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Risk and Manifestation of Cardiovascular Disease Among Cancer Caregivers: Effects of Stress, Depression, and Gender

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Family members and friends who provide unpaid care to an ill relative tend to experience higher levels of stress, more depressive symptoms, and greater vulnerability to disease than the general population (Pinquart & Sörensen, 2003). This study was to determine whether cancer caregivers experience an increased risk of cardiovascular diseases (CVD) and to examine the extent to which psychosocial variables related to the disease outcomes. A total of 896 caregivers participated in a national survey at two years after the diagnosis of their relative with cancer (T1), and 607 participated again at five years post-diagnosis (T2) provided self-report data on study variables. Raw prevalence rates for CVD risk conditions (hypertension, obesity, high cholesterol, and diabetes) and CVD manifestations (angina, coronary heart disease, cardiac arrest, congestive heart failure, heart attack, and stroke) were adjusted for age, race/ethnicity, and gender for comparison with similarly adjusted U.S. population rates. Comparisons showed that although cancer caregivers have comparable cardiovascular health at both two (T1) and five (T2) years post-diagnosis, caregivers had significant increases in prevalence of all conditions studied between observations.

Next, the extent to which three psychosocial variables related to the development of CVD risk conditions and manifestations was investigated using hierarchical logistic

regression analysis. Subjective caregiving stress at T1 marginally significantly predicted development of any of the CVD risk factors studied by T2. Greater levels of depressive symptoms at T1 significantly predicted the development of several risk conditions and manifestations at T2: obesity, any of the CVD manifestation conditions studied, and irregular heartbeat/CHF/heart attack. Greater depressive symptoms at T1 also aggravated the adverse effect of subjective caregiving stress on development of two CVD manifestations: development of any CVD manifestation studied and irregular heartbeat/ pacemaker/murmur specifically. Men were more likely to develop the CVD risk factor of high cholesterol and CVD manifestation of cardiac arrest/CHF/heart attack by T2 than women. Gender was not a significant moderator of the link between subjective caregiving stress and CVD outcomes. Findings suggest that while cancer caregivers as a whole have comparable cardiovascular health to the national population through five years after their relative's initial cancer diagnosis, distressed caregivers during earlier survivorship phase may be at a higher risk of developing CVDs later in the caregiving trajectory.

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Chapter 1: Overview

Informal family caregivers of patients report higher stress than the general population, and they are more vulnerable to disease than non-caregivers (Schulz, Visintainer, & Williamson, 1990; Vitaliano et al., 2002; Vitaliano, Zhang, & Scanlan, 2003). While much work has been conducted on the impact of caring for elderly frail persons and dementia patients, relatively little work to date exists on the health risks encountered from caregiving for patients with cancer. Cancer caregiving, a typically more acute and intensive caregiving experience, is in many ways unique from other kinds of caregiving, suggesting that previous research on the health effects of caregiving may not generalize to cancer caregivers (Clipp & George, 1993; Kim & Schulz, 2008). This study was unique in that it examined long-term health outcomes, focusing on risk of cardiovascular disease (CVD), in cancer caregivers compared to the general population and identified psychosocial predictors of CVD development.

Aims and Hypotheses

Caregivers report greater stress than the general population, and stress has been shown to negatively impact the cardiovascular system in numerous ways, including increasing blood pressure and circulating levels of cytokines (Pinquart & Sörensen, 2003; Schneiderman, Ironson, & Siegel, 2005). As cancer caregivers have been shown to have higher risk for several cardiovascular disease manifestations, such as coronary heart disease (CHD) and stroke (Ji, Zöller, Sundquist, & Sundquist, 2012), the present study hypothesized that cancer caregivers would be at greater risk for CVD risk conditions and manifestations than the general population (aim one; Hypothesis 1). This was evaluated by comparing self-reported standardized rates of CVD risk conditions and manifestations

in a national caregiver sample to those from the nationally-representative National Health and Nutrition Examination Survey (NHANES). For this study, CVD "risk conditions" referred to conditions that have been linked to increased risk for development of cardiovascular diseases; CVD risk conditions studied were hypertension, high cholesterol, obesity, and diabetes. CVD "manifestations" were defined in this study as diagnosis of a cardiovascular disease; CVD manifestations included in this study were angina/coronary heart disease (CHD), heart attack/congestive heart failure (CHF)/cardiac arrest, irregular heartbeat/pacemaker/murmur, and stroke. The CVD risk conditions and manifestations of caregivers were collected two (T1) and five (T2) years after the care recipient's cancer diagnosis. NHANES data in corresponding years were selected for comparison.

In addition to comparing CVD conditions of cancer caregivers with a nationally representative sample, this study examined the extent to which subjective caregiving stress at T1 predicted increased development of CVD risk conditions and manifestations in cancer caregivers three years later (T2) and whether depressive symptomatology and gender moderated this relationship (aim two). The present study hypothesized that increased subjective caregiving stress would be related to higher risk of developing CVD risk conditions and manifestations (Hypothesis 2.1). It was also hypothesized that greater depressive symptomatology (Hypothesis 2.2) and male gender (Hypothesis 2.3) would aggravate the adverse effects of subjective caregiving stress on developing CVD risk conditions and manifestations.

Results

Aim one: Prevalence of CVD risk conditions and manifestations in cancer caregivers. Prevalence rates of the CVD risk conditions and manifestations in both the caregiver sample and NHANES data were adjusted according to age, race/ethnicity, and gender, and then compared using standardized rate ratios. Results showed that caregivers overall had comparable cardiovascular health (CVD risks and manifestations) to the U.S. population. Specifically, no differences were found between the two samples on adjusted rates of hypertension, diabetes, stroke, angina/CHD, or cardiac arrest/CHF/heart attack at both T1 and T2. At T1, however, caregivers reported lower rates of high cholesterol and obesity than the NHANES sample. Three years later at T2, caregivers reported lower rates of only obesity than national rates. Findings therefore did not support Hypothesis 1 that caregivers would have poorer cardiovascular health than the U.S. population.

Aim two: Evaluating psychosocial variables as correlates of disease prevalence and as predictors of disease development.

Correlates of disease prevalence at T1. The extent to which three covariates (age, race/ethnicity, and patient functioning) and three demographic (gender) and psychosocial variables (subjective caregiving stress and depressive symptomology) correlated with the CVD risk conditions and manifestations at T1 was examined. Results showed that older age was associated with greater likelihood of receiving treatment for any of the CVD risk conditions studied, specifically hypertension and high cholesterol, and any of the CVD manifestations studied, specifically angina/CHD and cardiac arrest/CHF/heart attack. Women were more likely than men to have received treatment for obesity. Higher subjective stress from caregiving was associated with greater likelihood of receiving treatment for any of the CVD manifestations, specifically angina/CHD, cardiac

arrest/CHF/heart attack, and stroke. Finally, experiencing greater depressive symptoms was associated with greater likelihood of receiving treatment for any of the CVD risk conditions studied, specifically hypertension and obesity.

Predictors of disease development. The extent to which demographic and psychosocial variables measured at T1 prospectively predicted and moderated development of CVD risk conditions and manifestations by T2 was examined. Among covariates, older age at T1 predicted greater risk of developing high cholesterol at T2, and marginally significantly related to developing any of the CVD risk conditions studied. Minorities were more likely to develop any of the CVD risk conditions by T2. Poorer patient functioning at T1 predicted greater risk of experiencing cardiac arrest/CHF/heart attack by T2, and related marginally significantly to developing angina/CHD.

Among study predictors, higher subjective caregiving stress at T1 was marginally significantly related to developing any of the CVD risk conditions by T2, providing weak partial support for Hypothesis 2.1. Greater depressive symptoms at T1 predicted greater likelihood of developing obesity and any of the CVD manifestations studied, specifically irregular heartbeat/a condition requiring a pacemaker/murmur, by T2. Men were more likely than women to develop high cholesterol and cardiac arrest/CHF/heart attack by T2.

Depressive symptomatology moderated the relationship between subjective caregiving stress and development of CVD outcomes. Specifically, for caregivers who reported greater depressive symptoms, caregiving stress increased likelihood of developing any of the CVD manifestations studied and specifically irregular heartbeat/ pacemaker/murmur by T2. The opposite relationship existed for caregivers who reported

fewer depressive symptoms, where caregiving stress decreased the likelihood of developing those conditions—these findings provided partial support for Hypothesis 2.2. Finally, gender did not moderate the effect of subjective caregiving stress on the development of CVD outcomes, failing to support Hypothesis 2.3.

Implications

The findings of this study add to current literature by providing evidence of cancer caregivers' health in both the transition away from active caregiving and through extended survivorship. Although caregivers overall had comparable cardiovascular health to the national population, the significant rise in prevalence rates among caregivers for all the CVD risk conditions and manifestations over the three year period between T1 and T2 is alarming. The findings emphasize the importance of physicians and clinicians to attend to caregivers' mental and physical health needs alongside their cancer survivors', particularly beyond the early survivorship phase.

Furthermore, caregivers who had elevated depressive symptoms and experienced greater subjective stress from caregiving were at the most significant risk for developing CVD manifestations. Findings suggest that depressive symptomatology and subjective caregiving stress must be critical therapeutic targets of clinical interventions designed to ameliorate long-term CVD health risks in cancer caregivers.

Limitations of the study include small racial/ethnic minority representation, low power, and use of self-reported data only, which should be addressed in future studies. Future studies should also seek to add biobehavioral data to determine underlying mechanisms of the link of caregiving stress to cardiovascular health. Despite limitations, this study uniquely adds to literature by providing a clearer understanding of which CVD

conditions are more vulnerable to psychosocial variables pertinent to cancer caregiving, which has implication for public health interventions for cancer caregivers.

Chapter 2: Introduction

Informal caregivers of cancer patients provide invaluable instrumental and emotional support to their ill loved ones at sometimes great cost to their own physical and psychological health (Pinquart & Sörensen, 2003; Schulz et al., 1990). Study of health outcomes for caregivers has been of increasing interest in psychological research, but few have examined cancer caregivers specifically. With data accumulating that cancer caregivers are at increased risk for cardiovascular diseases (Ji et al., 2012), understanding how this risk compares to the general population as well as potential mechanisms of this increased risk is an important next research step, helping to direct future preventative medicine services for this growing and vulnerable population.

Cardiovascular Diseases

Cardiovascular diseases (CVDs) continue to be the leading cause of death in America and account for 30 percent of worldwide all-cause mortality (Murphy, Xu, & Kochanek, 2012). CVDs are a cluster of diseases of the heart and blood vessel system, including CHD, cerebrovascular disease, and congenital heart diseases (*International Classification of Diseases, 10th Revision*, codes I00 –I99; Roger et al., 2012). Clinical manifestations of CVD include myocardial infarction, angina pectoris, heart failure, and stroke (Schneiderman, Antoni, Saab, & Ironson, 2001; World Health Organization, 2011). Conditions that confer significantly increased risk for CVD include obesity, hypertension, high cholesterol, and diabetes (National Center for Health Statistics, 2011).

Atherosclerosis—the buildup of "fatty streaks" and protective fibrous caps in the arteries—underlies the development of coronary heart and cerebrovascular diseases, which is considered to be caused by vascular injury and response to injury. The first stage

in the development of atherosclerosis involves a lesion or damage to the endothelial cell layer of the intima. When damage occurs, cholesterol-laden low-density lipoproteins (LDLs) may enter the intimal layer and become stuck in the extracellular matrix and undergo an oxidative process. The oxidation of LDLs incites an inflammatory response by inducing cytokine release from vessel walls, which activate adhesion molecules on the endothelial cells to attract monocytes—this inflammatory response is the second stage of the atherosclerotic process. Monocytes are pulled through the endothelial cell layer by the adhesion molecules, where they mature into full macrophages, consuming the oxidized LDL particles and transforming into foam cells when engorged. The collection of foam cells constitutes the "fatty streak" which precedes more dangerous, fully developed atherosclerotic plaques (Fuster & Falk, 2011; Libby, 2012).

Not all fatty streaks will develop into full-blown plaques. However, when the amount of fat leaving the wall from foam cells exiting the intima is exceeded by LDLs entering the intima, foam cells may begin to accumulate in the vessel wall. Smooth muscle cells migrate from the medial layer of the vessel to repair the damaged intimal layer above the foam cells, forming a protective fibrous cap over the fatty, inflamed core. The buildup of fibrous tissue characterizes the transition from fatty streak to a fully developed atherosclerotic lesion. If the fibrous cap ruptures, due to deterioration from oxidative and inflammatory processes within the plaque core or damage from the sheer stress exerted by blood flow on vessel walls, a blood clot forms as blood from inside the vessel contacts clotting factors produced within the fatty plaque core (Fuster & Falk, 2011; Libby, 2012).

Coronary arteries tend to develop atherosclerosis before other arteries. This process occurs over decades and is typically benign, but atherosclerosis in the coronary arteries can cause chest pain from angina pectoris. Severe atherosclerosis in these arteries is called CHD and can cause myocardial infarction (Libby, 2012). Atherosclerosis may form elsewhere in the body, most frequently in vessels with disturbed blood flow and that experience more damaging sheer stress, such as the arteries supplying blood flow to the central nervous system. Plaques in these arteries can lead to strokes and transient cerebral ischemia (Libby, 2012).

Cardiovascular Disease Risk Factors

Several other health conditions have been shown to accentuate or accelerate the atherosclerotic process and may contribute to CVD development through alternate mechanisms as well. Obesity, hypertension, high cholesterol, and diabetes mellitus have all consistently been shown to be associated with increased CVD prevalence (Roger et al., 2012), and thus are considered risk factors for CVD development.

Obesity. Obesity is defined as having a body mass index (BMI) of 30 kg/m^2 and above, while being overweight is having a BMI of 25 kg/m^2 and above—67.3 percent of Americans are overweight by these standards, with 33.7 percent of Americans being obese (Roger et al., 2012). The American Heart Association has identified obesity with "marked excess mortality in the U.S. population" and increased risk for diabetes mellitus and many CVD endpoints, including CHD, stroke, and heart failure (Roger et al., 2012). Being overweight increased age-adjusted relative risk for CVD by 21 percent in men and 20 percent in women, while being obese increased risk by 46 percent in men and 64 percent in women (Wilson, D'Agostino, Sullivan, Parise, & Kannel, 2002). The

INTERHEART study identified abdominal obesity as increasing acute myocardial infarction risk 1.12- to 1.62-fold across age, gender, and geographic location (Yusuf et al., 2004). Obesity is also the most powerful predictor of diabetes—in the Nurses' Health Study, women with a BMI $\geq$ 35 kg/m^2 had a 38.8-fold higher risk of developing diabetes mellitus than women with a BMI < 23 kg/m^2 (Hu et al., 2001).

Abdominal, or visceral, fat stores are unique in that they contain glucocorticoid receptors which enhance fatty acid uptake. These fat stores are also implicated in the release of interleuken-6 (IL-6), contributing to the inflammatory response which leads to atherosclerosis and CVD development (Black, 2003). Consequences of abdominal obesity additionally include increased risk of Type 2 diabetes, atherogenic dyslipidemia, vascular inflammation, and hypertension—and each of these outcomes is also predictive of CHD (Black, 2003; Despres & Lemieux, 2006; Okosun, Prewitt, & Cooper, 1999; Schneiderman et al., 2005).

Hypertension. High blood pressure, or hypertension, is defined as either systolic blood pressure (SBP) $\geq$ 140 mm Hg with diastolic blood pressure (DBP) $\geq$ 90 mm Hg, use of antihypertensive medications, or being told at least twice by a physician or other health professional that one has high blood pressure (*ICD-10 I10-I15*; Roger et al., 2012). Among those with CVDs, prevalence of hypertension is 45 percent, whereas among those without CVDs prevalence is only 27 percent, with rates roughly equal between men and women (Roger et al., 2012). The INTERHEART study identified hypertension as increasing risk for acute myocardial infarction 1.91-fold (population attributable risk 17.9 percent; Yusuf et al., 2004). Even prehypertension, defined as 120 $\leq$ SBP < 140 mm Hg and 80 $\leq$ DBP < 90 mm Hg, increases risk 1.5- to 2-fold for major CVD events across all

age groups, with risk increasing with age (Lloyd-Jones, Evans, & Levy, 2005). High blood pressure both exaggerates existing endothelial injury from atherosclerotic plaques as well as increases release of IL-6 from exerting sheer stress on vessel walls (Black, 2003; Chae, Lee, Rifai, & Ridker, 2001). Angiotensin II, a hormone responsible for mediating blood pressure, also incites inflammation, which may also partially explain the link between hypertension and increased atherosclerosis (Libby, 2002; Schieffer et al., 2000).

High cholesterol. High cholesterol, or dyslipidemia, is defined as total cholesterol levels $\geq$ 240 mg/dL of blood or receiving medication to regulate cholesterol level (Roger et al., 2012). Prevalence of dyslipidemia in American adults with CVD is 35 percent, while prevalence in those without CVD is 25 percent (Roger et al., 2012). As described before, LDLs play a central role in atherosclerosis: when LDLs gather in excess in the inner lining of the vasculature, they become embedded and incite an inflammatory process which causes atherosclerotic plaques to form along vessel walls. In contrast, high-density lipoproteins (HDLs) play an anti-inflammatory role, thus dampening the atherosclerotic process, by transporting antioxidant enzymes along with cholesterol to help break down oxidized lipids within plaques (Libby, 2002; Robbesyn et al., 2003).

Diabetes mellitus. Diabetes is a state of recurrent hyperglycemia and insulin resistance, and is diagnosed by having a fasting plasma glucose level $\geq$ 126 mg/dL, plasma glucose $\geq$ 200 mg/dL in a glucose tolerance test, or glycated hemoglobin (HbA1C) $\geq$ 6.5 percent (World Health Organization, 1999). Prevalence of diabetes in American adults with CVD is 17 percent, but only nine percent of those without CVD

(Roger et al., 2012). Insulin resistance, like that from diabetes, results in a loss of ability to properly metabolize glucose, which results in hyperglycemia, increases in insulin, dyslipidemia with increased triglycerides and lowered HDL-C, hypertension, visceral obesity, increased sympathetic nervous system activation, and increased risk for blood clots (Black, 2003).

