines and/or trastuzumab treatment.

Time 2 Cluster 2 comprised 29 records of young breast cancer survivors. The mean age at diagnosis was 40.1 ± 3.1 years. The average body mass index was 28.9 ± 6.6 years. The excess heart age was 3.9 years at Time 1 and 4.6 years at Time 2, with an excess heart age difference of +0.7 year between time points. Records showed that 65.5% received anthracyclines and/or trastuzumab treatment.

Time 2 Cluster 3 comprised 68 records of young breast cancer survivors. The mean age at diagnosis was 38.7 ± 3.7 years. The average body mass index was 27.3 ± 7 years. The excess heart age was 4.2 years at Time 1 and 5.4 years at Time 2, with an excess heart age difference of +1.2 years between time points. Records indicated that 66.2% received anthracyclines and/or trastuzumab treatment.

Summary

Overall, young breast cancer survivors had an excess heart age of 4.2 years at diagnosis, which increased by 1.2 years at Time 2, although the increase was not statistically significant. Group A/T had an excess heart age of 4.3 years at diagnosis and similar excess heart age at two-year follow-up. Group No-A/T had an excess heart age of 4 years at diagnosis and exhibited a statistically significant increase of 3.1 years excess heart age at two-year follow-up. There were no statistically significant between-group differences at Time 1 or Time 2.

Multivariable linear regression identified factors that contribute to increase of excess heart age. At Time 1, stage was a predictor of increased excess heart age. Advancing age was associated with higher excess heart age at Time 1. At Time 2, hormone therapy and change in menopause status from premenopausal to

postmenopausal were predictors of excess heart age among young breast cancer survivors. Cluster analyses showed a distribution of excess heart age throughout clusters that were identified at Time 1 and Time 2. Percentage of breast cancer survivors receiving anthracyclines and/or trastuzumab varied across groups and characteristics were described. In summary, treatment with anthracyclines and/or trastuzumab did not influence excess heart age among this sample of young breast cancer survivors; however, hormone therapy and change in menopause status were significant predictors of increased excess heart age at two-year follow-up.

CHAPTER FIVE

DISCUSSION

This retrospective, two-year longitudinal study examined records of young breast cancer survivors for excess heart age at diagnosis and two-year follow-up and evaluated selected factors that contributed to increased excess heart age. To the investigator's knowledge, this study is one of the first to report cardiovascular disease risk using heart age among young breast cancer survivors and sets the foundation for future research within this age group. A discussion of major findings is summarized in this chapter. Strengths and limitations of the study, implications for advancing knowledge and policy, and future directions for research in this area are also addressed.

Summary of Major Findings

Excess Heart Age Among Young Breast Cancer Survivors

Overall sample. In this sample, records of young breast cancer survivors showed an average excess heart age of 4.2 years at diagnosis, which increased to 5.4 years at two-year follow-up. Although this difference was not statistically significant, there was an increase of 1.2 years. Studies indicate that heart failure may occur many years after treatment completion (Appel et al., 2012; Feola et al., 2011; Qin et al., 2015; Rayson et al., 2012; Yood et al., 2012). A seminal study found that cardiovascular disease risk was highest at seven years post treatment (Bradshaw et al., 2016). Since heart age does not

include risk factors of cancer treatment, the risk of cardiovascular disease within heart age may obscure actual risk influenced by treatment, since treatment is not taken into account. Regardless, an increase of 1.2 excess heart age years within two years for the overall sample may be clinically significant.

In comparison to cancer survivors from a representative sample in Alabama, the overall sample of young breast cancer survivors from this study had a similar body mass index (average of 28 kg/m^2). Excess heart age among cancer survivors was 14 years, but the sample was older (mean age of 61), included all types of cancer survivors, and was not specific to breast cancer (Vo, Raju, Kenzik, Landier, Scarabelli, & Meneses, 2017). Lifestyle changes may be necessary to prevent a trend in increasing excess heart age for young breast cancer survivors.

Group A/T. Group A/T had an average excess heart age of 4.3 years at diagnosis, which was slightly higher than the sample average. Notably, excess heart age did not increase at two-year follow-up. Prior research identified the risk of cardiovascular disease during treatment with anthracyclines and/or trastuzumab increased after one year post treatment completion (Appel et al., 2012; Bowles et al., 2012; Curigliano et al., 2012; Feola et al., 2011; Narayan et al., 2017; Qin et al., 2015; Rayson et al., 2012; Slamon et al., 2001; Yood et al., 2012). In examining the factors that comprise heart age, body mass index and blood pressure medication use had statistically significant increases. Yet, the culmination of factors calculated as heart age within Group A/T did not have a statistically significant increase from Time 1 to Time 2. While the overall excess heart age did not change, it is possible that damage to the heart was subclinical, as previous

research has demonstrated (Drafts et al., 2013), and the risk for cardiovascular disease could be much greater than excess heart age depicts.

Group No-A/T. At diagnosis, Group No-A/T had a slightly lower excess heart age than the total sample and Group A/T with a total excess of four years. However, Group No-A/T had a significantly higher excess heart age than Group A/T at Time 2 and showed an increase of 3.1 years in excess heart age from Time 1 to Time 2. The excess heart age was significantly higher in Group No-A/T than Group A/T despite no significant between-group differences in clinical characteristics. Group No-A/T had slightly higher averages in blood pressure, body mass index, and percentage of blood pressure medication use. Although not statistically significant, the differences were relevant enough to make the calculated heart age score significantly higher.

In comparison to Group A/T, records of Group No-A/T were older at diagnosis, had a higher percentage of hormone therapy use, and more ER+ and PR+ breast cancer types. The records of Group No-A/T were diagnosed with less advanced stages of breast cancer, with the majority diagnosed with Stage I (63%). Records of young breast cancer survivors who did not receive anthracyclines and/or trastuzumab within their cancer treatment regimen were more likely to be at higher risk for cardiovascular disease, as depicted by excess heart age. The between-group differences of excess heart age may not have been quite as large if heart age were able to capture treatment risk. Further exploration of excess heart age predictors was warranted, resulting in the identification of two significant predictors: hormone therapy and change in menopause status.

Impact of Hormone Therapy on Excess Heart Age

Menopause status and its reduction in estrogen levels are associated with increased cardiovascular disease risk (Rosano, Vitale, Marazzi, & Volterrani, 2007). For postmenopausal women, exclusive of breast cancer diagnosis, hormone replacement therapy increases estrogen levels and has positive outcomes on cardiovascular disease risk (Mosca et al., 2001; Rosano et al., 2007). Estrogen is associated with increases in high-density lipoprotein cholesterol, decreases in low-density lipoprotein cholesterol, and promotes clot formation (Mosca et al., 2001). Reduction in estrogen at menopause can lead to loss of estrogen's positive effects on the cardiovascular system. Hormone replacement therapy post natural menopause may improve the cardiovascular risk profile in women. However, hormone replacement therapy may have an inadvertent side effect with over-promotion of clot formation and may lead to stroke (Rosano et al., 2007).

For breast cancer survivors, hormone therapy reduces estrogen levels as cancer treatment includes tamoxifen or aromatase inhibitors. Tamoxifen and aromatase inhibitors are used to treat ER or PR positive breast cancer and are associated with clot formation, which may lead to stroke (Mehta et al., 2018; Saphner, Tormey, & Gray, 1991), similar to the aforementioned hormone replacement therapy post menopause. In this study, hormone therapy was a predictor of increased excess heart age. Since heart age is not specific to any one type of cardiovascular disease, the tool captured 10-year risk for developing the four major types of cardiovascular disease (i.e., coronary heart disease, cerebrovascular disease, peripheral artery disease, and heart failure). It is possible that heart age appropriately captured the 10-year risk for young breast cancer survivors to develop stroke, which is a type of cerebrovascular disease. A meta-analysis showed an

increased risk of stroke with tamoxifen (2.8%) compared to those treated with aromatase inhibitors (1.6%) (Amir et al., 2011). Yet, the benefits of tamoxifen often outweigh the risks because of its ability to successfully treat hormone-positive breast cancers and significantly reduce the risk of recurrence (Early Breast Cancer Trialists' Collaborative Group, 2011).

Hormone therapy is often given over an extended period of time (≥ 5 years). In this study, time points spanned two years. Therefore, many of the breast cancer survivors were likely still receiving hormone therapy and had not yet completed this treatment regimen. Breast cancer survivors are often considered to have "completed treatment" after primary regimens of chemotherapy, radiation, and/or surgery are complete, despite ongoing hormone therapy. With hormone therapy as a primary predictor of increased excess heart age, this risk may possibly increase at five years. Yet, national guidelines, including those developed by the National Comprehensive Cancer Network, American Cancer Society, American Society for Clinical Oncology, and American Heart Association, all recommend monitoring for cardiovascular disease risk at one-year post-treatment completion, which is often at approximately two-year follow-up from diagnosis. Additionally, the national guidelines are applicable to those treated with anthracyclines and/or trastuzumab. Currently, there are no recommendations for screening of cardiovascular disease specific to hormone therapy. With insufficient data to support the need for increased screening, healthcare providers may not identify subclinical cardiac changes that are often detected via screening. Early identification of cardiovascular disease often leads to early implementation of interventions and subsequently better prognoses.

Impact of Menopause Change on Excess Heart Age

Menopause has a different effect on breast cancer and cardiovascular disease risk (Mehta et al., 2018). Early menopause decreases the risk of developing breast cancer due to hormone changes and lower risk of developing hormone-dependent breast cancer. In contrast, early menopause is linked to increased risk of developing cardiovascular disease (Mehta et al., 2018). While research is limited on treatment-induced menopause, findings showed that records of young breast cancer survivors who entered early menopause had a higher excess heart age at two-year follow-up. Findings showed 14% of young breast cancer survivors were postmenopausal at diagnosis, which may be higher than the general population, as the average age of menopause is 51 years (The North American Menopause Society, 2017). The majority of the 14% postmenopausal women at breast cancer diagnosis were surgically-induced, which may or may not be related to patient's decision to lower the risk of breast cancer.

Approximately 27% of the sample changed from premenopausal to menopausal status at the time of two-year follow-up. This change in menopause status was a significant predictor of increased excess heart age. To examine this further, treatment was examined to determine any association with heightened risk for cardiovascular disease. Cyclophosphamide, which is an alkylating agent and common breast cancer treatment, is often associated with early menopause (Federal Drug Administration, 2013; Zhao et al., 2014). Findings indicated that cyclophosphamide was associated with menopause change; however, cyclophosphamide was not shown to be associated with excess heart age. Research indicates that risk of developing cardiovascular disease as a result of treatment with cyclophosphamide is low (Curigliano et al., 2012; Goldberg et al., 1986).

Therefore, cyclophosphamide may have had an indirect effect on cardiovascular disease risk. For this sample of young breast cancer survivors, menopause change at an early age (≤ 47 at two-year follow-up) was associated with increased excess heart age and may lead to premature development of cardiovascular disease.

Excess Heart Age

Bardia and colleagues (2012) used excess heart age to demonstrate cardiovascular disease risk. The authors utilized a sample of postmenopausal older breast cancer survivors (mean age = 60 years), and results showed an average excess heart age of seven years. In comparison, Group No-A/T had a similar excess heart age of seven years but were an average of 20 years younger. This increased risk suggests that young breast cancer survivors in this sample may develop cardiovascular disease prematurely.

Several studies in the literature review suggest that anthracyclines and/or trastuzumab were associated with increased cardiovascular disease risk (Appel et al., 2012; Bowles et al., 2012; Curigliano et al., 2012; Feola et al., 2011; Narayan et al., 2017; Qin et al., 2015; Rayson et al., 2012; Slamon et al., 2001; Yood et al., 2012). However, no identified study examined the association of excess heart age with cancer treatment. This study suggested that treatment with anthracyclines and/or trastuzumab did not increase excess heart age. However, there is a paucity of research examining the effects of anthracyclines and/or trastuzumab on cardiovascular disease risk in young breast cancer survivors. Pediatric literature shows that childhood cancer patients who receive anthracyclines treatment are at high risk for heart failure even up to 45 years after treatment completion (Mulrooney et al., 2009). Anthracyclines are used in both pediatric

and breast cancer survivors. Young breast cancer survivors (compared to older) may be more likely to develop late effects due to the long periods of survivorship similar to those of pediatric cancer survivors.

Risk Factors

Although treatment with anthracyclines and/or trastuzumab did not increase excess heart age, this study did identify statistically significant increases in several risk factors for cardiovascular disease similar to those found in identified studies in the literature (Obi et al., 2014; Weaver et al., 2013).

Weight gain. At breast cancer diagnosis, 65% of the sample were overweight or obese. At two-year follow-up, this percentage increased to 70%, with over 43% categorized as obese. Moreover, 22% of the entire sample had a weight gain of at least 10% of their breast cancer diagnosis weight. Overweight at body mass index ≥ 25 or obesity at ≥ 30 are major risk factors for cardiovascular disease (Poirier et al., 2006). Among Group No-A/T, this percentage was higher; 28% of the records in Group No-A/T documented at least 10% weight gain. This study did not examine the association between chemotherapy and weight gain; however, weight gain is a well-documented side effect of chemotherapy (Demark-Wahnefried et al., 2001; Demark-Wahnefried et al., 1993; Vance, Mourtzakis, McCargar, & Hanning, 2011) and more significant in premenopausal women with treatment-induced menopause (Goodwin et al., 1999; Vance et al., 2011).

Body mass index increased significantly within two years for the entire sample and in both groups. Obesity is a major risk factor for cardiovascular disease because

obesity is associated with atherosclerosis and increased metabolic demand that subsequently increases cardiac workload. As with any overworked muscle, overworking the heart can increase muscle mass and subsequently lead to a multitude of cardiac problems associated with obesity such as cardiomegaly, cardiac hypertrophy, cardiomyopathy, and/or heart failure (Poirier et al., 2006).

Blood pressure. The percentage of breast cancer survivors placed on antihypertensive medication nearly doubled for both groups at two-year follow-up. While blood pressure was not statistically different at the two time points, blood pressure medication likely disguised increases in blood pressure. Some studies have examined the use of blood pressure medication such as beta blockers or angiotensin-converting enzyme (ACE) inhibitors as methods to reduce the risk of anthracycline- and/or trastuzumab-induced cardiotoxicity (Cardinale et al., 2010; Kalay et al., 2006; Kaya et al., 2013; Seicean et al., 2013), but data are not sufficient to suggest implementation of this medical intervention. Research is currently ongoing to further explore the impact of antihypertensive medication on lowering the risk of cardiovascular disease (National Cancer Institute, 2018).

Use of dexrazoxane for prevention of anthracycline-induced cardiotoxicity is accepted and approved by the Federal Drug Administration (Bhave, Shah, Akhter, & Rosen, 2014; Federal Drug Administration, 2012; Kalam & Marwick, 2013). However, dexrazoxane is not recommended for all. It is recommended for women who receive at least 300 mg/m^2 because of its potential to reduce the effectiveness of cancer treatment and to increase risk of secondary cancers (Federal Drug Administration, 2012). In this sample, there was no documented use of dexrazoxane, potentially due to the expected

lower risk of cardiovascular disease in young women. Further research on antihypertensive medication use in breast cancer survivors is ongoing (National Cancer Insitute, 2016).

Diabetes. The percentage of diabetes in both groups was relatively low. Approximately 5% of records documented a history of diabetes, and three more records showed diagnosis by two-year follow-up in this sample. Diabetes is a major risk factor for cardiovascular disease and is a component of the heart age calculations (Mehta et al., 2018). While the percentage was low for this sample, risk factors for comorbidities such as obesity overlap with cancer diagnoses, and increasing body mass index also increases young breast cancer survivors' risk for developing diabetes.

Smoking. Smoking is a significant risk factor for cardiovascular disease (Benjamin et al., 2018). In this sample, the percentage of smokers was similar at Time 1 and Time 2. Records suggested that those who were smokers at diagnosis did not quit by their follow-up visit. Weaver and colleages (2013) reported that 15-30% of cancer survivors who were at risk for cardiovascular disease did not discuss health promotion with their healthcare providers. Health promotion education often consists of smoking cessation. Smoking is a modifiable risk factor that contributes to more than 480,000 deaths in the U.S. annually (Benjamin et al., 2018). Smoking cessation is warranted to reduce the risk of cardiovascular disease among young breast cancer survivors.

Limitations

Several limitations should be noted. First, the retrospective design limited data to medical records. The time period from 2012 to 2015 was selected due to the implementation of electronic medical records in the UAB Health System. Medical records first became electronic in 2011 (UAB Reporter, 2011). Therefore, data prior to this time were excluded due to lack of access to paper medical records. The time frame and the selection of young breast cancer survivors contributed to a small sample size of 152 records.

Second, due to the retrospective nature of this study, other variables of interest such as education were either not available or inconsistently charted. Other variables of interest such as dose of anthracyclines would have contributed to the study but were also inconsistently reported in the data. Large areas of missing data were noted for anthracyclines dose, radiation dose, and physical activity, and these variables were excluded. The researcher was unable to collect additional data related to these variables.

Third, heart age does not directly measure the development of cardiovascular disease. The young breast cancer survivors in this sample did not have cardiovascular disease. Therefore, this study did not measure outcomes, rather an estimate or probability of developing cardiovascular disease.

Fourth, there may be treatment selection bias. That is, the sample was divided into Group A/T and Group No-A/T based on treatment type. Findings showed that the group who received anthracyclines and/or trastuzumab had more advanced stages of breast cancer. Treatment selection bias may potentially have occurred, as women who receive anthracyclines at a young age are often diagnosed at later stages. However, Group A/T

did not have a change in excess heart age. Breast cancer survivors diagnosed with earlier stages may receive less aggressive forms of cancer treatment and may be at a lower risk for developing cardiovascular disease than women who have more advanced cancers and more aggressive treatments.

Finally, generalization of the study is limited. This sample excluded young breast cancer survivors in the age range 18 to 29 because heart age is applicable to ≥ 30 years. While breast cancer diagnoses under age 30 are possible but rare, the range of age at 30 to 44 years may be not be fully representative of young breast cancer survivors.

Strengths

Likewise, this dissertation has several potential strengths. This study is one of the first to measure excess heart age among young breast cancer survivors at two time points, before and after breast cancer treatment. Two-year follow-up after diagnosis is when national guidelines recommend that cancer survivors be screened for cardiovascular risk (one-year post-treatment completion). Therefore, this study was able to examine the cardiovascular disease risk at the estimated time when it is recommended that breast cancer survivors be screened per national guidelines.