Increased insulin resistance has been shown to be an independent predictor of CHD, predicting CHD incidence five to ten years after initial observation (Schneiderman & Skyler, 1996). The Multiple Risk Factor Intervention Trial (MRFIT) study showed a 3.2-fold risk increase of mortality from CHD for those with diabetes as opposed to participants without insulin or glucose irregularities (Stamler, Vaccaro, Neaton, Wentworth, & the Multiple Risk Factor Intervention Trial Research Group, 1993). Additionally, diabetes significantly increases risk of acute myocardial infarction (odds ratio 2.37, population attributable risk 9.9 percent; Yusuf et al., 2004) and stroke (risk ratio ranging from 1.8-10; Goldstein et al., 2010; Kissela et al., 2005). For each 10 year increase in duration of diabetes, risk factor adjusted relative risk of CHD incidence is 1.38 times higher (95 percent confidence interval [CI]: .99-1.92) and risk for CHD death is 1.86 times higher (95 percent CI: 1.17-2.93; Fox, Sullivan, D'Agostino, & Wilson, 2004).

Stress Effects on CVD Manifestation and Risk

Stress in itself is not pathological: short-term stress responses are evolutionarily designed responses to environmental stimuli to maintain bodily homeostasis, which in healthy people do not pose any especial health risk (Schneiderman et al., 2005).

However, while adaptive in acute and infrequent situations, this stress response becomes pathogenic if activated repeatedly or sustained.

Short-term, time-limited stressors are so-called "acute stresses," while prolonged stress such as from job strain, low socioeconomic status, or long-term caregiving are considered "chronic stresses" (Gottlieb, 1997). Beyond this simplistic breakdown by duration of stressors, others have added the functions of perception of persistence of threat and duration of response (Baum, Cohen, & Hall, 1993). However, acute and chronic stresses are not always easily differentiated, such as when acute stresses occur on top of chronic stresses (such as a childcare emergency happening within the context of role strain from working and being a single parent) or when a shorter, time-limited occurrence is re-experienced in a frequent, distressing way (such as experiencing post-traumatic stress from a violent car crash).

Schneiderman et al. (2005) described the human acute stress response and how it may become maladaptive. In the face of perceived danger, the body prepares via the sympathetic nervous system stimulating the adrenal medulla to release catecholamines into the blood system and stimulating the hypothalamic-pituitary-adrenal (HPA) cascade to release corticosteroids such as cortisol and aldosterone from the adrenal cortex. To prepare for potential injury or infection, the immune system is activated, raising the levels of circulating proinflammatory cytokines, the immune system's messenger cells. Catecholamines, corticosteroids, and cytokines (primarily IL-6) released in response to stress induce the production of acute phase proteins such as C-reactive protein (CRP; Black, 2003). Next, energy is diverted to tissues that are active during the "fight-or-flight" response, such as the brain and skeletal muscles, via increased blood pressure

from vasoconstriction and increased cardiac output (Schneiderman et al., 2005). This process is called the acute phase response (APR).

However, when acute, time-limited stressors are repeatedly faced or are prolonged into chronic stress, the body is depleted of its ability to adaptively cope with the stressful stimuli. Chronic, prolonged stress leads to increases in resting blood pressure and vascular hypertrophy, as well as hypertrophy of the left ventricle, which shoulders the responsibility of maintaining elevated cardiac output. Chronic activation of the APR over time leads to inflammation and metabolic changes that can culminate in insulin resistance and atherosclerosis (Libby, 2002). Additionally, chronic stress impairs feedback mechanisms in the HPA axis designed to downregulate the stress response after stress hormones are detected in the body, disabling the body's mechanism to shut off the stress hormone cascade (Checkley, 1996).

Repeated, acute psychological stress is sufficient to induce a consistently rallied APR as described above. Periodic and prolonged psychological stress has been shown to be a strong independent predictor of acute myocardial infarction across gender, age, and geographic location, even when controlling for socioeconomic status and smoking (Rosengren et al., 2004). The INTERHEART study found that reporting experiencing several periods of general stress was associated with 1.45 times greater risk of acute myocardial infarction (99 percent CI: 1.30-1.61), while experiencing permanent general stress was associated with 2.17 times greater risk (99 percent CI: 1.84-2.55; Rosengren et al., 2004).

Chronic stress has been shown to directly influence the development of major CVD risk conditions and the atherosclerotic process as a result. Psychosocial stress has

been shown to increase risk for insulin resistance, glucose intolerance, increased total cholesterol and triglycerides, and elevated blood pressure and inflammatory cytokine levels, all ultimately predicting increased CHD risk (Brownley, Hurwitz, & Schneiderman, 2000; Sarti & Gallagher, 2006; Schneiderman & Skyler, 1996; Vitaliano et al., 2002). Chronic activation of the HPA axis induces excess corticosteroid circulation, which promotes obesity via the buildup of visceral fat (Black, 2003).

Psychological stress stimulates the sympathetic nervous system, contributing to hypertension via increased heart contractility (Schneiderman et al., 2005), which can cause damage to the vessel walls (the first step towards atherosclerotic plaque development) and increase release of the APR-inducing cytokine IL-6. Chronic stress has been shown to predict elevated levels of LDLs (Siegrist, Peter, Cremer, & Seidel, 1997). Chronic stress also increases likelihood of Type II diabetes (Surwit, Ross, & Feingloss, 1991) and stressful incidents may also exacerbate Type I diabetes in children (Cox & Gonder-Frederick, 1991). Insulin counteracts the effects of stress hormones in the body, so reduced efficacy of insulin may lead to an increase in APR in the face of chronic stress for someone with diabetes compared to a non-diabetic, thus elevating circulation of IL-6, CRP, and other inflammatory molecules leading to increased atherosclerosis (Black, 2003). The “positive feedback loop” running between elevated sympathetic nervous system activity (which can be driven by chronic stress), insulin resistance, and hyperinsulemia has been hypothesized to be one of the major mechanisms underlying the progression of CHD (Schneiderman & Skyler, 1996).

Long-Term Health Outcomes of Caregiving

The caregiving experience has been shown to be sufficient to produce the prolonged stress required to produce these physical changes, leading to increased CVD risk (Ji et al., 2012; Vitaliano et al., 2002). Informal caregivers are usually family members or friends who provide unpaid assistance to someone who needs help with everyday activities due to some type of disability (Vitaliano et al., 2003). According to Pearlin, Mullan, Semple, and Skaff (1990), the caregiver stress process consists of background and contexts of caregiving stress, primary stressors leading to secondary stressors, stress mediators, and the outcomes from the stress process. The context of the caregiving stress includes the caregiver's status within their social environment as well as the history of their care provision. These include factors such as ethnicity/race, education, age, income, caregiving duration, and relationship to the patient—these impact the experience and outcomes of stressors as well as mediators of the stress process.

Stressors from caregiving are defined by Pearlin et al. (1990) as "conditions, experiences, and activities that are problematic for people… that threaten them, thwart their efforts, fatigue them, and defeat their dreams" (p. 586). The authors break down stressors into primary stressors, or those that drive the stress process, and secondary stressors, those that develop due to the primary stressors. Primary stressors include both objective stresses, such as the frequency and type of care tasks a caregiver provides and the patient's overall level of functioning, as well as subjective stress, the emotional appraisal of objective stressors and the subjective feelings of overload or burden from providing care. Secondary stresses include role strains and intrapsychic strains developed as a consequence of the primary stressor that can have an impact on stress outcomes.

Mediators, such as coping style and social support, can modulate the impact and experience of primary and secondary stressors as well as stress outcomes (Pearlin et al., 1990).

Within this larger framework, the current study sought to examine a selection of stressors and how those impact health outcomes. Among the various factors that comprise the Pearlin caregiver stress process, subjective stress—the personal appraisal of objective stressors—has been consistently shown to contribute to negative outcomes of psychological distress and physical ill health. Better physical and mental health outcomes during long-term caregiving have been associated with "benign stress appraisals," or the subjective ratings of caregiving as less stressful and having higher self-efficacy (Goode, Haley, Roth, & Ford, 1988). Subjective report of feeling overloaded from caregiving has also been shown to mediate the negative impact of objective caregiving stressors on caregivers' health (Son et al., 2007). Because subjective caregiving stress has been most consistently linked to health outcomes, the current study focused on the primary stressor of subjective stress from the Pearlin et al. stress model (1990) as opposed to objective stress.

As stress is implicated as a risk factor for the development of CVDs (Schneiderman et al., 2005; Vitaliano et al., 2002), these disorders are particularly relevant health outcomes to evaluate in informal cancer caregivers who often report experiencing persistent elevated stress levels compared to demographically similar non-caregivers (Kiecolt-Glaser et al., 1987; Pinquart & Sörensen, 2003; Schulz et al., 1990; Vitaliano et al., 2003). Not all caregivers report psychological strain as a consequence of caregiving, but negative psychological and physical health outcomes are most

pronounced for those who do report increased stress from caregiving (Schulz et al., 1997).

Caregivers appear to have an increased vulnerability to physical illness than demographically similar non-caregivers (Schulz et al., 1990). A meta-analysis of research on Alzheimer's caregivers showed that caregivers differed significantly from age and gender matched population controls in all health indicators, including subjective health ratings and objective physiological measures. Caregivers were found to be at a nine percent greater risk of health problems compared to the U.S. population, with 23 percent more stress hormones in circulation and 15 percent poorer antibody production (Vitaliano et al., 2003). In a national survey, 17 percent of all caregivers reported that they believed their health had deteriorated as a consequence of providing care (National Alliance for Caregiving, 2009).

Stress from caregiving persistently activates the HPA axis, which, as described before, can cause dysregulation and impairment of cardiovascular, metabolic, and immunologic systems over time (Vitaliano et al., 2003). A study of Alzheimer's caregivers showed that for male caregivers, chronic stress from caregiving predicted psychological distress upon study entry, which predicted elevated metabolic dysregulation and CVD risk factors (including irregular insulin, glucose, and lipids, elevated blood pressure, and obesity) at a 15 to 18 month follow up. This elevated metabolic dysregulation in the male caregivers then predicted CHD incidence at a 2.5 year follow-up. Women did not show this same "caregiving to CHD pathway." Instead, women (without hormone replacement therapy) regardless of caregiving status showed

significant relationships from distress to elevated CVD risk factors, which predicted later CHD incidence (Vitaliano et al., 2002).

Cancer Caregiving Compared to Other Types of Caregiving

As seen in the major studies listed above, much of the literature concerning health outcomes from caregiving has been based on samples of caregivers for elderly persons or patients with Alzheimer's or dementia with relatively little research on cancer caregivers specifically. This constitutes a limitation in the current caregiving research. With elder and dementia caregiving accounting for roughly one quarter of caregiving experiences (National Alliance for Caregiving, 2009), this has been a logical place to start studying caregiving. However, with a national survey showing that cancer was the third most common reason for providing care for older people (National Alliance for Caregiving, 2009), extending research to this class of caregivers is a logical next step. Research on health outcomes for caregivers of elderly and Alzheimer's patients may not generalize to cancer caregivers, as the experience of caring for dementia and Alzheimer's patients differs from cancer caregiving in several domains, underscoring the need for research on cancer caregivers specifically.

Cancer caregiving is less predictable and has different stress timeframes than other types of caregiving. Elliot and Eisdorfer's (1982) taxonomy breaks stressors into five categories: *acute time-limited stressors* such as laboratory challenges; *brief naturalistic stressors* when one confronts a real-life immediate challenge; *stressful event sequences* that are intense but time-limited; *chronic stressors* that are pervasive and have no guaranteed end point; and *distant stressors* that are traumatic occurrences in one's past that continue to cause distress. Caregiving typically is categorized according to the care

recipient's condition, where if the patient has a chronic disease such as Alzheimer's or diabetes, the patient's caregiver would be undertaking chronic caregiving. Alternatively, if the disease course includes a condition remission point, this is more likely to be acute caregiving, such as providing care for a patient with several broken bones.

Cancer caregiving is unique in that it can be both acute, such as a when a care recipient's cancer is successfully treated so intensive care is confined to the treatment period, as well as chronic, such as when a patient has more severe or recurrent cancer so care is extended and indefinite. With cancer outcomes more variable and uncertain than those of degenerative diseases such as dementia, this means caregivers also are more unsure of what to expect from their role. Caregivers may also provide long-term emotional support through cancer treatment and beyond, which has been rated by cancer caregivers as the most difficult and burdensome task (Carey, Oberst, McCubbin, and Hughes, 1991). Acute cancer-related stressors can continue long after treatment, such as cancer screenings to detect recurrence.

Kim and Schulz (2008) compared the experiences of caregivers of frail elders as well as of cancer, dementia, and diabetes patients. The authors found that caregivers for cancer and dementia patients reported increased burden compared to caregivers for elders or diabetes patients, with cancer and dementia caregivers reporting higher levels of physical strain and psychological distress as a result of providing care. Caregivers for cancer and dementia patients also reported providing assistance with similar numbers of care tasks and comparable levels of financial hardships (objective stresses), as well as similar levels of caregiver burden and emotional stress (subjective stresses). However, cancer care differed from dementia, frail elder, and diabetes care in that cancer caregiving

was more acute and periodical, and while cancer caregiving involved the shortest duration of care, it required the most number of hours per week to provide.

Findings by Kim and Schulz (2008) were consistent with an earlier study by Clipp and George (1993), who compared cancer caregivers and Alzheimer's caregivers. Cancer caregivers were on average six years younger than Alzheimer's caregivers, with cancer caregivers' respective patients being seven years younger on average than Alzheimer's patients. For both sets of caregivers, younger age was associated with lower reported subjective well-being, but better overall health ratings. Cancer caregivers were more likely to be employed, with 60 percent of cancer caregivers employed compared to 21 percent of Alzheimer's caregivers, but employment differences did not explain group differences in level of distress. Being employed could, however, increase psychological distress as a result of role confusion or subjective overload (Navaie-Waliser, Spriggs, & Feldman, 2002). Cancer caregivers also had shorter average duration of caregiving at the time of the survey, with an average of 2.2 years providing care as opposed to Alzheimer's caregivers providing care for an average of 5.6 years. However, duration of caregiving showed no relationship to negative physical or psychological outcomes of caregiving. The authors concluded that the subjective experience of providing care differs between cancer and Alzheimer's patients, which suggests that current health outcomes research on dementia caregivers may not directly generalize to cancer caregivers.

Even though cancer caregiving differs in duration and intensity than that of dementia patients, duration of caregiving has not been found to relate to physical or psychological health outcomes (Clipp & George, 1993), and cancer caregivers may still have long-term negative health outcomes from their more acute caregiving experiences.

In a laboratory-induced stress study, spouses who watched their partner with osteoarthritis perform a painful task showed significantly increased heart rate and blood pressure reactivity, greater than that from watching a stranger perform the same painful task. Psychological distress from watching the partner suffering causing cardiac reactivity was hypothesized as a potential mechanism of caregiving leading to increased CVD risk (Monin et al., 2010). Findings of this study suggest that even short-term experiences of witnessing a loved one suffering as a result of a health condition can increase sympathetic drive. By extension, it is possible that the repeated acute stresses of watching a relative endure rounds of cancer treatments may increase sympathetic drive, quickening the atherosclerotic process and increasing insulin resistance, leading to increased risk for later disease development.

Cancer caregiving follows the trajectory of cancer survivorship, where the patient's condition typically improves and caregivers' disease-related stress dampens over time, unlike the degenerative course of dementia. "Acute survivorship" has been defined as the time from initial diagnosis through completion of treatment, typically one to two years after diagnosis (Bloom, 2002; Kim & Given, 2008). This phase, specifically around the time of diagnosis and initial treatment, is typically when cancer caregivers report experiencing the most stress and distress (Kim & Given, 2008; Nijboer, Triemstra, Tempelaar, Sanderman, & van den Bos, 1999). This phase is followed by "extended survivorship," which begins with the benchmark of completing treatment or when the cancer is classified as in remission, typically from one to two years post-diagnosis to three years post-diagnosis. This marks the stage when cancer recurrence is at its highest probability (Bloom, 2002). While at this time physical strenuousness and amount of care

tasks may decrease, psychological stress can occur from the vigilance of watching for evidence of new or returning disease. Finally, "permanent survivorship" is reached when the probability of the disease returning is low enough that reoccurrence is unlikely (Mullan, 1985). The unique stresses that occur at each caregiving phase—from acute stresses during treatment such as rounds of chemotherapy to the more stable, day-to-day stresses of providing assistance on daily tasks such as bathing and worry about the patient's health—may all increase sympathetic drive and risk for development of CVD risk conditions and manifestations over time.

With the five year survival rate of all cancers at 67 percent, a steep improvement from 49 percent in 1971-1975 (American Cancer Society, 2012), more cancer survivors than ever before will reach extended survivorship, where the survivors and their caregivers will face the unique psychological stress of watching for new and returning disease. This stress is unique to cancer caregivers: unlike dementia caregivers whose patients have a degenerative course and typically need to provide hands-on care for longer than cancer caregivers (Clipp & George, 1993), cancer caregivers' stresses shift over the cancer survivorship trajectory from providing physical assistance during acute survivorship to psychological stresses of health monitoring and providing emotional support during extended survivorship. As the acute phase of survivorship melds into extended survivorship, cancer caregivers may be relieved of their more physically demanding care tasks but take on new psychological support roles, unlike dementia caregivers whose care tasks only become more demanding over time as the patient's functioning declines. Therefore, knowledge of health outcomes from research on

dementia caregivers may not apply to cancer caregivers later in the survivorship trajectory.

Caregivers of cancer patients, compared with other types of caregivers, experience unique challenges from their more acute yet intensive caregiving experiences, and understanding how their idiosyncratic care experience leads to particular health outcomes will be crucial to meeting cancer caregivers' specific needs. The American Cancer Society (2012) reports that there are nearly 12 million Americans alive today who have battled cancer, and over 1.6 million new cancer diagnoses are expected in 2012 alone. This suggests that millions of pre-existing cancer caregivers will be joined by millions more this year alone. With little known about the long-term health ramifications of providing the acute and strenuous care typically required during cancer caregiving, studying how this stress manifests as increased disease risk years later will be critically important to help develop programs to address caregiver needs and prevent negative outcomes from providing informal care.

Moderators of Cancer Caregiving Stress and CVD Conditions

With cancer caregiving differing subjectively and objectively from other forms of caregiving, extending the current research on long-term health outcomes from caregiving is critical. The stress imposed by cancer caregiving has been shown to increase caregivers' risk of CHD and strokes (Ji et al., 2012), so replicating these findings, as well as broadening the investigation to examining how risk for CVD risk conditions might be impacted by the unique, acute nature of cancer caregiving was an important next research step. Preexisting conditions and characteristics might be involved in augmenting or ameliorating the relationship between the stress resulting from cancer caregiving and

health outcomes. This study examined two in particular as potential moderators: depression and gender.

Depression. Results from the first National Health and Nutrition Examination Survey (NHANES), a national demographically-representative survey conducted in the U.S. from 1971-1975, indicated that depressed people were more likely to be diabetic, hypertensive, and have sedentary lifestyles (Ferketich, Schwartzbaum, Frid, & Moeschberger, 2000). Even when controlling for confounding factors including race, hypertension, diabetes, and smoking, depression predicted a higher risk of CHD in both men and women and increased risk of death from CHD in men (Ferketich et al., 2000). Depressed women had higher BMI scores than non-depressed women, a difference which was not seen in men (Ferketich et al., 2000).

Depression, especially clinically significant depression, has been shown to independently predict hypertension (Davidson, Jonas, Dixon, & Markovitz, 2002), heart rate reactivity to stressors (Kibler & Ma, 2004), and CHD incidence (Rugulies, 2002). The INTERHEART study found that reporting "feeling sad, blue, or depressed for two weeks or more in a row" was also more common in persons who had experienced an acute myocardial infarction compared to demographically-matched healthy controls (24.0 percent versus 17.6 percent respectively, odds ratio 1.55 [95 percent CI: 1.42-1.69]). Clinically diagnosed depression predicted acute myocardial infarction occurrence better than depressive mood only (Rosengren et al., 2004).

Caregivers report significantly greater depressive symptomatology than demographically comparable non-caregivers (Pinquart & Sörensen, 2003; Schulz et al., 1990; Vitaliano et al., 2003), and caregiver depression has been shown to remain

relatively consistent across the caregiving trajectory (Pruchno, Kleban, Michaels, & Dempsey, 1990). Depressed persons and caregivers even show similar cytokine profiles, with increased IL-6 and CRP (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; Penninx et al., 2003; Surtees et al., 2008). Stress imposed from caregiving has been shown to predict psychological distress including depression (Vitaliano et al., 2002), and depression has been shown to affect the subjective appraisals of the caregiving experience (Pruchno et al., 1990; Stommel, Given, & Given, 1990).

Depression might affect CVD risk in caregivers through comparable inflammatory pathways as chronic stress. Checkley (1996) described that the principle change in the HPA axis resulting from depression—increased general release of cortisol—results from similar mechanisms by which chronic stress leads to incessantly increased cortisol levels. Both depression and chronic stress cause damage to the negative feedback systems in the HPA axis, impairing ability to downregulate the stress response, as well as causing hypertrophy of the adrenal glands and increased drive from the paraventricular nucleus of the hypothalamus. In caregivers with pre-existing or concurrent depression, the depression might have already impaired their hormonal stress response systems before being subjected to stress from caregiving. The subjective stress from caregiving might then synergistically increase risk for CVD in depressed caregivers who are already vulnerable.

Depression has also appeared to affect perception of caregiving burden, with increased psychological distress associated with higher perceptions of subjective stress from providing care (Kim & Given, 2008; Nijboer et al., 1999; Stommel et al., 1990). Subjective stress from providing care has been shown to mediate the relationship between

patient functioning and negative health outcomes (Goode et al., 1998), and depression has been shown to direct caregivers' perceptions of burdens across multiple dimensions (Stommel et al., 1990). Experiencing depression concurrently to caregiving stress—either as a result of caregiving stress or as a pre-existing condition—might thus intensify the negative health outcomes caused by the chronic stress. Understanding under which conditions the unique stress from providing care to cancer patients might pose the greatest risk of negative health outcomes to cancer caregivers would allow for targeted, more effective health intervention measures.

Gender. Men and women have been shown to report experiencing different levels of psychological distress in response to caregiving and may react differently biologically as well. On a biological level, men show increased physiological response to stress compared to women (Earle, Linden, & Weinberg, 1999). In a study of spousal suffering on CVDs, husbands whose wives reported high suffering had a higher risk of CVD prevalence than those whose wives had less suffering, but there was no relation between husband suffering and CVD prevalence in wives (Schulz et al., 2009). In a sample of Alzheimer's caregivers, the relationship between distress and development of metabolic irregularities and CVD risk factors was three to 12 times greater in men than in women (Vitaliano et al., 2002). Also, major depression is more strongly associated to higher levels of IL-6 in men than women (Penninx et al., 2003). These biological differences may make men more vulnerable to CVD risk conditions and manifestations from caregiving stress, even if they report less overall stress than women.

Female caregivers report that they are in poorer overall health than both male caregivers and demographically similar non-caregiving women do, but these poorer

health self-reports are not consistently corroborated by objective measures of health (Navaie-Waliser et al., 2002; Vitaliano et al., 2003). As psychological distress itself can increase the likelihood of reporting health problems (Costa & McCrae, 1987; Schulz et al., 1994), examining differences in more objective indicators of health between men and women is warranted. Female caregivers also have been shown to typically provide more intensive care, be taking care of a sicker population, have unmet needs in providing care, and forego participating in respite activities (Navaie-Waliser et al., 2002).

While men have reacted more physiologically to caregiving stress, men have reported perceiving the caregiver role as a more positive experience than women (Nijboer et al., 1999). Women comprise 66 percent of caregivers, and female caregivers have been more likely to report more psychological distress than male caregivers, even when controlling for the health of the care recipient and amount of care provided (National Alliance for Caregiving, 2009; Navaie-Waliser et al., 2002; Nijboer et al., 1999; Schulz et al., 1990; Vitaliano et al., 2003). Female caregivers have also been more likely to report that their health had deteriorated as a consequence of their caregiving experience, with 20 percent of women endorsing this sentiment compared to only 12 percent of male caregivers (National Alliance for Caregiving, 2009).

Gender therefore might moderate the level of stress experienced from caregiving and the biological and behavioral ramifications of the experienced stress, thus causing the relationship between caregiving stress and CVD risk to differ between men and women. Understanding how gender might affect the relationship between subjective caregiving stress and health outcome would help indicate whether unique interventions by gender are warranted.

Age, Race/Ethnicity, and Patient Functioning: Covariates

Age, race, and the patient's level of functioning have been shown to be related to the development of CVD manifestations and risk factors in addition to subjective stress, depression, and gender. Older adults are at significantly greater risk for CVDs and CVD risk conditions, with adults over age 60 more likely to have hypertension and dyslipidemia than younger adults. The prevalence of diabetes in persons aged 20 or younger is 11.3 percent, compared to 26.9 percent of those aged 65 and older (Centers for Disease Control and Prevention, 2011). Mortality rates per 100,000 Americans from heart diseases also vary significantly across ages: rates of 1,183.4 deaths for adults ages 65 and older, 127.4 deaths for ages 45-64, and 16.4 deaths for ages 25-44 (Murphy, Xu, & Kochanek, 2012). Adults aged 65 and older are more likely to have multiple risk factors for CVD development (56.4 percent) compared to adults aged 50-64 (51.1 percent) and 35-49 (34.6 percent; Hayes, Greenlund, Denny, Croft, & Keenan, 2005). Age has also been shown to correlate with distress experienced during caregiving, although the literature is mixed on whether older or younger adults experience more distress (Clipp & George, 1993; Kim & Schulz, 2008).

Racial and ethnic minorities account for a disproportionate amount of diabetics in the United States, especially African Americans and Hispanics/Latinos (Roger et al., 2012). The prevalence of diabetes in non-Hispanic blacks is 18.7 percent, compared to 10.2 percent of non-Hispanic whites (Centers for Disease Control and Prevention, 2011). African Americans are more likely to have hypertension (33.8 percent) compared to whites (23.6 percent) and Hispanics/Latinos (22.5 percent; Roger et al., 2012). Obesity rates vary across ethnicities: in 2006, prevalence rates were 35.7 percent for non-Hispanic

blacks, 28.7 percent for Hispanics, and 23.7 percent for non-Hispanic whites (Roger et al., 2012). African Americans have a higher mortality rate attributable to CVDs than other races (Roger et al., 2012). The prevalence of having multiple risk factors for CVD development was highest among African Americans (48.7 percent) and lower in whites (35.5 percent; Hayes et al., 2005). Prevalence of major depression has been reported as significantly higher in whites compared to African Americans (odds ratios= 1.00 and 0.61, respectively), whereas prevalence of dysthymia was significantly higher in African Americans compared to whites (odds ratios= 1.00 and 1.27, respectively; Riolo, Nguyen, Greden, & King, 2005). Other studies have found that African Americans report higher levels of depressive symptomatology than non-Hispanic whites (Kessler et al., 2003). The prevalence of major depressive disorder has also been shown to be higher in Hispanics than in non-Hispanic whites (Minsky, Vega, Miskimen, Gara, & Escobar, 2003).

Objective stress from poorer patient functioning can also impact psychological distress levels—studies show that caregivers for more impaired patients and those with worse prognoses report higher levels of depression (Kim, Carver, Cannady, & Shaffer, under review; Schulz et al., 1990). This objective stress necessarily impacts the subjective stress and depression experienced by a caregiver as they grapple with the greater likelihood that their loved one will die as a result of their diagnosis.

Although these three factors have been shown to be significant predictors of study outcomes, due to limited sample size to fully test the main predictors, age, race/ethnicity, and patient functioning were included as covariates in analyses.

Objectives and Hypotheses

Existing literature shows that providing care for sick patients can induce psychological stress, which can produce increased risk for CVD risk conditions and manifestations. It is unknown how these findings that mainly come from studies of Alzheimer's and dementia caregivers may generalize to cancer caregivers whose stresses are unique from other types of caregivers. Beyond testing the link from stress to CVD with the new population, psychosocial factors that moderate this pathway were sought help to elucidate this relationship.

The objective of the current study was therefore two-fold. First, this study aimed to document the prevalence of CVD manifestations and risk conditions in caregivers during the end-stage acute survivorship phase as well as the extended survivorship phase. CVD risk conditions examined were self-reported diagnosis of hypertension, obesity, high cholesterol, and diabetes. CVD manifestations examined were self-reported angina, CHD, cardiac arrest, congestive heart failure (CHF), heart attack, heart murmur, irregular heartbeat, conditions requiring a pacemaker, and stroke. The prevalence rates of these conditions were compared to those of a sample representative of the U.S. population to determine whether cancer caregivers were at increased risk for CVDs compared to the general population. Prevalence rates of these conditions in cancer caregivers were obtained at two and five years after the care recipient's initial diagnosis. At two years post-diagnosis, caregivers typically conclude active care provision, while five years post-diagnosis generally begins extended survivorship phase when the chance of the patient's cancer returning is typically minimal (Bloom, 2002). It was hypothesized that due to the stresses and pressures faced by caregivers, cancer caregivers would have higher

prevalences of CVD risk conditions and manifestations than the general population at both two and five years after the care recipient's diagnosis (Hypothesis 1).

Second, this study examined whether the subjective stress of caregiving during the late acute survivorship phase predicted CVD risk condition and manifestation development three years later during the extended survivorship phase. Subjective caregiving distress was operationalized as emotional overload experienced as a result of providing care for a relative with cancer. The effect of subjective stress was examined controlling for covariates of age, race/ethnicity, and patient functioning (a measure referring to the severity of the care recipient's cancer based on the type and stage of cancer and time since diagnosis). It was hypothesized that higher reported subjective caregiving stress at two years post-diagnosis would predict significantly higher risk for developing CVD risk conditions and manifestations by five years post-diagnosis, above and beyond that which is accounted for by the study covariates (Hypothesis 2.1).

Depressive symptomatology and gender were investigated as moderators of the relationship between subjective caregiving stress and risk of developing CVD risk conditions and manifestations. It was hypothesized that greater levels of depressive symptomatology would confer greater risk from subjective stress on development of CVD risk conditions and manifestations (Hypothesis 2.2), and that men would have a stronger relationship between subjective caregiving stress and risk of developing CVD conditions than women (Hypothesis 2.3).

Cancer caregivers continue to be a relatively understudied population, and health ramifications of their particular caregiving experiences have still yet to be fully understood. This project was unique in its examination of cancer caregivers specifically,

and what long-term health tolls might be accrued from providing care to a cancer patient. This study sought to both confirm past findings on increased cardiovascular morbidity for cancer caregivers (e.g., Ji et al., 2012) and to extend current literature by examining risk of additional cardiovascular disease risk conditions and psychosocial factors that may explain any observed increased risk.

Findings from this study have the potential to both identify and address the excess morbidity and mortality faced by cancer caregivers. Better understanding of the specific health risks that cancer caregivers are prone to develop can inform early screening and prevention measures to better monitor and protect this growing population. Understanding psychosocial predictors of increased health risks can also inform intervention measures to improve both the mental and physical health of these caregivers. Ultimately, this project intended to extend and inspire research on the previously understudied population of cancer caregivers who would significantly benefit from increased knowledge on their unique health risks.

Chapter 3: Methods

Participants

The National Quality of Life Survey for Caregivers (Kim & Spillers, 2010) was designed and implemented through the American Cancer Society to assess quality of life of family members and close friends who provided care to a cancer survivor who participated in the Study of Cancer Survivors-I (SCS-I). The SCS-I initially identified 19,294 survivors through 11 SEER/NPCR state cancer registries. Eligibility criteria for cancer survivors included: (a) being 18 years of age or older at time of diagnosis, (b) being diagnosed during the 12-month eligibility period (excepting New Jersey with a 15-month eligibility period), (c) having a cancer diagnosis of one of the 10 most common cancers (bladder, breast, colorectal, kidney, lung, non-Hodgkin lymphoma, ovarian, prostate, skin melanoma, or uterine), (d) having a diagnosis with a SEER summary stage of localized, regional, or distant (excepting bladder cancer which included in situ; National Cancer Institute, 2005), (e) being fluent in either English or Spanish, and (f) being a resident of the United States. When it was possible, stratified samples based on survivors' age, cancer type, and race/ethnicity were drawn. Younger survivors (<55 years old), racial/ethnic minorities, and survivors of cancer diagnoses with higher mortality rates (e.g., lung, ovarian, and kidney) were purposely over-sampled to guarantee adequate representation of these demographics in the sample (Smith et al., 2007).

These survivors were then asked to nominate family members or family-like persons who provided constant care to them during their cancer experience. Eligibility criteria for caregivers included (a) being 18 years of age and older, (b) being fluent in either English or Spanish, and (c) being a resident of the United States. While the

samples of cancer survivors were stratified when possible, the response rate of patients (Smith et al., 2007) and nomination rate for caregivers (Kim et al., 2010) were much lower from racial and ethnic minorities than those from non-Hispanic whites, which caused skewing in the racial and ethnic composition in the caregiver sample.

The National Quality of Life Survey for Caregivers was both prospective and longitudinal: surveys were mailed to caregivers at two years post-diagnosis (T1) to assess short-term caregiving effects and later at five years post-diagnosis (T2) to assess longer-term effects. A total of 896 caregivers returned a baseline T1 survey for the second study cohort ("full T1 sample"), which contained questionnaires for the current study variables. At T2, 607 caregivers returned a complete survey ("full T2 sample"). Four hundred ninety-one caregivers returned completed surveys at both time points ("returners").

To examine the differences between cancer caregivers and the general population with standardized prevalence rates of CVD risk conditions and manifestations (aim one), data were analyzed from all surveys returned at T1 and T2. To examine whether caregiving stress explained significant variance in the development of CVD risk conditions and manifestations and whether that relationship varied as a function of depression or gender (aim two), data were analyzed from those caregivers who provided complete, valid data for age, race/ethnicity, gender, and stress overload and depression scales at T1. Completers and non-completers were compared based on these inclusion criteria to determine whether the samples differed systematically, which would limit the generalizability of results.

Procedure

This study complied with regulations of the Emory University Institutional Review Board. Nominated caregivers were sent a packet of information including an introduction letter, the survey questionnaire, a self-addressed postage-paid envelope, and a $10 gift card as compensation. Informed consent was implied from returning a survey. For each time point, two cycles of mailing and follow-up telephone calls were made during the eight-week data collection time span.

Measures

Subjective caregiving stress: Predictor. Subjective stress experienced as a result of providing care (i.e., the caregivers' reports of feeling overwhelmed by the responsibilities of task assistance) was measured by the four-item stress overload subscale of the Pearlin Stress Scale at two years post-diagnosis (T1; Pearlin et al., 1990). Response options were 1 *Not at All,* 2 *Somewhat,* 3 *Quite a bit,* and 4 *Completely*. The mean of these four items was used to indicate caregiver stress, with higher scores indicating greater subjective stress. The entire Pearlin Stress Scale was developed specifically to operationalize multiple stress domains in caregivers and contains 15 subscales, with the stress overload scale designed to capture the subjective indicators of primary stressors from caregiving (i.e., the hardships subjectively experienced by the caregivers). The scale was originally developed using a large sample of Alzheimer's caregivers, and the stress overload subscale was found to show good reliability (alpha= .80; Pearlin et al., 1990). The scale has since been used with cancer caregivers and has shown good reliability in this population as well (alpha= .79-.80; Gaugler et al., 2005;

Kim, Loscalzo, Wellisch, & Spillers, 2006). The stress overload subscale also showed acceptable reliability in the current sample (alpha= .802).