Further, this study examined treatment risk in relation to cancer treatment, specifically anthracyclines and trastuzumab, for which cardiovascular guidelines exist. Although it is known that anthracyclines and trastuzumab have potentially adverse effects of cardiotoxicity, not every patient treated with the drugs will develop a cardiovascular disease in their lifetime. The findings for this study provide a unique perspective for understanding cardiovascular disease risk. Comparing survivors treated with

anthracyclines and/or trastuzumab with those who did not receive anthracyclines and/or trastuzumab may lead to a better understanding of the cardiovascular risk profiles of patients who receive such drugs.

The Framingham Risk Score is a well-established tool to estimate the 10-year probability of developing a cardiovascular disease. Heart age uses the Framingham Risk Score to put the probability estimation in context of age to facilitate communication between patients and healthcare providers. Use of heart age may be indicated for oncology patient care to increase patients' and laypersons' understanding of cardiovascular disease risk. Additionally, heart age may increase understanding of cardiovascular disease risk for investigators, possibly cancer researchers, who are unfamiliar with cardiovascular risk models.

Implications

This study has implications for clinical practice, potential health policy, and future research.

Clinical Practice Implications

Clinical implications from this study include increasing patient education on the potential cardiovascular effects of cancer treatment, including hormone therapy and early menopause. Young women under 45 years of age are expected to be healthier and have fewer comorbidities than older women (such as those greater than 65 years at diagnosis). The treatment decision-making process likely does not account for cardiovascular disease risk, as the major concern is to treat the breast cancer and prolong survival.

Without patient education, young women may not consider the late effects of cancer treatment at the beginning of this life-altering experience of diagnosis. This study suggests that many young breast cancer survivors have increased excess heart age, and therefore, implications for this research study may include testing the use of heart age to increase knowledge and understanding of cardiovascular disease risk and promote heart-healthy lifestyles. Moreover, women who have high excess heart age at either diagnosis or at the follow-up period at the end of breast cancer treatment may require increased and/or regular long-term cardiovascular screening.

A second clinical implication is the possible need for a cardio-oncology subspecialty across all disciplines. Greater numbers of cardio-oncology clinics across the United States show the need for cardiac care among cancer survivor populations. Cardio-oncology organizations and research grants have become more prevalent, and cardio-oncology physician training programs are growing (Johnson, Steingart, & Carver, 2017). These advances and the growing body of cardio-oncology research pose the question of need for a cardio-oncology nursing subspecialty, in which nurses can be trained to understand cardiac needs of cancer patients, within cardio-oncology clinics and also in traditional cardiology and oncology settings. To increase patient education on cardiovascular late effects, healthcare providers must be aware of these possible issues.

Policy Implications

National guidelines for cardiovascular disease risk among breast cancer survivors were described in Chapter 2. In summary, the three U.S.-based organizations that recommend short-term guidelines applicable for breast cancer survivors include the

American Society for Clinical Oncology, American Heart Association, and National Comprehensive Cancer Network (Mehta et al., 2018; National Comprehensive Cancer Network, 2018; Runowicz et al., 2016). These guidelines apply to breast cancer survivors treated with either anthracyclines or trastuzumab, and recommendations suggest screening at six months and/or one year post-treatment completion. Research is growing to support the guidelines; however, continuing cardio-oncology research would better inform guidelines. Policy implications from this study include developing guidelines that address the impact of 1) hormone therapy, 2) treatment-induced menopause, and 3) obesity on cardiovascular disease risk among young breast cancer survivors.

Future Directions

The next step to advance the field of cardio-oncology research is to examine long-term risk for cardiovascular disease and incidence among young breast cancer survivors. Due to diagnosis at a young age and resulting longer potential survival than older women, young breast cancer survivors may have higher incidence of cardiovascular disease years or decades after treatment completion. Therefore, future research should apply similar methodological techniques in order to fully understand cardiovascular disease risk in young women. In this study, anthracyclines and trastuzumab were not associated with increased excess heart age at two-year follow-up after diagnosis. Examining long-term risk may provide context to other factors that influence cardiovascular disease risk in young women.

Further research is warranted to identify whether 1) heart age adequately captures cardiovascular disease risk in young breast cancer survivors or 2) if young breast cancer

survivors may not be susceptible to or may have protective mechanisms against excess heart age as a result of anthracyclines and/or trastuzumab treatment. Further examination of factors that increase cardiovascular disease risk, particularly long-term, could inform a risk model that includes cancer treatment risk factors in order to better estimate cardiovascular disease risk in breast cancer survivors. For example, heart age uses 10-year risk, and data from research that identifies incidence of cardiovascular disease at 10 years post diagnosis in breast cancer survivors may be able to inform inclusion of treatment risk factors in heart age.

Conclusions

Cardiotoxicity as a result of cancer treatment has become a research priority for many organizations including funding agencies and the National Cancer Institute. Increasing research in this area has led to the development of clinical guidelines for short-term screening for cardiovascular disease. Drugs such as anthracyclines and trastuzumab are commonly associated with cardiovascular disease, specifically heart failure. Research in this area of cardio-oncology has been primarily in older breast cancer survivors. Cancer treatment has advanced and leads to longer life expectancies. In young women, risk for cardiovascular disease may be higher than in older women because of potentially longer survivorship periods. Therefore, this study aimed to examine cardiovascular disease risk measured by excess heart age among young breast cancer survivors.

Findings suggested that young breast cancer survivors in this sample have a high excess heart age, or 10-year cardiovascular disease risk, at two-year follow-up. An excess heart age of 5.4 years may be clinically relevant because this suggests that a breast cancer

survivor diagnosed at 40 years old has a heart similar to one of a 45-year-old. Although breast cancer diagnosis is the primary concern, late effects of cancer treatment should also be addressed. Findings showed that young breast cancer survivors treated with anthracyclines and trastuzumab did not have a significant increase in excess heart age at two-year follow-up. Rather, those who did not receive anthracyclines and/or trastuzumab showed an increase of 3.1 years for an excess heart age of 7.1 years at two-year follow-up. Using multivariable linear regression, predictors of excess heart age at two-year follow-up included change in menopausal status and treatment with hormone therapy.

The findings from this study were both comparable to and different from previous research. Although anthracyclines and trastuzumab were not predictors of increased excess heart age, it is possible that subclinical changes to the heart occurred. Heart age does not incorporate treatment-related risk factors and did not account for possible damage from anthracyclines and trastuzumab. Findings showed that young breast cancer survivors treated with hormone therapy or who experienced treatment-induced menopause were more likely to have a higher cardiovascular disease risk. Therefore, implications include the need for guidelines to address the cardiovascular disease risks of hormone therapy and treatment-induced menopause.

Progression of cardio-oncology research will ultimately lead to improving the lives of breast cancer survivors by reducing cardiovascular disease morbidity and mortality. Early identification of cardiovascular disease can lead to improved prognosis. Yet, additional long-term data are needed to support increased screening if warranted. This study has evaluated cardiovascular disease risk of young breast cancer survivors,

added new knowledge to the literature on this topic, and set the tone for future research to ultimately improve the lives of young women experiencing breast cancer.

REFERENCES

American Cancer Society. (2016). *Cancer treatment & survivorship facts & figures 2016-2017*. Atlanta, GA: American Cancer Society.

American Cancer Society. (2017). *Breast cancer facts & figures 2017-2018*. Atlanta, GA: American Cancer Society.

Amin, M. B., Greene, F. L., Edge, S. B., Compton, C. C., Gershenwald, J. E., Brookland, R. K., ... Winchester, D. P. (2017). The Eighth Edition AJCC cancer staging manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA: A Cancer Journal for Clinicians, 67*(2), 93-99. doi:10.3322/caac.21388

Amir, E., Seruga, B., Niraula, S., Carlsson, L., & Ocaña, A. (2011). Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: A systematic review and meta-analysis. *Journal of the National Cancer Institute, 103*(17), 1299-1309. doi:10.1093/jnci/djr242

Appel, J. M., Zerahn, B., Møller, S., Christensen, H. M., Søgaard, P., Ejlertsen, B., . . . Nielsen, D. L. (2012). Long-term heart function after adjuvant epirubicin chemotherapy for breast cancer. *Acta Oncologica, 51*(8), 1054-1061. doi:10.3109/0284186X.2012.702920

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, 35*(8), 893-911. doi:10.1200/jco.2016.70.5400

Armenian, S. H., Xu, L., Ky, B., Sun, C., Farol, L. T., Pal, S. K., . . . Chao, C. (2016). Cardiovascular disease among survivors of adult-onset cancer: A community-based retrospective cohort study. *Journal of Clinical Oncology, 34*(10), 1122-1130. doi:10.1200/jco.2015.64.0409

Artinian, N. T., Fletcher, G. F., Mozaffarian, D., Kris-Etherton, P., Van Horn, L., Lichtenstein, A. H., . . . Burke, L. E. (2010). Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: A scientific statement from the American Heart Association. *Circulation, 122*(4), 406-441. doi:10.1161/CIR.0b013e3181e8edf1