CVD risk conditions and manifestations: Outcomes. CVD risk conditions and manifestations were assessed at both two (T1) and five years (T2) post-diagnosis using the 40-item Morbidities Index for Informal Caregivers of Chronic Illnesses (MICCI) questionnaire (Kim, Carver, Cannady, & Shaffer, in press). Adapted from Yancik and Ries (2000), this questionnaire asked participants to self-report whether they had ever been under a physician's care for certain ailments common in aging populations. Prevalence of CVD risk conditions and manifestations were measured by caregivers' self-report. The CVD risk conditions studied were hypertension, obesity, high cholesterol, and diabetes. The CVD manifestations studied were angina, CHD, cardiac arrest, CHF, heart attack, heart murmur, irregular heartbeat, conditions requiring a pacemaker, and stroke. From an analysis of 774 caregivers from the National Quality of Life Survey for Caregivers, the MICCI showed good construct and concurrent validity, significantly correlating with known risk factors of physical disease such as old age and male gender. The questionnaire was also related to established health surveys supporting its concurrent validity: physical conditions from the MICCI were strongly predicted from the Medical Outcomes Study Short Form Health Survey (MOS SF) physical functioning component summary. Construct validity of the questionnaire was supported from the five most commonly reported conditions from caregivers (hypertension, high cholesterol, chronic back pain, heart disease, and arthritis) matching to very commonly reported conditions from older adults in the general U.S. population (Kim et al., in press). Self-report data has been shown to be an efficient and effective means of acquiring health

outcomes data, with research showing substantial agreement for diabetes, hypertension, myocardial infarction, and stroke (kappa values= 0.71-0.80), with agreement tending to be higher for young women and participants with more education (Okura, Urban, Mahoney, Jacobsen, & Rodeheffer, 2004).

Depressive symptoms: Moderator. Depressive symptomatology experienced during the four week period preceding the survey completion was assessed at two years post-diagnosis (T1) using the 20-item Center for Epidemiologic Studies Depression scale (CES-D; Radloff, 1977). Response options were 0 *Rarely or none of the time,* 1 *Some or a little of the time*, 2 *Occasionally or a moderate amount of the time,* and 3 *Most or all of the time,* with the sum of scores from all items indicating an overall level of depressive symptomatology. Scores of 16 and above have been traditionally used to indicate clinically meaningful levels of depressive symptomatology, a cutoff point which shows optimal specificity (Beekman et al., 1997). The CES-D is a widely used measure of depressive symptomatology and has been shown to have high internal validity and good test-retest reliability, with reliability alpha coefficients of .85 in the general population (Radloff, 1977; Santor, Gregus, & Welch, 2006). The CES-D shows good discriminant validity (superior to that of the Beck Depression Inventory; Santor, Zuroff, Ramsay, Cervantes, & Palacois, 1995): the scale shows low correlations with age, gender, and socioeconomic status and is more closely correlated with the depression scale on the Symptom Checklist-90 than the other subscales (Weissman, Sholomskas, Pottenger, Prusoff, & Locke, 1977). Criterion validity has been established in older adults (aged 55-85; Beekman et al., 1997) and good reliability has been shown in cancer caregivers

(alpha= .92-.97; Gaugler et al., 2008; Nijboer et al., 1999). The CES-D also showed acceptable reliability in the current sample (alpha= .927).

Demographics: Moderator and covariates. Caregivers' self-reported gender (moderator), age and race/ethnicity (covariates) were assessed at two years post-diagnosis (T1).

Patient Functioning: Covariate. The severity (adjusted survival rate) of the care recipients' cancer was calculated for each survivor according to the patients' cancer type, stage, and time since diagnosis. This cancer severity index served as a measure of patient functioning related to objective stress from caregiving, which could be compared across 10 different cancer types studied. The survivors' cancer type, stage (localized, regional, or distant), and date of diagnosis were obtained from the state cancer registry (Smith et al., 2007). Higher scores reflected greater severity of illness and therefore lower patient functioning and greater objective caregiving stress.

Chapter 4: Statistical Analysis

Testing Aim One: Prevalence of CVD Risk Conditions and Manifestations in Cancer Caregivers

Calculating prevalence of CVD risk conditions and manifestation in caregivers. Data from all T1 and T2 surveys were used in the analysis for aim one. Morbidity from CVD risk conditions and manifestations in the caregiver population at both two years post-diagnosis (T1) and five years post-diagnosis (T2) was calculated according to frequency analysis of the caregivers' self-report of whether they ever received treatment from a physician for the outcome on the MICCI. CVD risk conditions were self-reported diagnosis of hypertension, high cholesterol, obesity, and diabetes. CVD manifestations were self-reported diagnosis of angina and/or CHD; cardiac arrest, CHF, and/or heart attack; heart murmur, irregular heartbeat, and/or a condition requiring a pacemaker; and stroke. To show change over time, raw prevalence rates at T1 and T2 were reported from those participants who completed surveys for both T1 and T2 ("returners"), and independent samples t-tests were conducted to determine whether prevalence of each CVD outcome increased significantly by T2. Incidence rates per 1,000 person-years seen between T1 and T2 were also calculated by dividing the number of new cases for a certain condition by the returner sample size times three years, then multiplying by 1,000. Returners who were included in analyses were compared to those who did not complete eligible surveys at both time points to determine whether returners differed systematically from non-returners on prevalence of disease.

Comparing age, race/ethnicity, and gender adjusted prevalence rates of CVD risk conditions and manifestations in caregivers to U.S. population rates. To compare the raw prevalence rates for the CVD risk conditions and manifestations from the

caregiver population to that of the U.S. national population (derived from National Health and Nutrition Examination Survey [NHANES] data), both sets of data were standardized according to age, gender, and race/ethnicity. Standardized weights were calculated based on the following categories: four age groups (18-44, 45-64, 65-74, and 75 and older), two racial/ethnic groups (non-Hispanic whites compared to not non-Hispanic whites), and two genders (women compared to men). Weights were calculated by dividing number of people belonging to each adjustment combination (age by race by gender) by the total population aged 18 and above, with all data coming from the 2000 U. S. Census (as T1 was assessed in 2003-2004 and T2 was assessed 2006-2007; see Table 1 for standardized weights). Data from the 2003-2004 and 2005-2006 NHANES surveys were also adjusted for the CVD risk conditions and manifestations according to these weights. Standardization to the national sample allowed for the removal of influence of extraneous variance caused by the weighting variables. All rate adjustments were conducted via SUDAAN statistical software release 10.0.1 (Research Triangle Institute, 2008).

Adjusted prevalences of CVD conditions in the caregiver and national samples were compared using standardized rate ratios and their 95 percent confidence intervals (CI) using the following formula (Formula 1: Boyle & Parkin, 1991; Smith, 1987):

$$(SR_1/SR_2)^{1 \pm (Z_{\alpha/2}/x)}$$

Where $X = \dfrac{(SR_1 - SR_2)}{\sqrt{(SE_{SR1})^2 + (SE_{SR2})^2}}$

And $Z_{\alpha/2} = 1.96$

And SR_1 = standardized rate for caregivers

SR_2 = standardized rate for the national sample

If the 95 percent CI included one, the standardized rates of the two populations were not significantly different. Hypothesis 1—cancer caregivers have higher incidence of CVD risk conditions and manifestations than the general population—would be supported if the standardized rate ratios for the CVD risk conditions and manifestations were significantly greater than one.

Both the NHANES 2003-2004 and 2005-2006 questionnaires included self-report items on hypertension, diabetes, high cholesterol, stroke, angina, CHD, CHF, and heart attack. Because the caregiver survey combined self-report on several heart-related conditions, the NHANES variables for angina and CHD were combined such that a positive response to angina and/or CHD counted once towards the combined "angina, CHD" variable. This procedure resulted in a combined NHANES variable suitable for comparison to the caregiver "angina, CHD" item. Likewise, NHANES variables for CHF and heart attack were combined to one "CHF, heart attack" variable more suitable for comparison with the caregiver "cardiac arrest, CHF, heart attack" variable.

For obesity, the caregiver survey asked whether patients had ever received treatment for the condition of "obesity (overweight)." For comparison to the national sample, the rate of overweight persons was calculated from NHANES data by calculating BMI scores from self-reported height and weight, with any person with a BMI over 25 considered overweight. These calculated prevalence rates from NHANES data were compared to the self-report obesity (overweight) prevalence from the caregiver survey. The 2005-2006 NHANES questionnaire added a question that asked whether a person had ever been told by a doctor that they are overweight, and this was also adjusted and compared to the caregiver obesity (overweight) rate at T2. Neither the NHANES 2003-

2004 nor 2005-2006 survey collected data for heart murmur, irregular heartbeat, or pacemakers, so this combined CVD endpoint was not compared between the caregivers and NHANES data.

Testing Aim Two: Evaluating Psychosocial Variables as Correlates of Disease at T1 and as Predictors of Disease Development from T1 to T2.

Comparing completers with non-completers. To examine correlates of disease presence at T1, participants with complete and valid data for age, gender, race/ethnicity, patient functioning, subjective caregiving stress (Pearlin stress overload scale mean score—required valid data for all four items), and depression (CES-D scale total score—required valid data for all 20 items) from the T1 survey were used in analyses. These variables were all used in examining the relationship between caregiving stress and CVD risk conditions and manifestations cross-sectionally at T1. Independent samples t-tests were used to compare participants who provided complete information on all study variables versus those who did not based on age, patient functioning, mean subjective stress score, and total CES-D score. Chi-square tests of independence were used to compare participants who completed all study variables to those who did not based on gender and race/ethnicity.

Correlates of disease presence at T1 were also studied using the returner-only sample. Returners were those participants who completed questionnaires at both T1 and T2. These were the participants used to examine the longitudinal question of whether T1 demographic and psychosocial variables predicted disease development at T2. Returners were compared to those who did not return a questionnaire at both time points: independent samples t-tests were used to compare returners to non-returners based on age, patient functioning, mean subjective stress score, and total CES-D score, and chi-

square tests of independence were used to compare returners to non-returners based on gender and race/ethnicity. All test statistics were evaluated at the .05 significance level. These comparisons helped to determine whether the participants who completed the study variables differed systematically from those who were not used in the analysis, which would limit the generalizability of results.

Calculating patient functioning. The cancer severity index score reflected the patient's level of functioning based on an adjusted survival rate for the care recipient's cancer calculated from type of cancer, time since diagnosis, and stage. Cancer stages were 0 *In Situ* (bladder cancer only)*,* 1 *Localized,* 2 *Regional,* 3 *Distant,* and 4 *Unstage/Unknown*. Time since diagnosis was broken into four categories: less than one year, one year to less than two years, two years to less than three years, and three years or longer. As the survival rate changes depending on the type of cancer, stage of cancer, and time since initial diagnosis, the cancer severity index was calculated in order to create a comparable severity index across the 10 different cancers studied (Kim, Baker, Spillers, 2007; Ries et al., 2007). Higher patient functioning scores indicate a more severe diagnosis and therefore higher objective stress for the caregivers.

For example, for a person who was diagnosed with localized Non-Hodgkin's Lymphoma (NHL) within the past year, the adjusted survival rate for this diagnosis is 87.5 percent. The cancer severity score inverts the survival rate, equaling 1 - .875 = .125. A patient with localized NHL who was diagnosed four years ago has an adjusted survival rate of 79.5 percent, so the cancer severity score would be 1 - .795 = .205. A patient with distant NHL who was diagnosed within the past year has an adjusted survival rate of 70.3 percent, so the cancer severity score would be 1 - .703 = .297.

In comparison to NHL, lung cancer has a much lower survival rate. For a patient diagnosed within the past year with localized lung cancer, the adjusted survival rate is 80.5 percent for that diagnosis, so the cancer severity score would be 1 - .805 = .195. For a patient diagnosed within the past year with distant lung cancer, the survival rate is 24.1 percent, so the cancer severity score would be 1 - .241 = .759. See Table 2 for cancer severity scores for all 10 included cancer diagnoses by stage and time since diagnosis.

Evaluating whether subjective stress from caregiving explains significant variance in development of disease, and whether depression and/or gender moderate that relationship. Hierarchical logistic regression analysis was used to test the hypothesis that subjective stress from caregiving at two years post-diagnosis (T1) explains significant variance in the development of CVD risk conditions and manifestations three years later (T2; Hypothesis 2.1). Hierarchical logistic regression analysis was also used to determine whether depression and gender play a moderating role in the relationship between subjective stress and development of CVD outcomes. First, hierarchical logistic regression analysis was conducted for both overall risk condition and CVD manifestation development using an outcome variable indicating whether an individual had developed any CVD risk condition or CVD manifestation between T1 and T2. Next, independent hierarchical logistic regression analyses were carried out for each CVD risk condition and manifestation separately. In order to examine disease development between T1 and T2, for each outcome, only returners who indicated that they had never received treatment for the outcome at T1 were included in the regression. This allowed for the differentiation between participants who developed

conditions between T1 and T2 as opposed to those who developed these conditions at any point before T1.

The hierarchical logistic regressions were run in three steps: covariates, main effects, and two-way interactions. Covariates of age, race, and patient functioning were entered into the regression analysis first to control for their effects on the study outcomes. Next in step two, subjective stress, depression, and gender were added to the regression to test the main effects of these variables on development of CVD risk conditions and manifestations. Data for subjective stress and depression were centered at the mean of each variable of the population used in each analysis, eliminating multicollinearity introduced by non-essential ill conditioning when the interaction variables were added to analyses. Hypothesis 2.1—increased subjective stress significantly predicts increased risk for CVD risk condition and manifestation development—would be supported if the Wald's tests of the partial regression coefficient for the mean subjective stress score were significant ($p < .05$). If the effect was significant, the linear increment in the log unit for the health outcome for a one-unit change in subjective stress would be significantly different from zero (Cohen, Cohen, West, & Aiken, 2003).

In step three, the two-way interactions of subjective stress and depression and subjective stress and gender were entered into the model to evaluate the moderation hypotheses. Hypothesis 2.2—depression would aggravate the negative effect of subjective stress on development of CVD outcomes—would be supported if the Wald's test of the partial regression coefficient for the interaction between subjective stress and depression scores was significant ($p < .05$). If the subjective stress by depression two-way interaction was significant, it would be investigated by generating three simple regression

equations, examining the effect of subjective stress on the health outcome of interest at depression scores at the CES-D score mean and one standard deviation above and below that mean (Aiken & West, 1991). Hypothesis 2.3—the negative effects of subjective stress on CVD outcome development would be stronger in men than women—would be supported if the odds ratio for the interaction between subjective stress mean score and gender was significantly greater than one ($p < .05$), with men dummy coded as one and women as zero.

Power analysis. While the samples used in the longitudinal disease development regressions had a large number of participants, the analyses for finding significant effects for the individual CVD outcomes may have been underpowered due to small effect sizes. Post-hoc power analyses for the combined risk overall and manifestation overall categories were conducted to determine the total power achieved to detect significant findings for CVD risk conditions and manifestations with the effect sizes found in the analyses. Convention holds that desired power (1- β) is 80 percent, leaving risk of Type II error (β) at 20 percent (Cohen, 1988).

The total achieved power for finding significant results for the main effects and two-way interactions was conducted using G*Power 3.1.3 (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007). Tests were two-tailed with alpha= .05, and the effect sizes used were those achieved when controlling for variance explained by the covariates, other main effects, and other two-way interaction. Predicted odds ratio equaled e^{Bi}, where B_i is the unstandardized partial regression coefficient for the main effect or interaction in the longitudinal regression, and event rate equaled frequency of newly developed disease cases divided by the total sample size.

Chapter 5: Results

Sample Characteristics

A total of 896 caregivers returned a T1 survey at approximately two years after their care recipient's cancer diagnosis. As shown in Table 3, the caregivers were middle aged, overwhelmingly non-Hispanic white, and predominantly women. Most caregivers were relatively affluent and educated. Approximately two-thirds of caregivers were the care recipient's spouse. The prevalence and stage of cancers in the sample resemble that of cancer incidence rates of the U.S. population (Howlader et al., 2012).

As shown in Table 4, at two years post-diagnosis, caregivers had provided care for an average of 18 months and for nine hours per day. About two-thirds of caregivers at five years post-diagnosis were no longer providing care to the survivor, whereas approximately 10 percent of the caregivers reported they had constantly provided care and additional five percent provided care intermittently since the initial diagnosis.

Testing Aim One: Prevalence of CVD Risk Conditions and Manifestations in Cancer Caregivers

The percentage of participants who marked "yes" for ever having been under a physician's care or taken prescription medication for each of the CVD risk conditions and manifestations served as the raw prevalence of disease endorsed by caregivers. This data and data obtained from the National Health and Nutrition Examination Survey (NHANES) were then standardized to the U.S. population according to race/ethnicity, age, and gender. The caregiver and NHANES adjusted rates were then compared using standardized rate ratios to determine whether caregivers had higher prevalence rates of CVD conditions than the general population (Hypothesis 1).

Comparing caregiver samples: Full sample to returner sample. Of the total 896 participants who returned a T1 survey ("T1 full sample") and the total 607 participants who returned a T2 survey ("T2 full sample"), 491 returned both surveys ("returners"). Returners were compared to those who did not return a T2 survey ("T2 non-returners"; *N*=405). Returners (at T1, *M*= 55.78 years, *SD*= 12.63) were significantly older than non-returners (*M*= 52.74, *SD*= 12.77), *t*(861)= -3.491, *p*= .001. There were no differences between returners and T2 non-returners on the other aim one study variables of race/ethnicity ($\chi^2(1)= .691$, *p*= .406) and gender ($\chi^2(1)= .198$, *p*= .657).

Raw prevalence rates of CVD risk and manifestation conditions are reported in Table 5. The CVD risk and manifestation raw prevalence rates did not differ at T1 between returners and T2 non-returners, $\chi^2< 2.101$, *p*s> .147), except that T2 non-returners reported more angina/CHD at T1 (11.6 percent compared with 6.9 percent of returners), $\chi^2= 5.912$, *p*= 0.015. Raw prevalences for CVD risk and manifestation conditions also did not differ at T2 between returners and caregivers who provided a T2 but not a T1 survey ("T1 non-returners"; *N*= 116, $\chi^2< 3.816$, *p*s> .051), except that returners reported more heart attack/CHF/cardiac arrest (8.1 percent compared with 2.6 percent of T1 non-returners) $\chi^2= 4.408$, *p*= .036 and more high cholesterol at T2 (47.9 percent compared with 26.7 percent of T1 Missing) $\chi^2= 17.029$, *p*< .001. From these comparisons, the returner sample is considered comparable to the T1 and T2 full samples, suggesting that findings may be generalized between the samples.

Correlations between CVD risk and manifestation conditions. At T1, the four CVD risk conditions were significantly correlated with each other ($.25 \leq \rho < .45$) as well as with the four CVD manifestation conditions ($.17 < \rho \leq .41$; Table 6 upper section). The

four CVD manifestation conditions were also significantly correlated with each other (.40 ≤ ρ < .61; Table 6 lower section), *p*s< .001.

As shown in Table 7, similar patterns of correlations among the risk conditions and manifestations emerged at T2, except cardiac arrest/CHF/heart attack was only marginally significantly correlated with hypertension at T2 (ρ= .079, *p*= .081) and irregular heartbeat/pacemaker/murmur was only marginally significantly correlated with high cholesterol at T2 (ρ= .088, *p*= .051). All other CVD risk conditions and manifestations were significantly correlated at T2 (.105 ≤ ρ < .601, *p*s < .020).

Change in disease prevalence from T1 to T2 in the caregiver population. To determine whether there were significant changes in prevalence in CVD risk and manifestation conditions from T1 to T2, paired-samples t-tests were performed to compare T1 and T2 raw prevalence rates for caregivers who completed both surveys (returners). All prevalences of CVD risk conditions and manifestations increased significantly between T1 and T2 (*p*s< .014; Table 8). Using data from returners only (*N*= 491), for risk factor conditions, hypertension increased by 33.7 percent (from 33.4 percent at T1 to 44.6 percent at T2), high cholesterol increased by 51.6 percent (from 31.6 to 47.9 percent), obesity increased by 45.5 percent (from 22.4 to 32.6 percent), and diabetes by 26.5 percent (from 9.8 to 12.4 percent). For manifestation conditions, the prevalence of ever receiving treatment for angina/CHD increased by 71.0 percent (from 6.9 to 11.8 percent), cardiac arrest/CHF/heart attack increased by 17.4 percent (from 6.9 to 8.1 percent), irregular heartbeat/pacemaker/murmur increased by 43.0 percent (from 12.8 to 18.3 percent), and stroke increased by 31.4 percent (from 5.1 to 6.7 percent). Incidence rates per 1,000 person years were 37.34 for hypertension, 54.31 for high

cholesterol, 8.83 for diabetes, 33.94 for obesity, 16.29 for angina/CHD, 4.07 for cardiac arrest/CHF/heart attack, 18.33 for irregular heartbeat/pacemaker/murmur, and 5.43 for stroke.

Correlations between new cases of CVD risk and manifestation conditions at T2 proved to be less significant overall (Table 9). New CVD risk conditions were significantly correlated with one another (ρs> .094, *p*s< .037) except new diabetes with new hypertension, high cholesterol, and obesity and new obesity with new high cholesterol (ρs< .070, *p*s> .120). New CVD risk conditions were less likely to be significantly correlated with new CVD manifestation conditions. New manifestation overall was significantly correlated with new risk overall, hypertension, and high cholesterol; new cardiac arrest/CHF/heart attack was significantly correlated with new diabetes; new irregular heartbeat/pacemaker/murmur was significantly correlated with new risk overall, hypertension, and high cholesterol; and new stroke was significantly correlated with new diabetes (ρs> .090, *p*s< .047). All other new CVD risk and manifestation correlations were non-significant (ρs< .079, *p*s> .084). New manifestation overall was significantly correlated with all new individual manifestation conditions, and new angina/CHD was significantly correlated with new cardiac arrest/CHF/heart attack and new irregular heartbeat/pacemaker/murmur (ρs> .111, *p*s< .014). All other new CVD manifestation correlations were non-significant (ρs< .054, *p*s> .228). New cases of CVD risk and manifestation conditions were therefore less significantly correlated than presence of CVD risk conditions and manifestation at T1 cross-sectionally.

Race, age, gender standardized rate adjustment procedure. Next, the raw prevalence rates among the caregiver sample were adjusted in order to compare with

those from a U.S. population-based sample. Raw prevalence rates from participants who completed a T1 survey (T1 full sample; *N*= 896) and participants who completed a T2 survey (T2 full sample; *N*= 607) were adjusted independently according to standardized weights for race/ethnicity, age, and gender groups derived from the 2000 U.S. Census. Race/ethnicity was condensed into non-Hispanic white vs. not non-Hispanic white; four age groups were created: 18-45, 45-65, 65-75, and 75 and older; and two gender groups were used (women vs. men; see Table 1 for standardized weights and Chapter 4 p. 41 for procedural description of calculating the standardized weights). Adjusted prevalence rates for the caregiver samples are presented in Table 10.

The STDVAR and STDWGT procedures of SUDAAN 10.0.1 were used to obtain the standardized estimates of the raw percentages. These procedures standardize the raw prevalence rates "directly to the distribution of the population as defined by the standardizing variables," (p. 385, Research Triangle Institute, 2008) which, in the case of this study, is to the distribution of the U.S. population according to race/ethnicity, age, and gender.

U.S. population-based data: The National Health and Nutrition Examination Surveys (NHANES). The NHANES studies (Centers for Disease Control and Prevention, 2012) collect health and nutritional status data on adults and children within the United States through both surveys and physical examinations. The program is conducted through the National Center for Health Statistics, under the Centers for Disease Control and Prevention (CDC). NHANES is a "continuous, annual survey of the noninstitutionalized civilian resident population of the United States… [comprising] a nationally representative sample" of U.S. residents (p. 2, Curtin et al., 2012) with data

released biannually to increase reliability. Sampling is designed in a four-step procedure to ensure national representability: first, primary sampling units (PSUs; i.e., counties to study) are selected from the pool of all U.S. counties using U.S. census data. Next, more defined samples are identified according to census blocks within the PSUs. The sampling procedure and rate is conducted to satisfy requirements to provide adequate sample size for sex by race/ethnicity by age domains. Rates are "set up to produce a national and approximately equal probability sample of households in most of the United States, with higher rates for the geographic strata with high minority concentrations" (p.7, Curtin et al., 2012). As such, NHANES is considered to provide nationally representative information on health statistics for the United States population.

NHANES data is publicly available through the CDC website. For this study, data from the 2003-2004 and 2005-2006 data release cycles were obtained, corresponding to the assessment time of T1 and T2 caregiver surveys, respectively. Variables for CVD risk conditions and manifestations studied were selected for adults aged 18 and older. Raw prevalence rates from NHANES data were then adjusted according to the same standardization procedure used for adjusting the caregiver raw prevalence rates (see Table 11 for adjusted prevalence rates from NHANES data).

Comparing adjusted caregiver CVD risk condition and manifestation prevalences to adjusted NHANES prevalences. Adjusted outcome prevalences from the caregiver and NHANES samples were compared using standardized rate ratios and their 95 percent CI (see Formula 1 on p. 41; Boyle & Parkin, 1991; Smith, 1987)

Two years post-diagnosis (T1). As shown in Table 12, adjusted prevalence rates of high cholesterol and obesity were significantly lower in the caregiver sample than the

NHANES sample. However, no significant differences in adjusted prevalences of reported hypertension, diabetes, angina/CHD, heart attack/CHF/cardiac arrest, or stroke existed between the two samples.

Five years post-diagnosis (T2). For comparing obesity rates, there was no significant difference between caregiver sample adjusted rates and NHANES rates from those reporting whether they have ever been told they are overweight by a doctor, but caregivers had a significantly lower rate when using NHANES rates from those with BMIs 25 or above. No significant differences in adjusted prevalences of reported hypertension, high cholesterol, angina/CHD, heart attack/CHF/cardiac arrest, or stroke existed between the two samples. See Table 13 for 95 percent CI for rate comparisons at T2.

Testing Aim Two: Evaluating Psychosocial Variables as Correlates of Disease at T1 and as Predictors of Disease Development from T1 to T2.

Subjective stress from caregiving was examined as a correlate of the CVD risk conditions and manifestations at T1 and as a predictor of CVD risk condition and manifestation development between T1 and T2 (Hypothesis 2.1) while controlling for covariates of age, race, and patient functioning. Additionally, depressive symptomatology and gender were examined as possible moderators of the relationship between subjective stress and disease (Hypotheses 2.2 and 2.3, respectively).

Comparing T1 completers to incompleters. Of the 896 participants who returned a survey at T1, 804 provided valid data for the covariates (race, age, and patient functioning), predictors (subjective stress, depressive symptomatology, and gender), and CVD outcomes. Participants who provided complete data ("T1 completers"; *N*= 804) did not differ from those who provided incomplete data ("T1 incompleters"; *N*= 92) on any

study variables: race/ethnicity ($\chi^2(1)= 3.343$, $p= .067$), age ($t(861)= 1.422$, $p= .155$), patient functioning ($t(885)= -1.105$, $p= .269$), subjective stress ($t(870)= .339$, $p= .734$), CES-D ($t(842)= .906$, $p= .365$), or gender ($\chi^2(1)= .015$, $p= .901$) at T1. Only T1 completers' data were included in subsequent aim two analyses that involve the T1 full sample.

Comparing T2 returners to non-returners. Of the total 896 participants who returned a T1 survey, 491 returned a T2 survey ("returners"). Returners were compared to those who did not return a T2 survey ("T2 non-returners"; N=405). As reported earlier under "Comparing caregiver samples" (p.49), returners did not differ from T2 non-returners in any study variables (race/ethnicity and gender), except age: returners were older than non-returners, $p= .001$. No significant differences between returners and non-returners were found in patient functioning ($t(885)= -.500$, $p= .617$), subjective caregiving stress ($t(870)= -.040$, $p= .968$), and CES-D score ($t(842)=.816$, $p= .415$).

Identifying correlates of disease presence at T1. Hierarchical logistic regression modeling was used to determine whether proposed predictors measured at two years post-diagnosis (T1) were associated with CVD risk and manifestation condition presence at that time. For each outcome, covariates (age, race/ethnicity, patient functioning) were entered in step one, main effects (subjective stress, CES-D, gender) in step two, and two-way interactions (stress by CES-D and by gender) in step three. These regressions were run both with the T1 completers (N= 804) and with the limited returners sample (N= 491). This was done to take advantage of the T1 completers sample's higher power to find significant correlations between the predictors and disease presence at T1, while being able to show these significant effects were not driven from the non-returners alone.

Comparing partial regression coefficients across the two samples ensures the generalizability of the full T1 completers sample results to returners.

As shown in Table 14 (see upper half), using the T1 completers (N= 804), the CVD risk conditions overall were related to older age (p< .001) and greater depressive symptoms (p= .001). Older age was strongly related to reporting specific CVD risk conditions that required physician's care or prescription medication, such as hypertension and high cholesterol (ps< .001). Reporting more depressive symptoms was also related to specific CVD risk conditions, such as hypertension and obesity (ps< .035). Although gender was not related to the overall CVD risk condition (p= .213), women were more likely than men to endorse requiring physician's care or prescription medication for obesity (p< .001). There also was a marginally significant trend for a positive association between subjective stress and diabetes (p= .062), even though subjective stress was not related to risk conditions overall (p= .917). Race/ethnicity, patient functioning, and two-way interactions were not related to any CVD risk condition at T1 (ps> .114).

Also shown in Table 14 (see lower half), the CVD manifestations overall were related to older age (p< .001) and greater subjective stress from caregiving (p= .010). Older age was strongly related to reporting specific CVD manifestations that required physician's care or prescription medication, such as angina/CHD and cardiac arrest/CHF/heart attack (ps< .001). Experiencing greater subjective stress from caregiving was also related to the specific conditions of angina/CHD, cardiac arrest/CHF/heart attack, and also stroke (ps< .039). Race/ethnicity, patient functioning, CES-D, gender, and two-way interactions were not related to any CVD manifestation at T1 (ps> .156).

Next, the same hierarchical logistic regression modeling was performed for returners' T1 data (*N*= 491). As shown in Table 15 (see upper half), the CVD risk conditions overall were related significantly only to older age (*p*< .001), with a moderately significant trend for association with greater depressive symptomatology (*p*= .078). Older age was strongly related to reporting needing clinical care for the specific CVD risk conditions of hypertension and high cholesterol (*p*s< .001). Endorsing more depressive symptoms was positively related to hypertension (*p*= .004). While gender was not related to CVD risk conditions overall (*p*= .545), women were more likely to require a physician's care or prescription medication for obesity (*p*= .048). Race/ethnicity, patient functioning, subjective stress, and two-way interactions were not related to any CVD risk conditions at T1 (*p*s> .296).

Also shown in Table 15 (see lower half), the CVD manifestations were strongly related to older age (*p*< .001), and had a marginally significant positive association with subjective stress (*p*= .068). Older age was strongly related to requiring care for the specific manifestation conditions of angina/CHD, cardiac arrest/CHF/heart attack, and irregular heartbeat/pacemaker/murmur (*p*s< .030), and there was a marginally significant positive trend with stroke (*p*= .084). Subjective stress showed a marginally significant positive trend with the specific conditions of cardiac arrest/CHF/heart attack and irregular heartbeat/pacemaker/murmur (*p*s< .090). Race/ethnicity, patient functioning, CES-D, gender, and two-way interactions were not related to any CVD manifestation at T1 (*p*s> .157).

While *p*-values tended to be larger in the returner sample compared to the full sample, the direction and values of the regression coefficients remained comparable

between the two samples. This indicates that the removal of non-returners from the analyses does not dramatically change the patterns of results, but that changes in results are due to a loss of power from reduced sample size.

Predicting development of CVD risk and manifestation conditions between two and five years post-diagnosis. The same three-step hierarchical regression model used to identify correlates of disease at T1 (two years post-diagnosis) was used to discover what demographic and psychosocial factors predict CVD risk and manifestation condition development between T1 and T2 (five years post-diagnosis). For each outcome, only returners who did not endorse ever receiving treatment for the condition at T1 were used in the analysis, allowing the regression to evaluate the power of the covariates and psychosocial variables to predict development of disease between T1 and T2.

As shown in Table 16, the proposed covariates (age, race/ethnicity, and patient functioning) were related to development of CVD conditions. Older participants at T1 were more likely to develop high cholesterol by T2 (p= .001), and there was a marginally significant trend towards older participants being more likely to develop any risk condition by T2 (p= .071). Racial/ethnic minorities were more likely to develop any risk condition between T1 and T2 (p= .019). Poorer patient functioning predicted greater risk of reporting heart attack/CHF/cardiac arrest between T1 and T2 (p= .042), and it showed a marginally significant trend for predicting greater risk of developing angina/CHD between T1 and T2 (p= .078).

After controlling for the variances accounted for by covariates, the unique contribution of main effects of subjective stress, depressive symptoms, and gender were examined. As shown in the middle columns of Table 16, reporting higher subjective

stress from caregiving at T1 showed a marginally significant trend for greater risk of developing any of the risk conditions studied by T2 (p= .098). Endorsing more depressive symptoms at T1 predicted higher risk for developing obesity and any of the manifestations studied, specifically pacemaker/murmur/irregular heartbeat by T2 (ps< .044). Men were more likely to develop high cholesterol and heart attack/CHF/cardiac arrest between T1 and T2 (ps< .021).

Next, to evaluate the extent to which the study variables have additive or synergistic effects on CVD conditions, two-way interaction effects between main study variables (specifically between subjective stress and depressive symptoms and between subjective stress and gender) were tested. The interaction between subjective stress and CES-D significantly predicted greater risk for developing any of the manifestations studied (p= .039) and irregular heartbeat/pacemaker/murmur (p= .006). In order to help interpret the interactions, presence of a newly developed CVD condition was regressed on CES-D values centered at one standard deviation above and below the mean (M= 10.483, SD= 9.945) as a function of the other covariates, main effects, and two-way interaction. For manifestations overall, at high levels of depressive symptomatology (one SD above the CES-D mean), subjective stress was a positively associated but non-significant predictor of the conditions (B_{stress}= .684, SE_{stress}= .689, p = .321). However, at low levels of depressive symptomatology (one SD below the CES-D mean), subjective stress was a negatively associated but non-significant predictor of the conditions (B_{stress}= -.359, SE_{stress}= .772, p = .642).

For irregular heartbeat/pacemaker/murmur, the same new CES-D centering procedure was followed (CES-D M= 10.337, SD= 9.716) and the two new hierarchical

logistic regressions run. The same pattern of interaction as seen for manifestations overall was seen with this specific condition: at high levels of depressive symptomatology, subjective stress was a positively associated but non-significant predictor of the conditions (B_{stress}= .923, SE_{stress}= .826, p = .264), while at low levels of depressive symptomatology, subjective stress was a negatively associated but non-significant predictor of the conditions (B_{stress}= -.680, SE_{stress}= .930, p = .464).

For both overall manifestation and irregular heartbeat/pacemaker/murmur, greater caregiving stress is associated with increased risk developing the conditions among caregivers who report greater levels of depressive symptoms, whereas greater caregiving stress is associated with less risk of developing the conditions among caregivers who report lower levels of depressive symptoms.