Bandera, E. V., Chandran, U., Hong, C. C., Troester, M. A., Bethea, T. N., Adams-Campbell, L. L., . . . Rosenberg, L. (2015). Obesity, body fat distribution, and risk of breast cancer subtypes in African American women participating in the AMBER Consortium. *Breast Cancer Research and Treatment, 150*(3), 655-666. doi:10.1007/s10549-015-3353-z

Bardia, A., Arieas, E. T., Zhang, Z., Defilippis, A., Tarpinian, K., Jeter, S., . . . Stearns, V. (2012). Comparison of breast cancer recurrence risk and cardiovascular disease incidence risk among postmenopausal women with breast cancer. *Breast Cancer Research and Treatment, 131*(3), 907-914. doi:10.1007/s10549-011-1843-1

Benjamin, E. J., Virani, S. S., Callaway, C. W., Chamberlain, A. M., Chang, A. R., Cheng, S., ... de Ferranti, S. D. (2018). Heart disease and stroke statistics—2018 update:

A report from the American Heart Association. *Circulation, 137*(12), e67-e492. doi:10.1161/CIR.0000000000000558

Berry, G. J., & Jorden, M. (2005). Pathology of radiation and anthracycline cardiotoxicity. *Pediatric Blood & Cancer, 44*(7), 630-637. doi:10.1002/pbc.20346

Bhatia, N., Lenihan, D., Sawyer, D. B., & Lenneman, C. G. (2016). Getting the SCOOP-Survey of cardiovascular outcomes from oncology patients during survivorship. *American Journal of the Medical Sciences, 351*(6), 570-575. doi:10.1016/j.amjms.2016.01.025

Bhave, M., Shah, A. N., Akhter, N., & Rosen, S. T. (2014). An update on the risk prediction and prevention of anticancer therapy-induced cardiotoxicity. *Current Opinion in Oncology, 26*(6), 590-599. doi:10.1097/CCO.0000000000000132

Boekel, N. B., Schaapveld, M., Gietema, J. A., Russell, N. S., Poortmans, P., Theuws, J. C., . . . van Leeuwen, F. E. (2016). Cardiovascular disease risk in a large, population-based cohort of breast cancer survivors. *International Journal Radiation Oncololgy*Biology*Physics, 94*(5), 1061-1072. doi:10.1016/j.ijrobp.2015.11.040

Boerman, L. M., Berendsen, A. J., van der Meer, P., Maduro, J. H., Berger, M. Y., & de Bock, G. H. (2014). Long-term follow-up for cardiovascular disease after chemotherapy and/or radiotherapy for breast cancer in an unselected population. *Supportive Care in Cancer, 22*(7), 1949-1958. doi:10.1007/s00520-014-2156-9

Boerman, L. M., Maass, S., van der Meer, P., Gietema, J. A., Maduro, J. H., Hummel, Y. M., . . . Berendsen, A. J. (2017). Long-term outcome of cardiac function in a

population-based cohort of breast cancer survivors: A cross-sectional study. *European Journal of Cancer, 81*, 56-65. doi:10.1016/j.ejca.2017.05.013

Bowles, E. J., Wellman, R., Feigelson, H. S., Onitilo, A. A., Freedman, A. N., Delate, T., . . . Wagner, E. H. (2012). Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: A retrospective cohort study. *Journal of the National Cancer Institute, 104*(17), 1293-1305. doi:10.1093/jnci/djs317

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. doi:10.1097/ede.0000000000000394

Burnett, D., Kluding, P., Porter, C., Fabian, C., & Klemp, J. (2013). Cardiorespiratory fitness in breast cancer survivors. *Springerplus, 2*(1), 68. doi:10.1186/2193-1801-2-68

Burstein, H. J., Temin, S., Anderson, H., Buchholz, T. A., Davidson, N. E., Gelmon, K. E., ... Stearns, V. (2014). Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. *Journal of Clinical Oncology*, *32*(21), 2255-2269. doi:10.1200/JCO.2013.54.2258

Cardinale, D., Colombo, A., Lamantia, G., Colombo, N., Civelli, M., De Giacomi, G., ... Cipolla, C. M. (2010). Anthracycline-induced cardiomyopathy: Clinical relevance and response to pharmacologic therapy. *Journal of the American College of Cardiology, 55*(3), 213-220. doi:10.1016/j.jacc.2009.03.095

Caro-Moran, E., Fernandez-Lao, C., Galiano-Castillo, N., Cantarero-Villanueva, I., Arroyo-Morales, M., & Diaz-Rodriguez, L. (2016). Heart rate variability in breast

cancer survivors after the first year of treatments: A case-controlled study. *Biological Research for Nursing, 18*(1), 43-49. doi:10.1177/1099800414568100

Centers for Disease Control and Prevention. (2016). Breast cancer in young women. Retrieved from https://www.cdc.gov/cancer/dcpc/resources/features/breastcanceryoungwomen/index.htm

Chaosuwannakit, N., D'Agostino, R., Jr., Hamilton, C. A., Lane, K. S., Ntim, W. O., Lawrence, J., . . . Hundley, W. G. (2010). Aortic stiffness increases upon receipt of anthracycline chemotherapy. *Journal of Clinical Oncology, 28*(1), 166-172. doi:10.1200/jco.2009.23.8527

Children's Oncology Group. (2013). Heart link: Healthy living after treatment of childhood cancer (v. 4.0). Retrieved from http://survivorshipguidelines.org/pdf/healthlinks/English/heart_health_Eng.pdf

Children's Oncology Group. (2018). Children's Oncology Group: About us. Retrieved from https://www.childrensoncologygroup.org/

Chotenimitkhun, R., D'Agostino, R., Jr., Lawrence, J. A., Hamilton, C. A., Jordan, J. H., Vasu, S., . . . Hundley, W. G. (2015). Chronic statin administration may attenuate early anthracycline-associated declines in left ventricular ejection function. *Canadian Journal of Cardiology, 31*(3), 302-307. doi:10.1016/j.cjca.2014.11.020

Christian, A. H., O'Malley, D., Barac, A., Miller, S. M., & Hudson, S. V. (2017). Cardiovascular risk and communication among early stage breast cancer survivors. *Patient Education and Counseling, 100*(7), 1360-1366. doi:10.1016/j.pec.2017.02.010

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. Hillsdale, NJ: Lawrence Earlbaum Associates.

Curigliano, G., Cardinale, D., Suter, T., Plataniotis, G., De Azambuja, E., Sandri, M. T., ... & ESMO Guidelines Working Group. (2012). Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Annals of Oncology*, 23(Suppl. 7), vii155-vii166. doi:10.1093/annonc/mds293

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: The Framingham Heart Study. *Circulation, 117*(6), 743-753.

D'Agostino, R. B., Wolf, P. A., Belanger, A. J., & Kannel, W. B. (1994). Stroke risk profile: Adjustment for antihypertensive medication. The Framingham Study. *Stroke, 25*(1), 40-43. doi:10.1161/01.STR.25.1.40

Darby, S. C., Ewertz, M., McGale, P., Bennet, A. M., Blom-Goldman, U., Brønnum, D., ... Jensen, M. B. (2013). Risk of ischemic heart disease in women after radiotherapy for breast cancer. *New England Journal of Medicine, 368*(11), 987-998. doi:10.1056/NEJMoa1209825

Dawber, T. R., Meadors, G. F., & Moore Jr., F. E. (1951). Epidemiological approaches to heart disease: The Framingham Study. *American Journal of Public Health and the Nation's Health, 41*(3), 279-286.

de Azambuja, E., Ameye, L., Diaz, M., Vandenbossche, S., Aftimos, P., Bejarano Hernandez, S., . . . Piccart-Gebhart, M. (2015). Cardiac assessment of early breast cancer patients 18 years after treatment with cyclophosphamide-, methotrexate-,

fluorouracil- or epirubicin-based chemotherapy. *European Journal of Cancer, 51*(17), 2517-2524. doi:10.1016/j.ejca.2015.08.011

Demark-Wahnefried, W., Peterson, B. L., Winer, E. P., Marks, L., Aziz, N., Marcom, P. K., …Rimer, B. K. (2001). Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. *Journal of Clinical Oncology, 19(*9), 2381-2389. doi:10.1200/JCO.2001.19.9.2381

Demark-Wahnefried, W., Winer, E. P., & Rimer, B. K. (1993). Why women gain weight with adjuvant chemotherapy for breast cancer. *Journal of Clinical Oncology, 11*(7), 1418-1429. doi:10.1200/JCO.1993.11.7.1418

Doyle, J. J., Neugut, A. I., Jacobson, J. S., Grann, V. R., & Hershman, D. L. (2005). Chemotherapy and cardiotoxicity in older breast cancer patients: A population-based study. *Journal of Clinical Oncology, 23*(34), 8597-8605. doi:10.1200/JCO.2005.02.5841

Drafts, B. C., Twomley, K. M., D'Agostino, R., Lawrence, J., Avis, N., Ellis, L. R., . . . Hundley, W. G. (2013). Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. *JACC: Cardiovascular Imaging, 6*(8), 877-885. doi:10.1016/j.jcmg.2012.11.017

Early Breast Cancer Trialists' Collaborative Group. (2011). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: Patient-level meta-analysis of randomised trials. *The Lancet, 378*(9793), 771-784. doi:10.1016/S0140-6736(11)60993-8

Enright, K. A., & Krzyzanowska, M. K. (2010). Control of cardiovascular risk factors among adult cancer survivors: A population-based survey. *Cancer Causes Control, 21*(11), 1867-1874. doi:10.1007/s10552-010-9614-6

Federal Drug Adminstration. (2006). Epirubicin hydrochloride for injection. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/050807lbl.pdf

Federal Drug Administration. (2010a). Doxorubicin hydrochloride for injection, USP. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/050467s070lbl.pdf

Federal Drug Adminstration. (2010b). Herceptin (trastuzumab) label. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf

Federal Drug Adminstration. (2012). Zinecard (dexrazoxane for injection). Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020212s013lbl.pdf

Federal Drug Adminstration. (2013). Cyclophosphamide for injection, USP. Cyclophosphamide tablets, USP. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/012142s109lbl.pdf

Feola, M., Garrone, O., Occelli, M., Francini, A., Biggi, A., Visconti, G., . . . Merlano, M. (2011). Cardiotoxicity after anthracycline chemotherapy in breast carcinoma: Effects on left ventricular ejection fraction, troponin I and brain natriuretic peptide. *International Journal of Cardiology, 148*(2), 194-198. doi:10.1016/j.ijcard.2009.09.564

Florescu, M., Cinteza, M., & Vinereanu, D. (2013). Chemotherapy-induced cardiotoxicity. *Maedica, 8*(1), 59.

Franco, V. I., & Lipshultz, S. E. (2015). Cardiac complications in childhood cancer survivors treated with anthracyclines. *Cardiology in the Young, 25*(S2), 107-116. doi:10.1017/S1047951115000906

Gallucci, G., Coccaro, M., Storto, G., Lapadula, L., Tartarone, A., Nappi, A., . . . Aieta, M. (2010). The clinical impact of a cardiologic follow-up in breast cancer survivors: An observational study. *International Journal of Immunopathology Pharmacology, 23*(4), 1221-1227. doi:10.1177/039463201002300426

Goff, D. C., Lloyd-Jones, D. M., Bennett, G., Coady, S., D'Agostino, R. B., Gibbons, R., ... & Robinson, J. G. (2014). 2013 ACC/AHA guideline on the assessment of cardiovascular risk. *Circulation, 129*(25, Suppl. 2), S49-S73. doi:10.1161/01.cir.0000437741.48606.98

Goldberg, M. A., Antin, J. H., Guinan, E., & Rappeport, J. M. (1986). Cyclophosphamide cardiotoxicity: An analysis of dosing as a risk factor. *Blood, 68*(5), 1114-1118.

Goodwin, P. J., Ennis, M., Pritchard, K. I., Trudeau, M., & Hood, N. (1999). Risk of menopause during the first year after breast cancer diagnosis. *Journal of Clinical Oncology, 17*(8), 2365-2370. doi:10.1200/jco.1999.17.8.2365

Guimaraes, S. L., Brandao, S. C., Andrade, L. R., Maia, R. J., & Markman Filho, B. (2015). Cardiac sympathetic hyperactivity after chemotherapy: Early sign of cardiotoxicity? *Arquivos Brasileiros de Cardiologia, 105*(3), 228-234. doi:10.5935/abc.20150075

Haque, R., Prout, M., Geiger, A. M., Kamineni, A., Thwin, S. S., Avila, C., ... Yood, M. U. (2014). Comorbidities and cardiovascular disease risk in older breast cancer survivors. *The American Journal of Managed Care, 20*(1), 86.

Haque, R., Yood, M. U., Geiger, A. M., Kamineni, A., Avila, C. C., Shi, J., ... Quinn, V. P. (2011). Long-term safety of radiotherapy and breast cancer laterality in older survivors. *Cancer Epidemiology and Prevention Biomarkers, 20*(10), 2120-2126. doi:10.1158/1055-9965.EPI-11-0348

Harris, J. R., Lippman, M. E., Osborne, C. K., & Morrow, M. (2012). *Diseases of the breast*. Philadelphia, PA: Lippincott Williams & Wilkins.

Ho, E., Brown, A., Barrett, P., Morgan, R. B., King, G., Kennedy, M. J., & Murphy, R. T. (2010). Subclinical anthracycline- and trastuzumab-induced cardiotoxicity in the long-term follow-up of asymptomatic breast cancer survivors: A speckle tracking echocardiographic study. *Heart, 96*(9), 701-707. doi:10.1136/hrt.2009.173997

Hooning, M. J., Botma, A., Aleman, B. M., Baaijens, M. H., Bartelink, H., Klijn, J. G., . . . 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. doi:10.1093/jnci/djk064

Howlader, N., Noone, A., Krapcho, M., Miller, D., Bishop, K., Kosary, C., . . . Cronin, K. (Eds.) (2017). SEER cancer statistics review, 1975-2014. Retrieved from https://seer.cancer.gov/csr/1975_2014/

Hunt, S. A., Abraham, W. T., Chin, M. H., Feldman, A. M., Francis, G. S., Ganiats, T. G., …Yancy, C. W. (2009). 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults. *Circulation, 119,* e391-e479. doi:10.1161/CIRCULATIONAHA.109.192065

Hunt, S. A., Baker, D. W., Chin, M. H., Cinquegrani, M. P., Feldman, A. M., Francis, G. S., . . . Smith, S. C. (2001). ACC/AHA guidelines for the evaluation and

management of chronic heart failure in the adult: Executive summary. *Journal of the American College of Cardiology, 38*(7), 2101-2113. doi:10.1016/S0735-1097(01)01683-7

Inanc, M. T., Karadavut, S., Aytekin, M., Duran, A. O., Derya, M., Akpek, M., . . . Inanc, M. (2016). The relationship between plasma hyaluronan levels and anthracycline-related cardiotoxicity in breast cancer patients. *International Journal of Cardiology, 218*, 246-251. doi:10.1016/j.ijcard.2016.05.054

Institute of Medicine and National Research Council. (2006). *From cancer patient to cancer survivor: Lost in transition*. Washington, DC: The National Academies Press. doi:10.17226/11468

Johnson, M. N., Steingart, R., & Carver, J. (2017). How to develop a cardio-oncology fellowship. *Heart Failure Clinics, 13*(2). 361-366. doi:10.1016/j.hfc.2016.12.012

Johnson, N. L., Giarelli, E., Lewis, C., & Rice, C. E. (2013). Genomics and autism spectrum disorder. *Journal of Nursing Scholarship, 45*(1), 69-78. doi:10.1111/j.1547-5069.2012.01483.x

Jones, L. W., Haykowsky, M., Peddle, C. J., Joy, A. A., Pituskin, E. N., Tkachuk, L. M., . . . Mackey, J. R. (2007). Cardiovascular risk profile of patients with HER2/neu-positive breast cancer treated with anthracycline-taxane-containing adjuvant chemotherapy and/or trastuzumab. *Cancer Epidemiology Biomarkers & Prevention, 16*(5), 1026-1031. doi:10.1158/1055-9965.epi-06-0870

Kalam, K., & Marwick, T. H. (2013). Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: A systematic review and meta-analysis. *European Journal of Cancer, 49*(13), 2900-2909. doi:10.1016/j.ejca.2013.04.030

Kalay, N., Basar, E., Ozdogru, I., Er, O., Cetinkaya, Y., Dogan, A., ... Inanc, T. (2006). Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *Journal of the American College of Cardiology, 48*(11), 2258-2262. doi:10.1016/j.jacc.2006.07.052

Kaya, M. G., Ozkan, M., Gunebakmaz, O., Akkaya, H., Kaya, E. G., Akpek, M., ... Berk, V. (2013). Protective effects of nebivolol against anthracycline-induced cardiomyopathy: A randomized control study. *International Journal of Cardiology, 167*(5), 2306-2310. doi:10.1016/j.ijcard.2012.06.023

Koelwyn, G. J., Lewis, N. C., Ellard, S. L., Jones, L. W., Gelinas, J. C., Rolf, J. D., . . . Eves, N. D. (2016). Ventricular-arterial coupling in breast cancer patients after treatment with anthracycline-containing adjuvant chemotherapy. *Oncologist, 21*(2), 141-149. doi:10.1634/theoncologist.2015-0352

Krieger, N. (1994). Epidemiology and the web of causation: Has anyone seen the spider? *Social Science & Medicine*, *39*(7), 887-903. doi:10.1016/0277-9536(94)90202-X

Landier, W., Bhatia, S., Eshelman, D. A., Forte, K. J., Sweeney, T., Hester, A. L., ... Freeman, C. R. (2004). Development of risk-based guidelines for pediatric cancer survivors: The Children's Oncology Group long-term follow-up guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. *Journal of Clinical Oncology*, *22*(24), 4979-4990. doi:10.1200/JCO.2004.11.032

Levy, W. C., Mozaffarian, D., Linker, D. T., Sutradhar, S. C., Anker, S. D., Cropp, A. B., ... Pitt, B. (2006). The Seattle heart failure model. *Circulation, 113*(11), 1424-1433. doi:10.1161/CIRCULATIONAHA.105.584102

Liu, Y., Nguyen, N., & Colditz, G. A. (2015). Links between alcohol consumption and breast cancer: A look at the evidence. *Women's Health, 11*(1), 65-77.