Power analysis. The total achieved power for finding significant results for the main effects and two-way interactions was conducted using G*Power 3.1.3 (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007). As shown in Table 17, CES-D was the most underpowered predictor ($1-\beta < .054$) due to the small effect size, while gender and subjective stress achieved higher power ($1-\beta > .420$). The two-way interactions were also significantly underpowered ($1-\beta < .188$), except stress by gender for risk overall approached adequate power ($1-\beta = .776$).

Chapter 6: Discussion

The current study compared cancer caregivers with an age-, gender-, and race/ethnicity-matched U.S. national sample to determine whether caregivers had higher prevalence rates of CVD risk conditions and manifestations (Hypothesis 1). The CVD risk conditions studied included hypertension, obesity, diabetes, and high cholesterol; CVD manifestations studied included angina/CHD, cardiac arrest/CHF/heart attack, and stroke. Results showed that at two and five years after the care recipient's cancer diagnosis, cancer caregivers had comparable cardiovascular health to the general population.

The second aim of the study was to examine the extent to which earlier subjective caregiving stress predicted development of CVD risk conditions and manifestations (Hypothesis 2.1) and to determine whether depressive symptomology and gender moderated the links between caregiving stress and development of CVD conditions (Hypotheses 2.2 and 2.3, respectively). Hierarchical logistic regressions revealed that caregiving stress, depressive symptoms, and gender were related to CVD conditions studies in different ways. Specifically, caregiving stress at two years post-diagnosis was positively associated with the presence of several markers of CVD manifestations at that time, and only marginally with the development of any CVD risk conditions by three years later. On the other hand, depressive symptomatology was positively associated with CVD risk condition presence at T1 and significantly associated with the development of several CVD outcomes by three years later. Women were more likely to be obese at two years post-diagnosis, while men were more likely to develop high cholesterol and cardiac arrest/CHF/heart attack by five years post-diagnosis.

In addition to these main effects, two interaction effects were also significant. At high levels of depressive symptomatology, subjective caregiving stress at two years post-diagnosis increased likelihood of developing any CVD manifestation and irregular heartbeat/pacemaker/murmur specifically by three years later. In contrary, at low levels of depressive symptomatology, the opposite relationship was found. The two-way interactions (including stress by gender) were not significantly associated with the presence or development of any other CVD risk condition or manifestation.

Aim One: Prevalence of Risk Conditions and Manifestations of CVD in Cancer Caregivers

It was hypothesized that cancer caregivers would show higher prevalence of CVD risk conditions and manifestations than the general population at both two (T1) and five (T2) years post-diagnosis, due in part to the stress of providing functional and emotional support to their care recipients (Hypothesis 1). Results revealed caregivers had comparable prevalence rates of CVD risk conditions and manifestations compared with the age-, race/ethnicity-, and gender-matched data from NHANES, except for two conditions at T1 (high cholesterol and overweight) and one condition at T2 (overweight [BMI $\geq$ 25]). Although results overall failed to support Hypothesis 1, these results come as good news about the overall state of cardiovascular health of cancer caregivers. Our results showed that cancer caregivers in general had comparable cardiovascular health to the general population, a finding which is mostly consistent with larger caregiving literature, although mainly for caregivers of patients with dementia. Two reviews also found only a minute average effect size for poorer health in caregivers compared to non-caregivers (Pinquart & Sörensen, 2003, Vitaliano et al., 2003).

However, our findings are not consistent with the recent study by Ji and colleagues (2012) that showed that spouses of cancer patients had greater risk for CHD and stroke after their spouse was diagnosed compared to those without a spouse with cancer. This difference was present immediately after diagnosis (<1 year since diagnosis) through extended survivorship (>5 years post-diagnosis). Their sample was considerably older than our caregiver sample, approximately 11 years older on average, perhaps contributing to differences in our findings. Different findings between Ji and colleagues' (2012) study and our study may also be attributable to differences in method of data collection (medical record review versus self-report) and familial relationship of caregivers to the patient (spouse versus any informal family and close friends).

Despite the overall comparable cardiovascular health of our caregivers to the matched U.S. population at two and five years post-diagnosis, there are indications that cancer caregivers may be at increased risk for CVD conditions at later time points than the national population. At T1, caregivers had a significantly lower rate of high cholesterol than the national sample; however, at T2 that difference had disappeared. At both T1 and T2, caregivers who had received treatment for "obesity (overweight)" was significantly lower, when compared with a BMI of 25 and above in NHANES. This difference, however, became non-significant when compared with the prevalence from a NHANES question whether participants had ever been told by a doctor that they were overweight. Results from this latter question, being more comparable to the self-report question caregivers answered about receiving treatment for "obesity (overweight)," suggests that rates of medically attended weight problems between the two populations are comparable.

It is also telling that the raw prevalence of all CVD risk conditions and manifestations had significantly increased from T1 to T2 among caregivers who completed both surveys. Incidence rates for the CVD conditions in caregivers participating at both of our study's time points appear to be higher than those at the average age of our caregivers. Nationally, men aged 55-64 have a combined incidence of heart attack, angina, coronary insufficiency, and fatal CHD of 16.4 cases per 1,000 person-years and women of the same age have 6.4 cases, while our caregivers have a rate of 20.36 cases per 1,000 person-years for angina/CHD and cardiac arrest/CHF/ heart attack. Similarly, for stroke, men aged 55-64 have a national average of 4.3 cases per 1,000 person-years and women have 2.2 cases, while our caregivers had 5.43 (National Heart, Lung, and Blood Institute, 2006). Were these rates to remain at the same pace between T1 and T2 over time, these caregivers as a whole may end up with higher adjusted disease prevalences than the national sample over several additional years' time.

This finding contrasts with another study of Alzheimer's caregivers that reported no significant increase in major illnesses in older caregivers across a 15 to 18 month follow up period (Vitaliano, Russo, Young, Teri, & Maiuro, 1991), supporting the call for more studies of caregivers through long-term extended survivorship as well as of cancer caregivers specifically. Other studies have shown immunological dysregulation in caregivers (Kiecolt-Glaser et al., 2002; Vitaliano et al., 2003) that may lead to increased CVD risk over a longer time period as well. Future study should seek to examine whether these rapid rates of disease increase seen between T1 and T2 continue to grow exponentially, or whether they plateau after a certain time post-diagnosis.

Several trajectories of health across caregiving have been proposed—including *gradual decline/wear and tear,* where health slowly declines over time; *decline and recovery*, where health declines sharply through caregiving but rebounds across time (presumably post-caregiving duties), and *decline and stability,* where the caregiver's health declines through caregiving but plateaus after time (Schulz et al., 1990; Nijboer et al., 1999). Our results showing marked increase in CVD risk conditions and manifestations opposes proposed trajectories of *stability* (health remains stable through caregiving) and *gradual improvement* (health improves across caregiving; Schulz et al., 1990; Nijboer et al., 1999). Further investigation at another later time point will help to determine which pattern of caregivers' health through survivorship exists, based on whether rates of disease accrual accelerate, stabilize, or decline over time. While results from the current study indicate that cancer caregivers do not face higher CVD rates than their non-caregiving peers at the transition out of acute caregiving and the beginning of extended survivorship, the sharp disease prevalence rate increases documented in this study suggest caregivers may have higher CVD risk condition and manifestation rates than the general population in the longer-term.

Aim Two: Evaluating Psychosocial Variables as Correlates of Disease at T1 and as Predictors of Disease Development from T1 to T2.

It was hypothesized that caregiving stress at two years post-diagnosis would predict higher risk of developing CVD risk conditions and manifestations between two and five years post-diagnosis (Hypothesis 2.1). It was additionally hypothesized that depression and gender would moderate the relationship between caregiving stress and increased risk of developing CVD conditions, such that the positive relationship between

stress and CVD conditions will be more prominent among caregivers with higher levels of comorbid depressive symptomatology (Hypothesis 2.2) and men (Hypothesis 2.3).

Correlates at T1. Among covariates tested, only age was significantly related to any of the CVD risk conditions or manifestations. Older age related to reporting having received treatment for any risk condition, hypertension and high cholesterol specifically, and any manifestation condition, angina/CHD and cardiac arrest/CHF/heart attack specifically. Neither race/ethnicity nor patient functioning was significantly correlated with any study health outcome, which was unexpected. As African Americans and Hispanics/Latinos tend to have higher rates of CVD risk conditions such as diabetes, hypertension, and obesity (Centers for Disease Control and Prevention, 2011; Roger et al., 2012), it is possible that the small representation of racial and ethnic minorities in our sample limited our power to find a significant effect. Poorer patient functioning from more lethal cancer diagnoses has been related to elevated levels of psychological distress (Kim et al., under review; Schulz et al., 1990), but our data suggested it is not associated with CVD risk condition or manifestation presence within two years of the diagnosis. These findings support the weak and inconsistent effect of patients' functioning on caregivers' health found in a meta-analysis (Pinquart & Sörensen, 2003) from mainly studies with caregivers of dementia patients.

Appraisal of objective stressors (our subjective caregiving stress variable), depressive symptomology, and gender were proposed as primary correlates of CVD conditions beyond these covariates. Caregiving stress at T1 was associated with reporting having received treatment for most CVD manifestations—all manifestations combined, angina/CHD, cardiac arrest/CHF/heart attack, and stroke—as well as marginally

significantly associated with the CVD risk condition of diabetes. This finding is supported by previous findings showing caregivers with poorer health report more burden (Pratt, Schmall, Wright, & Cleland, 1985). As this is a cross-sectional analysis, directionality cannot be determined. It could also be possible that a third variable caused the association, such as caregivers with low income had less resources to help provide care, making caregiving more burdensome, and less likely to have insurance to cover health screenings for early detection of any illnesses. Nonetheless, stress from dementia caregiving has been shown to be associated with poorer immune functioning (Kiecolt-Glaser et al., 1987) and dysregulation of cardiovascular and metabolic systems (Vitaliano et al., 2003) , so it is possible stress early in the cancer trajectory increased our cancer caregivers' risk of cardiovascular conditions during early survivorship.

However, as the conditions associated with subjective stress tended to be more severe health events, it is possible that the increased pressure of recovering one's self from the major health event further drained these caregivers' coping resources, making caregiving a more stressful experience for unhealthy caregivers. In future studies, data on subjective stress and cardiovascular health self-report and biomarkers should be collected across the acute survivorship phase to discover whether causation exists between subjective caregiving stress and CVD manifestations early in the cancer caregiving trajectory. Determining whether directionality exists in this relationship will help to determine whether psychosocial or preventive medicine programs may be targeted for certain populations: whether caregivers experiencing their situation as burdensome should be targeted for cardiovascular health programs, or whether caregivers who

themselves have suffered major health events should be counseled on ways to positively cope with caregiving for their cancer survivor.

Whereas subjective caregiving stress was correlated with most of the CVD manifestations, endorsing greater depressive symptoms at T1 was more closely correlated with the CVD risk conditions, including receiving treatment for any risk factor, hypertension, and obesity. These results support findings that indicate those with depressive symptoms are at higher risk for cardiovascular diseases (Carney et al., 1988; Rugulies, 2002). As this was a cross-sectional analysis, however, this may also reflect the fact that those with high depressive symptomatology are more likely to report health problems than those in less psychological distress (Costa & McCrae, 1987; Schulz et al., 1994). Biobehavioral markers may play either a mediating or third-variable role in the association between depressive symptomatology and CVD risk conditions: caregivers have been shown to have higher circulating levels of inflammatory molecules such as IL-6 (Kiecolt-Glaser et al., 2002) which can contribute to CVD development (Black, 2003) and increases likelihood of having depression (Penninx et al., 2003). Collecting markers of inflammation in future studies would help clarify the nature of the relationship between CVD risk conditions and depressive symptomatology in cancer caregivers, and would help to identify potential psychoneuroimmunological mechanisms of this relationship.

Women were more likely to be obese at T1 than men, consistent with national data showing that a slightly higher proportion of adult women are obese than adult men (35.2 to 32.4 percent, respectively; Roger et al., 2012). Previous literature has shown that female caregivers as a whole are more likely to report that caregiving has negatively

impacted their health (National Alliance for Caregiving, 2009), but from the self-report data from our study, women were not more likely to have poorer overall cardiovascular health from caregiving by the time care provision had ended for the majority of participants. These results lend support to previous findings that female caregivers' lower subjective health ratings are not substantiated by more objective measures of health (Navaie-Waliser et al., 2002; Vitaliano et al., 2003).

Neither of the two-way interactions (subjective caregiving stress by depressive symptomatology and subjective stress by gender) was significantly associated with any CVD risk condition or manifestation at T1. This suggests that while subjective stress and depressive symptomatology were independently associated with CVD manifestations and risk factors, respectively, effects between diagnosis and two years post-diagnosis are not likely synergistic. While women were more likely at T1 to be obese than men, subjective caregiving stress is not disproportionately associated with obesity in women than in men. Previous research has suggested that women are more likely to report psychological distress during caregiving than men (Navaie-Waliser et al., 2002; Nijboer et al., 1999), and that higher psychological distress is associated with greater likelihood of reporting disease and use of health services (Costa & McCrae, 1987; Schulz et al., 1994), but these effects did not appear to affect report of receiving treatment for the CVD risk conditions and manifestations in this study.

Prediction of disease development: Covariates. Hierarchical logistic regression modeling was used to predict the development of disease (operationalized as starting treatment for a disease) between two years (T1) and five years (T2) post-diagnosis by main predictors measured at T1, controlling for the variances accounted for by covariates.

Among covariates, older age predicted the development of high cholesterol and a trend towards predicting the development of any risk factor overall. This was expected and supports existing findings that older populations have higher risks of developing CVD (Roger et al., 2012).

Unlike cross-sectional associations discussed in the previous section, race/ethnicity and patient functioning became significant predictors of disease development. Racial/ethnic minorities were more likely to develop any risk factor condition by T2. The significant effect found for this more powerful combined condition alludes to race/ethnicity effects in the other risk conditions, which perhaps would have been seen had the sample included a higher proportion of racial/ethnic minorities. This significant effect, and the suggestion that additional race/ethnicity effects may exist, is supported by literature that shows racial/ethnic minorities suffering higher rates of CVD risk conditions than non-Hispanic whites (Roger et al., 2012). One problem faced with the race/ethnicity covariate was the lack of a minority case developing diabetes, cardiac arrest/CHF/heart attack, and stroke between T1 and T2, meaning this covariate was not able to be studied as a predictor for those outcomes.

Being a caregiver for patients diagnosed with lower survival rate (poorer patient functioning) significantly predicted the development of cardiac arrest/CHF/heart attack and a trend toward predicting the development of angina/CHD three years later. That patient functioning was not associated with disease early in the cancer trajectory, but predicted development of disease by the beginning of extended survivorship, suggests a delayed effect of this variable on health. While intended as a proxy of level of objective caregiving stress, where patients with more severe disease are assumed to require help

with more care tasks, it may also have served as a proxy for length of care provision. As such, it is possible that it was not the patient's level of functioning at T1 affecting cardiovascular health, but instead the long-term caregiving beyond the typical one to two years most cancer caregivers spend that was contributing to CVD development. Examining the association of more specific caregiving variables such as ADL/IADL and time spent providing care may help to determine what specifically may have contributed to the greater risk of CVD development from patient functioning by five years post-diagnosis.

Prediction of disease development: Main effects. Beyond these effects of covariates, our primary study variables predicted unique variance in the development of CVD conditions in the caregivers studied. Subjective caregiving stress predicted only the development of any risk factor of CVD, although marginally significantly, providing weak partial support of Hypothesis 2.1. Subjective caregiving stress has previously been supported as an important predictor of caregivers' long-term health, primarily in studies of dementia caregivers (Goode et al., 1988; Son et al., 2007; Vitaliano et al., 2002). The failure replicating such finding with our data may be due to several reasons. First, it is possible that subjective caregiving stress may not predict or contribute to CVD development in cancer caregivers. While levels of caregiving burden have been shown to be comparable between cancer and dementia caregivers during active caregiving, the shorter typical duration of cancer caregiving compared with that for dementia may keep subjective stress below a health-altering threshold. Second, the study design may have impacted results: capturing caregiving stress at real time (while they are actively engaging in caregiving activities) would have been a more accurate representation than

the use of the retrospective report, as approximately half of our caregivers had completed their cancer caregiver role when they completed T1 survey.

Third, it is possible that the effects from caregiving stress may manifest in conditions related to cardiovascular disease over a longer time period than the three years between time points. While Ji et al. (2012) found significant risk increase for stroke and CHD within one year of the spouse's diagnosis, their study benefitted from approximately 14 times more cases with more precise outcome measurement. Further investigation at an extended time point may allow effects to be shown in our smaller sample size for these outcomes (as more time would allow more cases to develop, increasing the event rate and power to detect significant effects). Our study also included more chronic, slowly developing conditions such as obesity, diabetes, and cardiac dysrhythmias. Extending time between observations would allow the slower, chronic conditions to more fully develop to require clinical attention, increasing the event rate for these conditions as well. Finally, while subjective stress may not act as a consistent predictor of CVD risk condition and manifestation development, a third variable might moderate the association between caregiving stress and development of CVD conditions. This potential reason was further investigated testing Hypotheses 2.2 and 2.3.

The degree to which caregivers experienced depressive symptomology while they provided cancer care to their relative was proposed as a moderator of the association between subjective caregiving stress and the development of CVD conditions (Hypothesis 2.2). Unexpectedly, main effects for depressive symptomatology on development of CVD were found to be stronger than those for subjective stress. Higher levels of depressive symptomatology reported at T1 significantly predicted increased risk

of developing obesity, and any of the manifestations studied, specifically irregular heartbeat/pacemaker/murmur by T2.

These findings are partially consistent with the existing literature, where depressive symptomatology has been linked to increased risk of CVD development (Pozuelo et al., 2009; Rosengren et al., 2004; Rugulies, 2002). However, depressive symptomatology has also been shown to significantly predict the study outcomes of hypertension (Davidson et al., 2000) and cardiac events (Frasure-Smith et al., 1995), which was not replicated in our results. It is possible that low power (only five percent achieved for both risk and manifestation combined conditions) prevented analyses from yielding more significant findings for this predictor. That risk of developing certain CVD risk conditions and manifestations varies significantly across the continuum of depressive symptomatology suggests that all caregivers' health may benefit interventions that are successful in ameliorating any symptoms of depression, such as fatigue, trouble with sleeping and appetite, anhedonia, and dysphoric mood, rather than only those with clinically significant depression.