Lloyd-Jones, D. M., Hong, Y., Labarthe, D., Mozaffarian, D., Appel, L. J., Van Horn, L., ... Arnett, D. K. (2010). Defining and setting national goals for cardiovascular health promotion and disease reduction: The American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation, 121*(4), 586-613. doi:10.1161/CIRCULATIONAHA.109.192703

Lloyd-Jones, D. M., Wilson, P. W., Larson, M. G., Beiser, A., Leip, E. P., D'Agostino, R. B., & Levy, D. (2004). Framingham risk score and prediction of lifetime risk for coronary heart disease. *American Journal of Cardiology, 94*(1), 20-24. doi:10.1016/j.amjcard.2004.03.023

MacMahon, B., & Pugh, T. F. (1970). *Epidemiology: Principles and methods*. Boston, MA: Little, Brown and Company.

Matthews, R., & Moore, A. (2013). Babies are still dying of SIDS. *The American Journal of Nursing, 113*(2), 59-64. doi:10.1097/01.NAJ.0000426692.19202.5a

Mehta, L. S., Watson, K. E., Barac, A., Beckie, T. M., Bittner, V., Cruz-Flores, S., ... Piña, I. L. (2018). Cardiovascular disease and breast cancer: Where these entities intersect: A scientific statement from the American Heart Association. *Circulation, 137*(8), e30-e66. doi:10.1161/CIR.0000000000000556

Mertens, A. C., Yasui, Y., Neglia, J. P., Potter, J. D., Nesbit Jr, M. E., Ruccione, K., ... Robison, L. L. (2001). Late mortality experience in five-year survivors of childhood and adolescent cancer: The Childhood Cancer Survivor Study. *Journal of Clinical Oncology, 19*(13), 3163-3172.

Mosca, P. C., Herrington, D. M., Mendelsohn, M. E., Pasternak, R. C., Robertson, R. M., Schenck-Gustafsson, K., …Wenger, N. K. (2001). Hormone replacement therapy and cardiovascular disease. *Circulation, 104*, 499-503. doi:10.1161/hc2901.092200

Mullan, F. (1985). Seasons of survival: Reflections of a physician with cancer. *New England Journal of Medicine, 313*(4), 270-273. doi:10.1056/nejm19507253130421

Mulrooney, D. A., Yeazel, M. W., Kawashima, T., Mertens, A. C., Mitby, P., Stovall, M., ... Leisenring, W. M. (2009). Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: Retrospective analysis of the Childhood Cancer Survivor Study cohort. *British Medical Journal, 339*, b4606. doi:10.1136/bmj.b4606

Murtagh, G., Lyons, T., O'Connell, E., Ballot, J., Geraghty, L., Fennelly, D., . . . Walshe, J. M. (2016). Late cardiac effects of chemotherapy in breast cancer survivors treated with adjuvant doxorubicin: 10-year follow-up. *Breast Cancer Research and Treatment, 156*(3), 501-506. doi:10.1007/s10549-016-3781-4

Narayan, H. K., Finkelman, B., French, B., Plappert, T., Hyman, D., Smith, A. M., . . . Ky, B. (2017). Detailed echocardiographic phenotyping in breast cancer patients: Associations with ejection fraction decline, recovery, and heart failure symptoms over 3 years of follow-up. *Circulation, 135*(15), 1397-1412. doi:10.1161/circulationaha.116.023463

National Cancer Institute. (2015). NCI Dictionaries. Retrieved from https://www.cancer.gov/publications/dictionaries

National Cancer Institute. (2017). Heart attack, stroke risk may be elevated following cancer diagnosis. Retrieved from https://www.cancer.gov/news-events/cancer-currents-blog/2017/heart-attack-stroke-risk-cancer

National Cancer Institute. (2018). Cancer treatment-related cardiotoxicity. Retrieved from https://epi.grants.cancer.gov/cardiotoxicity/

National Coalition for Cancer Survivorship. (1986). National Coalition for Cancer Survivorship. Retrieved from https://www.canceradvocacy.org/about-us/our-history/

National Comprehensive Cancer Network. (2017). NCCN clinical practice guidelines in oncology breast cancer: Version 3.2017. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

National Comprehensive Cancer Network. (2018). NCCN clinical practice guidelines in oncology survivorship: Version 3.2017. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf

Nichols, H. B., Trentham-Dietz, A., Egan, K. M., Titus-Ernstoff, L., Holmes, M. D., Bersch, A. J., . . . Newcomb, P. A. (2009). Body mass index before and after breast cancer diagnosis: Associations with all-cause, breast cancer, and cardiovascular disease mortality. *Cancer Epidemiology, Biomarkers & Prevention, 18*(5), 1403-1409. doi:10.1158/1055-9965.epi-08-1094

The North American Menopause Society. (2017). *Menopause guidebook* (8th ed.). Pepper Pike, OH: The North American Menopause Society.

Obi, N., Gornyk, D., Heinz, J., Vrieling, A., Seibold, P., Chang-Claude, J., & Flesch-Janys, D. (2014). Determinants of newly diagnosed comorbidities among breast

cancer survivors. *Journal of Cancer Survivorship, 8*(3), 384-393. doi:10.1007/s11764-013-0338-y

Patnaik, J. L., Byers, T., DiGuiseppi, 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. doi:10.1186/bcr2901

Piccirillo, J. F., Vlahiotis, A., Barrett, L. B., Flood, K. L., Spitznagel, E. L., & Steyerberg, E. W. (2008). The changing prevalence of comorbidity across the age spectrum. *Critical Reviews in Oncology/Hematology, 67*(2), 124-132. doi:10.1016/j.critrevonc.2008.01.013

Poirier, P., Giles, T. D., Bray, G. A., Hong, Y., Stern, J. S., Pi-Sunyer, X., & Eckel, R. H. (2006). Obesity and cardiovascular disease: Pathophysiology, evaluation, and effect of weight loss. *Circulation, 113*, 898-918.

Polit, D. F., & Beck, C. T. (2017). *Nursing research: Generating and assessing evidence for nursing practice* (10th ed). London, England: Lippincott Williams & Wilkins.

Qin, A., Thompson, C. L., & Silverman, P. (2015). Predictors of late-onset heart failure in breast cancer patients treated with doxorubicin. *Journal of Cancer Survivorship, 9*(2), 252-259. doi:10.1007/s11764-014-0408-9

Rayson, D., Suter, T. M., Jackisch, C., van der Vegt, S., Bermejo, B., van den Bosch, J., . . . Richel, D. J. (2012). Cardiac safety of adjuvant pegylated liposomal doxorubicin with concurrent trastuzumab: A randomized phase II trial. *Annals of Oncology, 23*(7), 1780-1788. doi:10.1093/annonc/mdr519

Reulen, R. C., Winter, D. L., Frobisher, C., Lancashire, E. R., Stiller, C. A., Jenney, M. E., ... British Childhood Cancer Survivor Study Steering Group. (2010). Long-term cause-specific mortality among survivors of childhood cancer. *Journal of the American Medical Association, 304*(2), 172-179. doi:10.1001/jama.2010.923

Romond, E. H., Perez, E. A., Bryant, J., Suman, V. J., Geyer Jr, C. E., Davidson, N. E., ... Swain, S. M. (2005). Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *New England Journal of Medicine*, *353*(16), 1673-1684. doi:10.1056/NEJMoa052122

Rosano, G. C., Vitale, C., Marazzi, G., & Volterrani, M. (2007). Menopause and cardiovascular disease: The evidence. *Climacteric, 10*(Suppl. 1), 1019-1024. doi:10.1080/13697130601114917

Ruhl, J. L., Callaghan, C., Hurlbut, A., Ries, L. A. G., Adamo, P., Dickie, L., & Schussler, N. (2018). *Summary stage 2018: Codes and coding instructions*. Bethesda, MD: National Cancer Institute.

Runowicz, C. D., Leach, C. R., Henry, N. L., Henry, K. S., Mackey, H. T., Cowens-Alvarado, R. L., ... Hurria, A. (2016). American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. *CA: A Cancer Journal for Clinicians, 66*(1), 43-73. doi:10.3322/caac.21319

Sadurska, E. (2015). Current views on anthracycline cardiotoxicity in childhood cancer survivors. *Pediatric Cardiology, 36*(6), 1112-1119. doi:10.1007/s00246-015-1176-7

Saphner, T., Tormey, D. C., & Gray, R. (1991). Venous and arterial thrombosis in patients who received adjuvant therapy for breast cancer. *Journal of Clinical Oncology, 9*(2), 286-294. doi:10.1200/JCO.1991.9.2.286

Seicean, S., Seicean, A., Alan, N., Plana, J. C., Budd, G. T., & Marwick, T. H. (2013). Cardioprotective effect of β-Adrenoceptor blockade in patients with breast cancer undergoing chemotherapy. *Circulation: Heart Failure, 6*(3), 420-426. doi:10.1161/CIRCHEARTFAILURE.112.000055

Siegel, R. L., Miller, K. D., & Jemal, A. (2018). Cancer statistics, 2018. *CA: A Cancer Journal for Clinicians, 68*(1), 7-30. doi:10.3322/caac.21442

Shankar, S. M., Marina, N., Hudson, M. M., Hodgson, D. C., Adams, M. J., Landier, W., ... Steinberger, J. (2008). Monitoring for cardiovascular disease in survivors of childhood cancer: Report from the Cardiovascular Disease Task Force of the Children's Oncology Group. *Pediatrics, 121*(2), e387-e396. doi:10.1542/peds.2007-0575

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). doi:10.1093/jnci/dju232

Shum, K., Solivan, A., Parto, P., Polin, N., & Jahangir, E. (2016). Cardiovascular risk and level of statin use among women with breast cancer in a cardio-oncology clinic. *Ochsner Journal, 16*(3), 217-224.

Šimůnek, T., Štěrba, M., Popelová, O., Adamcová, M., Hrdina, R., & Geršl, V. (2009). Anthracycline-induced cardiotoxicity: Overview of studies examining the roles of

oxidative stress and free cellular iron. *Pharmacological Reports, 61*(1), 154-171. doi:10.1016/S1734-1140(09)70018-0

Slamon, D. J., Leyland-Jones, B., Shak, S., Fuchs, H., Paton, V., Bajamonde, A., ... Baselga, J. (2001). Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *New England Journal of Medicine*, *344*(11), 783-792. doi:10.1056/NEJM200103153441101

Sulpher, J., Mathur, S., Graham, N., Crawley, F., Turek, M., Johnson, C., . . . Dent, S. (2015). Clinical experience of patients referred to a multidisciplinary cardiac oncology clinic: An observational study. *Journal of Oncology, 2015*, 671232. doi:10.1155/2015/671232

Tamimi, R. M., Spiegelman, D., Smith-Warner, S. A., Wang, M., Pazaris, M., Willett, W. C., ... Hunter, D. J. (2016). Population attributable risk of modifiable and nonmodifiable breast cancer risk factors in postmenopausal breast cancer. *American Journal of Epidemiology, 184*(12), 884-893. doi:10.1093/aje/kww145

Tan, C. H., Chao, T. T., Liu, J. C., Lin, C. H., Huang, Y. S., Chang, C. M., . . . Lee, C. C. (2016). Breast cancer therapy and age difference in cardiovascular disease risks: A population-based cohort study in Taiwan. *Taiwan Journal of Obstetretics and Gynecology, 55*(1), 98-103. doi:10.1016/j.tjog.2015.12.005

Turnbull, C., & Rahman, N. (2008). Genetic predisposition to breast cancer: Past, present, and future. *Annual Review of Genomics and Human Genetics, 9*, 321-345. doi:10.1146/annurev.genom.9.081307.164339

UAB Reporter. (2011). UAB Medicine launches one patient record for all clinics. Retrieved from http://www.uab.edu/reporter/know-more/patient-care/item/1333-uab-medicine-launches-one-patient-record-for-all-clinics

U.S. Cancer Statistics Working Group. (2017). United States cancer statistics: 1999-2014 incidence and mortality web-based report. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute. Retrieved from www.cdc.gov/uscs

U.S. Department of Health & Human Services. (1979). *The Belmont Report*. Washington, D.C. Retrieved from http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html#xbound

U.S. Preventive Services Task Force. (2016). Final recommendation statement: Breast cancer screening. *Annals of Internal Medicine, 164*(4), 279-296. Retrieved from https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/breast-cancer-screening1

Vance, V., Mourtzakis, M., McCargar, L., & Hanning, R. (2011). Weight gain in breast cancer survivors: Prevalence, pattern and health consequences. *Obesity Reviews, 12*(4), 282-294. doi:10.1111/j.1467-789X.2010.00805.x

Vo, J.B., Raju, D., Kenzik, K., Landier, W., Scarabelli, T., & Meneses, K. (2017). Comparing heart age among Alabama residents with and without a history of cancer. *Cancer Epidemiology, Biomarkers, & Prevention, 26*(2). doi: 10.1158/1538-7755.DISP16-B16

Weaver, K. E., Foraker, R. E., Alfano, C. M., Rowland, J. H., Arora, N. K., Bellizzi, K. M., . . . Aziz, N. M. (2013). Cardiovascular risk factors among long-term

survivors of breast, prostate, colorectal, and gynecologic cancers: A gap in survivorship care? *Journal of Cancer Survivorship, 7*(2), 253-261. doi:10.1007/s11764-013-0267-9

Wilson, P. W., D'Agostino, R. B., Levy, D., Belanger, A. M., Silbershatz, H., & Kannel, W. B. (1998). Prediction of coronary heart disease using risk factor categories. *Circulation, 97*(18), 1837-1847.

Wong, F. L., Bhatia, S., Landier, W., Francisco, L., Leisenring, W., Hudson, M. M., ... Lyman, G. H. (2014). Cost-effectiveness of the children's oncology group long-term follow-up screening guidelines for childhood cancer survivors at risk for treatment-related heart failure. *Annals of Internal Medicine, 160*(10), 672-683. doi:10.7326/M13-2498

World Health Organization. (2017). *WHO Model List of Essential Medicines* (20th ed.). Retrieved from http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf?ua=1

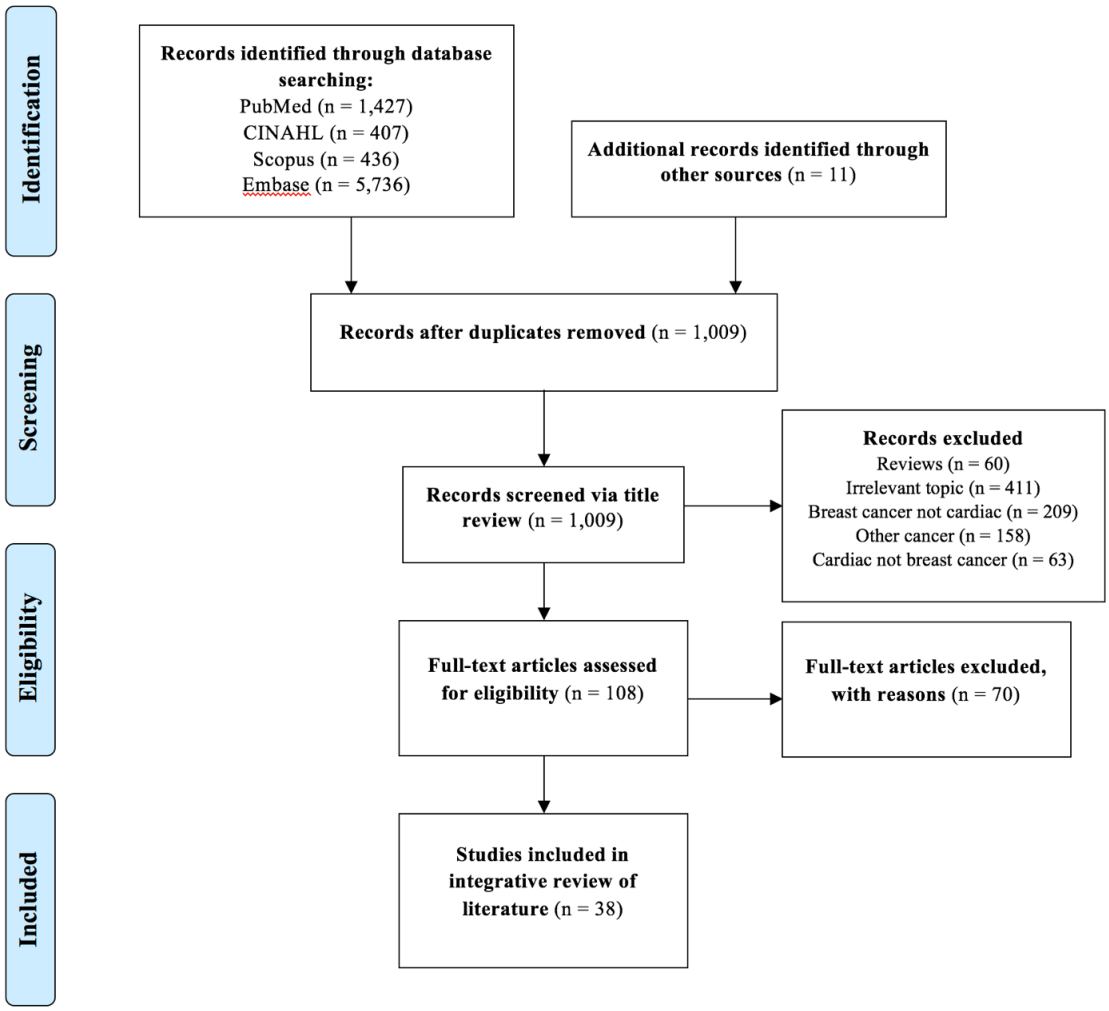
Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Drazner, M. H., ... Johnson, M. R. (2013). 2013 ACCF/AHA guideline for the management of heart failure. *Circulation, 128*(16). doi:10.1161/CIR.0b013e31829e8776

Yood, M. U., Wells, K. E., Alford, S. H., Dakki, H., Beiderbeck, A. B., Hurria, A., . . . Oliveria, S. A. (2012). Cardiovascular outcomes in women with advanced breast cancer exposed to chemotherapy. *Pharmacoepidemiology Drug Safety, 21*(8), 818-827. doi:10.1002/pds.323

Zhao J., Liu J., Chen K., Wang, Y., Yang, T., Deng, H., …Su, F. (2014). What lies behind chemotherapy-induced amenorrhea for breast cancer patients: A meta-analysis. *Breast Cancer Research and Treatment, 145*(1), 113-128. doi: 10.1007/s10549-014-2914-x

APPENDIX A

PRISMA DIAGRAM


Identification
Screening
Eligibility
Included
Records identified through database searching:
PubMed (n = 1,427)
CINAHL (n = 407)
Scopus (n = 436)
Embase (n = 5,736)
Additional records identified through other sources (n = 11)
Records after duplicates removed (n = 1,009)
Records screened via title review (n = 1,009)
Records excluded
Reviews (n = 60)
Irrelevant topic (n = 411)
Breast cancer not cardiac (n = 209)
Other cancer (n = 158)
Cardiac not breast cancer (n = 63)
Full-text articles assessed for eligibility (n = 108)
Full-text articles excluded, with reasons (n = 70)
Studies included in integrative review of literature (n = 38)

APPENDIX B

UAB INSTITUTIONAL REVIEW BOARD APPROVAL

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on November 8, 2021. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

Principal Investigator: Vo, Jacqueline B

Co-Investigator(s):

Protocol Number: **X170328008**

Protocol Title: *Cardiovascular Disease Risk Among Breast Cancer Survivors*

The IRB reviewed and approved the above named project on 4/17/17. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.