Main effects were also shown for gender: male caregivers were more likely to develop high cholesterol and cardiac arrest/CHF/heart attack between T1 and T2. This is consistent with existing literature, which shows that men experience more CVD events related to CHD proportionally than do women before the age of 75 (National Heart, Lung, and Blood Institute, 2006; Roger et al, 2012).

Prediction of disease development: Moderator effects. Importantly, these three study variables were shown to play a significant synergistic role in CVD development. In other words, while subjective caregiving stress did not play a significant role in

predicting development of CVD conditions alone, it did when interacting with the degree to which the caregiver experienced comorbid depressive symptomology. This was particularly true for the development of any manifestation and of irregular heartbeat/ pacemaker/murmur. Findings showed that caregivers who simultaneously reported feeling overwhelmed by providing care along with high depressive symptomatology were more likely to develop any CVD manifestation condition and specifically irregular heartbeat/pacemaker/murmur than those who experienced only elevated subjective stress with average levels of depressive symptomatology. The opposite pattern (caregiving stress inversely related to the development of such CVD condition) was the case among those who experienced lower than average levels of depressive symptomology while providing care.

This significant shift in the relationship between subjective caregiving stress and CVD manifestation development risk supports Hypothesis 2.2, which proposed that at higher levels of depressive symptomatology, subjective stress would have a more detrimental effect on CVD risk condition and manifestation development. These findings imply that subjective stress may be an important warning sign for future CVD risk in caregivers who experience higher than average depressive symptomatology, whereas for those caregivers who are experiencing very few depressive symptoms, subjective stress may not pose a significant health threat. Clinically, this suggests that depressive symptomatology may be a more important intervention target to ameliorate long-term increased risk of CVD development.

Potential mechanisms of this additive effect between subjective caregiving stress and depression may be psychological in nature. At higher levels of depressive symptoms,

caregivers may be less able to enact effective coping methods to deal with subjective burden, such as rally social support, thus failing to alleviate stress and leading to increased health risk. Comorbid depressive symptoms and feelings of being overwhelmed may also interact to significantly impact caregivers' health behaviors, causing caregivers to neglect their own dietary and exercise needs. Immunological mechanisms may also underlie the synergistic effect of comorbid depressive symptoms and subjective stress. As depression and stress affect the body through similar pathways by flooding the body with stress hormones (Checkley, 1996), the double dose of stress hormones may hit a critical threshold to cause lasting physiological damage.

The association between subjective caregiving stress and development of CVD conditions was not moderated by caregivers' gender, failing to support Hypothesis 2.3, suggesting that caregiver stress experienced throughout the extended survivorship trajectory impacts men's and women's cardiovascular health comparably. Vitaliano et al. (2002) found that chronic stress induced from long-term dementia caregiving affected men's risk of CHD through psychological distress significantly more than for women, but this caregiving stress by psychological distress interaction was not found in our caregivers. Their study differed from ours in several crucial ways: caregivers were on average 15 years older than the current sample, had been providing care for an average of approximately four years at study outset, and were providing active care to a degenerative spouse during the entirety of their caregiving. Differences in gender by caregiving stress findings may be a result of caregiving factors such as intensity and duration or of sample characteristics. These different findings echo the message of the review of caregiving by Clipp and George (1993), who suggested that due to significant differences in caregiving

factors and typical age differences, the caregiving experiences of cancer and dementia caregivers are not comparable.

Clinically, findings that depressive symptomatology both predicted and moderated development of CVD manifestations suggest that interventions to ameliorate depressive symptoms in caregivers may not only improve caregiver quality of life, but decrease risk for CVD development over time. Targeting depressive symptomatology may also decrease the negative impacts of subjective stress from caregiving, as suggested from the moderation analyses. These results additionally emphasize the importance of reminding distressed caregivers and those whose care recipients have more severe cancer diagnoses of the importance of taking care of themselves in the midst of taking care of another, such as with recommended health behaviors such as healthy diet and exercise.

Limitations

Limitations of this study hinge around the questionnaire design of the project, including use of self-report data, lack of biobehavioral markers, and sampling bias. While the questionnaire design allowed for efficient and feasible data collection on a large national sample, questionnaires rely on accuracy of self-report data, which can be skewed. Female caregivers are more likely to report psychosocial distress than their male counterparts (Navaie-Waliser et al., 2002; Nijboer et al., 1999), and those who are in greater psychological distress tend to have a negative memory bias and report they are in poorer health (Costa & McCrae, 1987; Schulz et al., 1994). These effects have the possibility of confounding the two-way interaction between subjective stress and gender, biasing the effects towards women reporting more stress and disease than their male counterparts. However, women have also been shown to be more accurate in disease self-

report (Okura et al., 2004), and as no effect was found for the subjective stress by gender interaction, confounding is not a significant concern. Additionally, while self-report for receiving treatment for major and prevalent diseases such as those chosen for the CVD risk conditions and manifestations tends to be well remembered and closely correlated with actual disease (Okura et al., 2004), self-report is less accurate than data collected directly from medical records. While medical record review is more accurate, this would not be a feasible method of data collection for the large sample size of the current project without national medical registries.

This study also did not include the collection of biological markers of stress and CVD such as inflammatory markers like IL-6 or stress hormones like cortisol. As discussed in aim two correlational analyses, biomarkers may act as clues to underlying physical mechanisms of psychosocial variables' effects on CVD development. Increased risk of disease development as a result of the various study variables may also be due to a number of causes outside of factors related to psychoneuroimmunology (PNI), including situational factors such as poorer health behaviors and adherence to medical regimens resulting from psychological distress. For instance, inflammatory markers have been found to be significantly higher in depressed patients (Penninx et al., 2003), and depressive symptoms have also been associated with poorer health behaviors (Allgöwer, Wardle, & Steptoe, 2001), both of which can negatively impact cardiovascular health. Without information on inflammation and stress biomarkers, the causes of changes in health due to psychosocial distress cannot be reliably attributed to PNI-related factors.

Another limitation of the current study is the narrow sample diversity resulting from sampling bias. While the original sampling distribution for the Study of Cancer

Survivors I was stratified to accrue a sizable number of minority participants, fewer minority cancer survivors returned the original survey, including nominations of family members for the National Quality of Life Survey for Caregivers. Within this smaller pool of minority family member nominations, fewer of these nominees returned their caregiver surveys. Therefore, minorities comprised less than 10 percent of the final participants. These relatively unitary sample demographics limit the generalizability of results, so caution is indicated when generalizing findings to non-Hispanic whites.

The caregiver sample also had a high SES overall, with the majority of participants having household incomes over $40,000 per year and receiving at least some college or vocational school education or more. As an inverse relationship exists between SES and cardiovascular health, possibly mediated by psychosocial distress (Gallo & Matthews, 2003), findings from this high-SES population may not accurately capture the health risks accrued from adding pressures of caregiving on top of pressures of a lower-SES lifestyle.

Finally, while this survey is the largest study of cancer caregivers to date with a large sample size (896 returning T1 and 491 returning both T1 and T2), as the event rates for CVD risk conditions and manifestations can be low and the effect sizes small, power for the analyses was limited. With low minority participation, standard error in the standardized disease prevalence rates for caregivers was high, thus limiting the ability to detect significant differences from the national sample rates. Power was also limited to find significant effects of predictors on CVD risk condition and manifestation development, most significantly for CES-D which only had an achieved power of .052 for predicting the development of any risk factor and .054 for any manifestation.

Achieved power for the predictors of subjective stress and gender, however, were higher, with power of .827 and .510 achieved for any risk factor, respectively, and .420 and .626 for any manifestation, respectively.

Future Directions

While power to identify and generalize significant results from this study is limited for the aforementioned reasons, the National Quality of Life Survey for Caregivers is the single largest survey of cancer caregivers to date. As such, this data contains valuable clues to cancer caregivers' unique experiences and needs. More sophisticated methodological and statistical plans, such as more targeted hypothesis testing and use of structural equation and hierarchical linear modeling techniques, should be utilized to improve power in analyses with this data set. Future studies should seek to supplement questionnaire data by collecting biomarkers associated with psychological and physiological disease, such as IL-6, TNF-α, and cortisol. These biomarkers would help illuminate underlying biological mechanisms that may drive the effect of psychological distress from caregiving manifesting into CVD. Along with these biological mechanisms, behavioral mechanisms such as diet and exercise habits should also be investigated as potential underlying driving forces of the effect between psychological distress and disease development.

While it is impressive that results were seen across the short time lapse of three years between T1 and T2, discovering how stress and depressive symptomatology from caregiving impacts the development of these chronic conditions farther into extended survivorship will provide a more complete understanding of the ramifications of the caregiving experience on long-term health outcomes. While the atherosclerotic process

typically develops over decades, distress during cancer caregiving may spark a "period of rapid evolution" (part 10, section 5; Libby, 2012) manifesting in disease across the decade post-diagnosis. The median follow-up time in a major meta-analysis of studies showing effects of depression on CVD was 8.65 years (Rugulies, 2002); including a third investigation time point at eight years post-diagnosis should show distress effects on health at that time if they exist in this population. This would also produce a symmetrical study design with three years between each time point.

Tracking the health risk of caregivers farther into the extended survivorship phase would allow us to track whether spikes in risk for CVD in caregivers seen immediately after diagnosis (e.g., Ji et al., 2012) are attenuated (decline and recovery pattern) or grow exponentially over time (wear and tear pattern), and what mechanisms may contribute to these risk patterns. This ability to track caregiving outcomes would be facilitated by national health registries such as those used by Ji et al. (2012) in Sweden, thus echoing the call by others for comprehensive health registries in the U.S. to facilitate long-term, large-scale studies on cancer caregivers (Schneiderman, Kim, & Shaffer, 2012) as well as innumerable other populations

These results ultimately suggest that findings from studies on elder and dementia caregiving which have been foremost in the caregiving literature should not be blindly generalized to the cancer caregiving population. Others have highlighted major differences between these caregiving experiences (Clipp & George, 1993; Kim & Schulz, 2008), and this study provides preliminary evidence that the differences in length of caregiving and kinds of care tasks required by cancer versus dementia care may lead to different health outcomes through different psychological mechanisms. Future studies

should seek to study cancer caregivers specifically to determine what psychological and preventive medicine measures may be most effective in keeping cancer caregivers healthy as this population continues to grow substantially each year.

Conclusion

Findings suggests that cancer caregivers have comparable cardiovascular health to the general population at both two and five years after their care recipient's cancer diagnosis, but that the psychosocial variables of caregiving stress and depressive symptomatology may put caregivers at a higher risk of developing CVD risk conditions and manifestations over time. These results significantly add to current understanding of cancer caregivers by showing caregiving-specific factors and psychosocial factors, depressive symptomatology most especially, uniquely predict onset of illness in caregivers above and beyond that which is accounted for by demographic factors between active caregiving and extended survivorship phases. These findings not only expand our current understanding of the pathways of health risks incurred by cancer caregivers, but also by failing to find results comparable to studies on dementia caregivers, justify the expansion of current research on the experiences and health of cancer caregivers specifically. This study provides a preliminary understanding what specific health risks cancer caregivers face across the early caregiving trajectory, building a foundation for future studies to discover what interventions may best support these caregivers and how to keep this population healthy while they are supporting their own relatives back to health.

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Table 1

Standardized Weights for Age, Race/Ethnicity, and Gender Subgroups Calculated According to the 2000 United States Census

Gender	Race	Age	Frequency	Weight
Men	Non-Hispanic white	18-44	37715	0.185009
		45-64	23320	0.114395
		65-74	6764	0.033180
		75+	5333	0.026161
	Not non-Hispanic white	18-44	16340	0.080155
		45-64	6206	0.030443
		65-74	1416	0.006946
		75+	833	0.004086
Women	Non-Hispanic white	18-44	37319	0.183066
		45-64	24204	0.118731
		65-74	8061	0.039543
		75+	8969	0.043997
	Not non-Hispanic white	18-44	16778	0.082304
		45-64	7262	0.035623
		65-74	1895	0.009296
		75+	1440	0.007064
Total:			203855	1.000000

Table 2

Cancer Severity Index: Patient Functioning Scores by Cancer Type, Stage, and Time Since Diagnosis

Cancer Site	SEER Stage	< 1 year	1 year to < 2 years	2 years to < 3 years	≥ 3 years
Bladder	Stage 0	0	0	0.003	0.010
	Localized	0.095	0.148	0.185	0.209
	Regional	0.265	0.466	0.554	0.587
	Distant	0.719	0.878	0.914	0.922
	Unstage/Unknown	0.105	0.155	0.181	0.200
Breast	Localized	0	0	0.003	0.008
	Regional	0.020	0.065	0.104	0.144
	Distant	0.376	0.527	0.635	0.720
	Unstage/Unknown	0.038	0.081	0.122	0.157
Colorectal	Localized	0.042	0.049	0.059	0.073
	Regional	0.098	0.169	0.228	0.269
	Distant	0.538	0.745	0.840	0.879
	Unstage/Unknown	0.213	0.307	0.364	0.401
Kidney	Localized	0.030	0.046	0.066	0.093
	Regional	0.161	0.263	0.338	0.383
	Distant	0.664	0.808	0.861	0.885
	Unstage/Unknown	0.265	0.345	0.383	0.410
Lung	Localized	0.195	0.316	0.395	0.451
	Regional	0.388	0.600	0.692	0.739
	Distant	0.759	0.905	0.944	0.957
	Unstage/Unknown	0.607	0.768	0.822	0.847
Melanoma of Skin	Localized	0	0	0.004	0.010
	Regional	0.069	0.172	0.302	0.356
	Distant	0.584	0.726	0.784	0.825
	Unstage/Unknown	0.038	0.071	0.098	0.116
Non-Hodgkin's Lymphoma	Localized	0.125	0.163	0.187	0.205
	Regional	0.199	0.265	0.305	0.324
	Distant	0.297	0.379	0.425	0.452
	Unstage/Unknown	0.278	0.365	0.410	0.444
Ovarian	Localized	0.019	0.038	0.048	0.048
	Regional	0.124	0.186	0.237	0.270
	Distant	0.313	0.469	0.592	0.661
	Unstage/Unknown	0.300	0.448	0.523	0.568

Prostate	Localized	0	0	0	0
	Regional	0	0	0	0
	Distant	0.236	0.427	0.550	0.606
	Unstage/Unknown	0.032	0.063	0.091	0.112
Uterine	Localized	0.080	0.202	0.202	0.346
	Regional	0.259	0.510	0.533	0.641
	Distant	0.766	0.851	0.930	N/A
	Unstage/Unknown	0.467	0.573	0.626	0.643

Table 3

Sample Descriptives: Demographics and Patient Functioning Score by Study Aims

	Aim 1: T1 Full Sample N= 896			Aim 2: Returners N= 491		
	Mean	(SD)	Range	Mean	(SD)	Range
Age	54.42	(12.77)	18.32-89.98	55.78	(12.63)	18.32-89.98
Patient Functioning	0.17	(0.23)	0-0.94	0.17	(0.25)	0-0.94
Stress Overload	1.59	(0.60)	1-4	1.59	(0.58)	1-4
CES-D	10.69	(10.05)	0-55	10.44	(9.53)	0-48

		T1 Full Sample N (%)		Returners N (%)	
Race/Ethnicity	African American	44	(4.9)	22	(4.5)
	Hispanic	10	(1.1)	2	(0.4)
	Non-Hispanic white	797	(89.0)	443	(90.2)
	Other	23	(2.5)	15	(3.0)
	Missing	22	(2.5)	9	(1.8)
Gender	Women	580	(64.7)	321	(65.4)
	Men	316	(35.3)	170	(34.6)
Household Income	Less than $20,000	41	(4.6)	19	(3.8)
	$20,000- $39,999	123	(13.7)	70	(14.3)
	$40,000-$74,999	288	(32.1)	159	(32.4)
	$75,000 or more	293	(32.7)	151	(30.8)
	Missing	151	(16.9)	92	(18.7)
Educational Attainment	Less than a high school degree	24	(2.7)	11	(2.2)
	High school degree	197	(22.0)	104	(21.2)
	Vocational school or some college	263	(29.4)	141	(28.7)
	College degree	215	(24.0)	129	(26.3)
	Professional or graduate school	176	(19.6)	97	(19.8)
	Missing	21	(2.4)	9	(1.8)
Relationship to Survivor	Spouse/Partner	587	(65.5)	345	(70.3)
	Child/Child-in-law	150	(16.8)	67	(13.6)
	Sibling	66	(7.3)	35	(7.1)
	Parent	37	(4.1)	22	(4.5)
	Friend	34	(3.8)	16	(3.3)
	Other	19	(2.1)	4	(0.8)
	Missing	3	(0.3)	2	(0.4)

Survivor Diagnosis	Bladder	23	(2.6)	12	(2.4)
	Breast	241	(26.9)	129	(26.3)
	Colorectal	129	(14.4)	67	(13.6)
	Kidney	39	(4.4)	20	(4.1)
	Lung	99	(11.0)	61	(12.4)
	Non-Hodgkin lymphoma	76	(8.5)	37	(7.5)
	Ovarian	57	(6.4)	29	(5.9)
	Prostate	158	(17.6)	93	(18.9)
	Skin melanoma	34	(3.8)	22	(4.5)
	Uterine	40	(4.5)	21	(4.3)
Survivor's SEER Cancer Stage	In Situ	19	(2.1)	12	(2.4)
	Localized	454	(50.7)	252	(51.3)
	Regional	260	(29.0)	141	(28.7)
	Distant	130	(14.5)	68	(13.8)
	Unstage/Unknown	29	(3.2)	15	(3.1)
	Missing	4	(0.4)	3	(0.6)