IRB Approval Date: 4-17-17

Date IRB Approval Issued: 4/17/17

IRB Approval No Longer Valid On: 4/17/18

HIPAA Waiver Approved?: Yes

Expedited Reviewer
Member - Institutional Review Board
for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

PI: Vo, Jacqueline B

Protocol # X170328008

UAB IRB Approval of
Waiver of Informed Consent and/or Waiver of Patient Authorization

☑ **Approval of Waiver of Informed Consent to Participate in Research.** The IRB reviewed the proposed research and granted the request for waiver of informed consent to participate in research, based on the following findings:

1. The research involves no more than minimal risk to the subjects.
2. The research cannot practicably be carried out without the waiver.
3. The waiver will not adversely affect the rights and welfare of the subjects.
4. When appropriate, the subjects will be provided with additional pertinent information after participation.

Check one:
- ☑ **and** Waiver of Authorization (below)
- ☐ **or** Waiver of Authorization (below)
- ☐ Waiver of Authorization not applicable

☑ **Approval of Waiver of Patient Authorization to Use PHI in Research.** The IRB reviewed the proposed research and granted the request for waiver of patient authorization to use PHI in research, based on the following findings:

1. The use/disclosure of PHI involves no more than minimal risk to the privacy of individuals
   - i. There is an adequate plan to protect the identifiers from improper use and disclosure.
   - ii. There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention that is otherwise required by law.
   - iii. There is an assurance that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted.
2. The research cannot practicably be conducted without the waiver or alteration.
3. The research cannot practicably be conducted without access to and use of the PHI.

—OR—

☐ **Full Review**

The IRB reviewed the proposed research at a **convened meeting** at which a majority of the IRB was present, including one member who is not affiliated with any entity conducting or sponsoring the research, and not related to any person who is affiliated with any of such entities. The waiver of authorization was approved by the majority of the IRB members present at the meeting.

Date of Meeting

Signature of Chair, Vice-Chair or Designee

Date

☑ **Expedited Review**

The IRB used an **expedited review procedure** because the research involves no more than minimal risk to the privacy of the individuals who are the subject of the PHI for which use or disclosure is being sought. The review and approval of the waiver of authorization were carried out by the Chair of the IRB, or by one of the Vice-Chairs of the IRB as designated by the Chair of the IRB.

4-17-17
Date of Expedited Review

Signature of Chair, Vice-Chair or Designee

Date 4-17-17

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APPENDIX C

DATA COLLECTION FORM

FORM 101: Data Collection Form

Dissertation Title: Cardiovascular disease risk among breast cancer survivors

Initials of Person Collecting:	Date completed:	Date Amended:
Patient DOB:	Patient ID#:	MRN#:

#	Data Element	Value	Instructions/Comments
1	**Gender**	[ ] Male [ ] Female	
2	**Race**	[ ] White/Caucasian [ ] Black/African American [ ] American Indian/Alaska Native [ ] Native Hawaiian/Pacific Islander [ ] Asian [ ] Other (_____)	
3	**Ethnicity**	[ ] Hispanic [ ] Non-Hispanic	
4	**Marital Status**	[ ] Never Married [ ] Married [ ] Separated [ ] Divorced [ ] Widowed [ ] Other (_____)	
5	**Employment**	[ ] Employed full time [ ] Employed part time [ ] Unemployed or seeking work [ ] Temporary medical leave [ ] Student [ ] Homemaker [ ] Disabled [ ] Retired [ ] Other (_____)	

#	Data Element	Value	Instructions/Comments
6	**Date of breast cancer diagnosis**	L ____ /____ /_____ R ____ /____ /_____	
7	**Stage of breast cancer at diagnosis**	[ ] Stage 1 [ ] Stage 2 [ ] Stage 3	
8	**Type of breast Cancer**	[ ] ER + [ ] ER – [ ] PR + [ ] PR – [ ] HER2 + [ ] HER2 –	
9	**Genetic Testing**	[ ] BRCA 1 + [ ] BRCA 2 + [ ] Negative for both	
10	**First Degree Family History**	[ ] Breast Cancer [ ] Cardiovascular disease: [ ] Stroke [ ] Heart failure [ ] Coronary artery disease [ ] Peripheral disease [ ] Neither	
11	**Treatment:** Radiation	[ ] Yes [ ] No	If yes, answer #9 If no, skip to #10
12	**Treatment:** Radiation	Date initiated: _____ Date completed: _____ Total dose (Gy): _____ Field: _____	
13	**Treatment:** Surgery	[ ] Lumpectomy [ ] Mastectomy [ ] None	
14	**Treatment:** Surgery – Reconstruction	[ ] Yes [ ] No	

#	Data Element	Value	Instructions/Comments
15	**Treatment:** Systemic Therapy	[ ] Chemotherapy (_____) [ ] Immunotherapy (_____) [ ] None	
16	**Treatment:** Cardiotoxic Systemic therapy	[ ] Anthracycline (dose _____) [ ] Trastuzumab (dose _____) [ ] None	Duration?
17	**Treatment:** Hormone Therapy	[ ] Yes, Type (_____) [ ] No	Duration?
18	**Time 1**	Date: ___ /___ / ____	
19	**Time 1:** Age	_____ years	
20	**Time 1:** Heart rate	_____bpm	
21	**Time 1:** Blood pressure	Systolic: _____ Diastolic: _____	
22	**Time 1:** Antihypertensive medication	[ ] Yes (type: _____) [ ] No	
23	**Time 1:** Body metrics	Height: _____ ft Weight: _____ lbs BMI: _____kg/m^2	
24	**Time 1:** Smoking history	[ ] Current [ ] Former (Last _____) [ ] Never [ ] Unknown	
25	**Time 1:** Diabetes history	[ ] Yes [ ] No	If yes, complete #26 & #27 If no, skip to #28
26	**Time 1:** Diabetes history	[ ] Type I [ ] Type II	

#	Data Element	Value	Instructions/Comments
27	**Time 1:** Diabetes history	Medication: _____	
28	**Time 1:** Exercise	[ ] Yes [ ] No	
29	**Time 1:** Exercise	Type: _____ Duration: _____ Times per week: _____	
30	**Time 1:** Alcohol	[ ] Never [ ] Beer: (Amt _____) [ ] Liquor: (Amt _____) [ ] Wine: (Amt _____)	
31	**Time 1:** Menopause	[ ] Premenopausal [ ] Perimenopausal [ ] Postmenopausal [ ] Unknown	
32	**Time 1:** Last Menstrual Period	___ /___ / ____	
33	**Time 1:** Birth Control	[ ] Yes, type (_____) [ ] No [ ] Unknown	
34	**Time 1:** Other medication history		
35	**Time 1:** Other medical history		
36	**Time 2**	Date: ___ /___ / ____	
37	**Time 2:** Age	_____ years	

#	Data Element	Value	Instructions/Comments
38	**Time 2:** Heart rate	_____bpm	
39	**Time 2:** Blood pressure	Systolic: _____ Diastolic: _____	
40	**Time 2:** Antihypertensive medication	[ ] Yes (type: _____) [ ] No	
41	**Time 2:** Body metrics	Height: _____ ft Weight: _____ lbs BMI: _____m^2	
42	**Time 2:** Smoking history	[ ] Current [ ] Former (Last _____) [ ] Never [ ] Unknown	
43	**Time 2:** Diabetes history	[ ] Yes [ ] No	If yes, complete #26 & #27 If no, skip to #28
44	**Time 2:** Diabetes history	[ ] Type I [ ] Type II	
45	**Time 2:** Diabetes history	Medication: _____	
46	**Time 2:** Exercise	[ ] Yes [ ] No	
47	**Time 2:** Exercise	Type: _____ Duration: _____ Times per week: _____	
48	**Time 2:** Alcohol	[ ] Never [ ] Beer: (Amt _____) [ ] Liquor: (Amt _____) [ ] Wine: (Amt _____)	
49	**Time 2:** Menopause	[ ] Premenopausal [ ] Perimenopausal [ ] Postmenopausal [ ] Unknown	

#	Data Element	Value	Instructions/Comments
50	**Time 2:** Last Menstrual Period	___ /___ / ____	
51	**Time 2:** Birth Control	[ ] Yes, type (_____) [ ] No [ ] Unknown	
52	**Time 2:** Other medication history		Any new since Time 1?
53	**Time 2:** Other medical history		Any new since Time 1?