Table 4
Descriptives of Caregiving Variables

At T1: Caregiving	T1 Full Sample N= 896 Mean (SD)	Range	Returners N= 491 Mean (SD)	Range
In Months	18.46 (15.05)	0.5-221.0	18.78 (14.24)	0.5-120.0
Hours per Day	8.74 (8.43)	0 -24.0	9.07 (8.45)	0-24.0

At T2: Currently providing care	T2 Full Sample N= 607 N (%)		Returners N= 491 N (%)	
No	400	(65.9)	334	(68.0)
Yes- constantly since patient's diagnosis	58	(9.6)	50	(10.2)
Yes- on and off since patient's diagnosis	30	(4.9)	26	(5.3)
Yes- stopped for a while but recently began again	3	(0.5)	3	(0.6)
Missing	116	(19.1)	78	(15.9)

Note. T1 Full Sample refers to all caregivers who returned a T1 survey; T2 Full Sample refers to all caregivers who returned a T2 survey; Returners refer to caregivers who returned both a T1 and T2 survey

Table 5

Raw Prevalence Rates of CVD Risk Conditions and Manifestations

Condition		Full Sample T1 (N=896) N Yes (%)	Full Sample T2 (N=607) N Yes (%)	Returners at T1 (N=491) N Yes (%)	Returners at T2 (N=491) N Yes (%)
Risk	Hypertension	297 (33.1)	260 (42.8)	164 (33.4)	219 (44.6)
	High Cholesterol	281 (31.4)	266 (43.8)	155 (31.6)	235 (47.9)
	Diabetes	100 (11.2)	73 (12.0)	48 (9.8)	61 (12.4)
	Obesity	190 (21.2)	187 (30.8)	110 (22.4)	160 (32.6)
Manifestation	Angina, CHD	81 (9.0)	67 (11.0)	34 (6.9)	58 (11.8)
	Cardiac Arrest, CHF, Heart Attack	67 (7.5)	43 (7.1)	34 (6.9)	40 (8.1)
	Irregular Heartbeat, Pacemaker, Murmur	117 (13.1)	107 (17.6)	63 (12.8)	90 (18.3)
	Stroke	47 (5.2)	38 (6.3)	25 (5.1)	33 (6.7)

Table 6

Correlations between CVD Risk Conditions and Manifestations Present at T1Using Full T1 Sample (N= 896)

Spearman's ρ*	Hypertension	High Cholesterol	Diabetes	Obesity
Hypertension	-			
High Cholesterol	.449	-		
Diabetes	.308	.310	-	
Obesity	.284	.250	.371	-
Angina/CHD	.315	.315	.358	.208
Cardiac Arrest/ CHF/ Heart Attack	.260	.293	.411	.268
Irregular Heartbeat/ Pacemaker/Murmur	.199	.174	.231	.220
Stroke	.228	.240	.394	.258

Spearman's ρ*	Angina/ CHD	Cardiac Arrest/ CHF/ Heart Attack	Irregular Heartbeat/ Pacemaker/Murmur
Angina/CHD	-		
Cardiac Arrest/ CHF/ Heart Attack	.606	-	
Irregular Heartbeat/ Pacemaker/Murmur	.421	.419	-
Stroke	.502	.599	.399

* all *p*s< .001

Table 7

Correlations between CVD Risk Conditions and Manifestations Present at T2 Using Full T2 Sample (N= 607)

Spearman's ρ*	Hypertension	High Cholesterol	Diabetes	Obesity
Hypertension	-			
High Cholesterol	.446	-		
Diabetes	.227	.258	-	
Obesity	.303	.209	.286	-
Angina/CHD	.105 (.020)	.209	.301	.215
Cardiac Arrest/ CHF/ Heart Attack	.079 (.081)	.173	.334	.193
Irregular Heartbeat/ Pacemaker/Murmur	.072	.088 (.051)	.106 (.019)	.143
Stroke	.114 (.012)	.205	.397	.197

Spearman's ρ*	Angina/ CHD	Cardiac Arrest/ CHF/ Heart Attack	Irregular Heartbeat/ Pacemaker/Murmur
Angina/CHD	-		
Cardiac Arrest/ CHF/ Heart Attack	.601	-	
Irregular Heartbeat/ Pacemaker/Murmur	.335	.288	-
Stroke	.389	.440	.240

* all *p*s< .001, unless otherwise noted in parentheses

Table 8

Tests of Significance between T1 and T2 Raw Prevalence Rates and Incidence Rates for CVD Risk Conditions and Manifestations in Returners (N= 491)

Condition	Returners at T1 N Yes (%)	Returners at T2 N Yes (%)	SE	t-value	p-value	New cases at T2 N (%)	Incidence per 1000 person-years
Hypertension	164 (33.4)	219 (44.6)	.01	7.86	<.001	55 (11.20)	37.34
High Cholesterol	155 (31.6)	235 (47.9)	.02	9.77	<.001	80 (16.29)	54.31
Diabetes	48 (9.8)	61 (12.4)	.01	3.65	<.001	13 (2.65)	8.83
Obesity	110 (22.4)	160 (32.6)	.01	7.45	<.001	50 (10.18)	33.94
Angina/CHD	34 (6.9)	58 (11.8)	.01	5.02	<.001	24 (4.89)	16.29
Cardiac Arrest/CHF/Heart Attack	34 (6.9)	40 (8.1)	.01	2.46	.014	6 (1.22)	4.07
Irregular Heartbeat/Pacemaker/Murmur	63 (12.8)	90 (18.3)	.01	5.34	<.001	27 (5.50)	18.33
Stroke	25 (5.1)	33 (6.7)	.01	2.85	.005	8 (1.63)	5.43

Table 9

Correlations between CVD Risk Conditions and Manifestations New at T2 among Returners (N= 491)

Spearman's ρ*	New Risk Overall	New Hypertension	New High Cholesterol	New Diabetes	New Obesity
New Risk Overall	-				
New Hypertension	.530 (.019)	-			
New High Cholesterol	.659	.245	-		
New Diabetes	.246	.062 (.170)	.030 (.503)	-	
New Obesity	.503	.094 (.037)	.070 (.120)	.028 (.531)	-
New Manifestation Overall	.109 (.019)	.096 (.033)	.154 (.001)	.061 (.180)	-.015 (.742)
New Angina/CHD	.032 (.478)	-.021 (.649)	.079 (.080)	-.037 (.408)	.017 (.701)
New Cardiac Arrest/ CHF/ Heart Attack	.006 (.899)	.078 (.084)	.001 (.980)	.097 (.031)	.024 (.598)
New Irregular Heartbeat /Pacemaker/Murmur	.090 (.047)	.113 (.013)	.160	-.040 (.379)	-.052 (.253)
New Stroke	.053 (.241)	.056 (.213)	.030 (.502)	.179	-.043 (.338)

Spearman's ρ*	New Manifestation Overall	New Angina/ CHD	New Cardiac Arrest/ CHF/ Heart Attack	New Irregular Heartbeat/ Pacemaker/ Murmur
New Manifestation Overall	-			
New Angina/CHD	.632	-		
New Cardiac Arrest/ CHF/ Heart Attack	.310	.233	-	
New Irregular Heartbeat/ Pacemaker/ Murmur	.672	.111 (.014)	.054 (.228)	-
New Stroke	.359	.045 (.315)	-.014 (.752)	.040 (.382)

* all *p*s< .001, unless otherwise noted in parentheses

Table 10

Aim One: Age, Race, and Gender Adjusted Prevalence Rates for Caregivers' CVD Risk Conditions and Manifestations

	T1 Full Sample N= 896		T2 Full Sample N= 607		Returners at T1 N= 491		Returners at T2 N= 491	
Condition	% Yes	SE (%)	% Yes	SE (%)	% Yes	SE (%)	% Yes	SE (%)
Hypertension	38.89	5.31	38.30	7.70	26.50	6.39	38.44	7.84
High Cholesterol	21.07	5.38	34.25	7.66	18.59	6.58	36.14	7.84
Diabetes	16.94	5.21	15.75	6.15	14.00	5.96	14.00	5.96
Obesity	24.91	5.66	34.68	8.97	19.85	6.94	34.55	9.10
Angina/CHD	7.90	3.86	7.08	5.21	2.29	2.22	7.35	5.31
Cardiac Arrest/CHF/Heart Attack	3.59	2.65	2.02	1.96	2.29	2.22	2.29	2.22
Heart Murmur/Pacemaker/Irregular Heartbeat	10.61	4.03	14.16	7.01	9.64	5.69	14.70	7.14
Stroke	4.73	2.86	4.05	2.69	4.59	3.02	4.59	3.02

Table 11

Aim One: Age, Race, and Gender Adjusted Prevalence Rates for National Sample's CVD Risk Conditions and Manifestations

	NHANES 2003-2004 N= 5397		NHANES 2005-2006 N=5393	
Condition	% Yes	SE (%)	% Yes	SE (%)
Hypertension	33.03	1.15	32.69	1.14
High Cholesterol	37.37	1.69	34.27	1.62
Diabetes	12.60	0.90	13.81	0.99
Overweight (BMI $\geq$ 25)	66.09	1.28	65.13	1.31
Overweight (told by doctor)	N/A	N/A	34.72	1.27
Angina	2.90	0.47	2.21	0.45
CHD	2.18	0.40	1.94	0.42
Combined Angina and CHD	4.31	0.56	3.87	0.58
CHF	1.99	0.39	2.82	0.50
Heart attack	3.03	0.48	1.82	0.42
Combined CHF and Heart Attack	4.09	0.55	4.20	0.62
Stroke	3.06	0.48	3.57	0.58

Table 12

Aim One: Standardized Rate Ratio Confidence Intervals at T1

	Caregiver T1 Full Sample N= 896		NHANES 2003-2004 N= 5397		95% CI Upper	95% CI Lower
Condition	% Yes	SE (%)	% Yes	SE (%)		
Hypertension	38.89	5.31	33.03	1.15	1.582	0.876
High Cholesterol	21.07	5.38	37.37	1.69	0.830	0.383
Diabetes	16.94	5.21	12.60	0.90	2.716	0.666
Overweight (BMI $\geq$ 25)	24.91	5.66	66.09	1.28	0.493	0.288
Angina/CHD	7.90	3.86	4.31	0.56	6.617	0.508
Cardiac Arrest/CHF/Heart Attack	3.59	2.65	4.09	0.55	3.476	0.222
Stroke	4.73	2.86	3.06	0.48	6.755	0.354

Table 13

Aim One: Standardized Rate Ratio Confidence Intervals at T2

	Caregiver T2 Full Sample N= 607		NHANES 2005-2006 N= 5393		95% CI Upper	95% CI Lower
Condition	% Yes	SE (%)	% Yes	SE (%)		
Hypertension	38.30	7.70	32.69	1.14	1.798	0.763
High Cholesterol	34.25	7.66	34.27	1.62	1.561	0.640
Diabetes	15.75	6.15	13.81	0.99	2.597	0.501
Overweight (BMI $\geq$ 25)	34.68	8.97	65.13	1.31	0.768	0.369
Overweight (Told by Doctor)	34.68	8.97	34.72	1.27	1.662	0.600
Angina/CHD	7.08	5.21	3.87	0.58	12.522	0.267
Cardiac Arrest/CHF/Heart Attack	2.02	1.96	4.20	0.62	1.848	0.125
Stroke	4.05	2.69	3.57	0.58	4.648	0.277

Table 14

Aim Two: Correlates of Disease Presence at T1 with Full T1 Sample (N= 804)

	Covariates						Main Effects						Two-Way Interactions			
	Age		Race/ Ethnicity*		Patient Functioning		Subjective Stress		CES-D		Gender†		Subjective Stress x CES-D		Subjective Stress x Gender	
Condition	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p
Risk Overall	.066 (.007)	<.001	.076 (.269)	.778	-.399 (.323)	.217	-.015 (.141)	.917	.028 (.008)	.001	-.200 (.161)	.213	.005 (.012)	.651	-.054 (.285)	.850
Hyper-tension	.056 (.007)	<.001	.349 (.281)	.214	-.307 (.343)	.370	.210 (.146)	.152	.018 (.008)	.035	-.087 (.167)	.601	.006 (.012)	.590	-.175 (.293)	.551
High Cholesterol	.060 (.007)	<.001	.027 (.300)	.928	-.564 (.356)	.114	.094 (.152)	.534	.014 (.009)	.102	.036 (.168)	.829	-.004 (.013)	.774	-.338 (.299)	.258
Diabetes	.013 (.009)	.137	.469 (.356)	.187	-.484 (.514)	.347	.357 (.191)	.062	.008 (.012)	.473	-.092 (.239)	.701	-.012 (.016)	.479	-.223 (.393)	.570
Obesity	.009 (.007)	.198	.041 (.309)	.894	-.362 (.385)	.347	-.011 (.157)	.946	.024 (.009)	.007	-.737 (.201)	<.001	-.002 (.013)	.856	.044 (.363)	.903
Manifestation Overall	.037 (.008)	<.001	.020 (.339)	.952	-.425 (.405)	.295	.420 (.163)	.010	.005 (.010)	.617	.159 (.188)	.397	-.019 (.014)	.171	.312 (.331)	.346
Angina/CHD	.055 (.011)	<.001	-.505 (.614)	.411	-.441 (.578)	.446	.545 (.227)	.016	.013 (.013)	.339	.287 (.260)	.271	-.006 (.019)	.767	.516 (.461)	.263
Cardiac Arrest/CHF/ Heart Attack	.039 (.011)	.001	-.843 (.737)	.253	-.575 (.638)	.368	.617 (.239)	.010	.003 (.015)	.849	.395 (.279)	.156	-.004 (.021)	.847	-.087 (.456)	.849
Irregular Heartbeat/ Pacemaker/ Murmur	.013 (.008)	.103	.106 (.364)	.770	-.483 (.472)	.306	.267 (.180)	.138	.009 (.011)	.402	-.273 (.225)	.224	-.015 (.015)	.314	.395 (.406)	.330
Stroke	.014 (.013)	.256	-.189 (.620)	.760	-.986 (.808)	.222	.538 (.261)	.039	.011 (.016)	.473	-.288 (.354)	.415	-.003 (.022)	.882	-.371 (.555)	.503

*Non-Hispanic white=0, Not non-Hispanic white=1 †Women=0, Men=1

Table 15

Aim Two: Correlates of Disease Presence at T1 with Returner Sample (N= 491)

	Covariates						Main Effects						Two-Way Interactions			
	Age		Race/ Ethnicity*		Patient Functioning		Subjective Stress		CES-D		Gender†		Subjective Stress x CES-D		Subjective Stress x Gender	
Condition	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p
Risk Overall	.064 (.010)	<.001	-.168 (.377)	.656	-.095 (.411)	.818	-.067 (.194)	.729	.021 (.012)	.078	-.132 (.218)	.545	-.007 (.018)	.673	-.212 (.414)	.609
Hyper-tension	.060 (.010)	<.001	.305 (.398)	.444	-.027 (.431)	.950	.148 (.206)	.472	.036 (.012)	.004	.130 (.230)	.570	.011 (.018)	.530	-.320 (.429)	.457
High Cholesterol	.077 (.011)	<.001	.190 (.427)	.657	-.377 (.460)	.413	-.004 (.220)	.986	.003 (.013)	.849	-.050 (.237)	.833	-.004 (.021)	.863	-.421 (.461)	.361
Diabetes	.010 (.014)	.469	.548 (.525)	.296	-.153 (.683)	.823	.210 (.293)	.473	.023 (.017)	.177	-.088 (.358)	.806	-.021 (.026)	.409	.076 (.662)	.909
Obesity	.009 (.009)	.319	-.332 (.469)	.479	-.019 (.463)	.967	-.118 (.218)	.589	.018 (.013)	.164	-.512 (.259)	.048	-.018 (.019)	.355	.037 (.512)	.942
Manifestation Overall	.046 (.011)	<.001	-.129 (.512)	.800	-.332 (.517)	.521	.421 (.230)	.068	.002 (.015)	.893	.090 (.263)	.732	-.025 (.022)	.259	.135 (.498)	.787
Angina/CHD	.067 (.017)	<.001	-.541 (1.050)	.607	-.035 (.764)	.964	.305 (.364)	.402	.028 (.021)	.191	.549 (.388)	.157	-.012 (.032)	.707	.868 (.762)	.255
Cardiac Arrest/CHF/ Heart Attack	.063 (.017)	<.001	-.483 (1.052)	.646	-.293 (.830)	.724	.642 (.359)	.074	.029 (.022)	.184	.524 (.409)	.200	-.020 (.033)	.544	-.555 (.697)	.426
Irregular Heartbeat/ Pacemaker/ Murmur	.026 (.012)	.030	-.081 (.561)	.885	-.597 (.625)	.340	.429 (.253)	.090	.010 (.016)	.538	-.177 (.310)	.568	-.003 (.023)	.906	-.294 (.550)	.593
Stroke	.032 (.018)	.084	.309 (.782)	.692	-.382 (.946)	.687	.527 (.378)	.163	.023 (.023)	.335	.129 (.465)	.781	-.019 (.035)	.595	-.735 (.782)	.347

*Non-Hispanic white=0, Not non-Hispanic white=1 †Women=0, Men=1

Table 16

Aim Two: Predicting Development of Disease at T2 from Predictors at T1

		Covariates						Main Effects						Two-Way Interactions			
		Age		Race/ Ethnicity*		Patient Functioning		Subjective Stress		CES-D		Gender†		Subjective Stress x CES-D		Subjective Stress x Gender	
Condition	N	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p
Risk Overall	215	.024 (.013)	.071	1.101 (.470)	.019	.497 (.590)	.399	.443 (.268)	.098	.018 (.018)	.326	.300 (.330)	.364	-.014 (.025)	.568	.414 (.586)	.479
Hyper-tension	297	.018 (.014)	.194	.423 (.541)	.434	-.422 (.683)	.537	.172 (.288)	.550	-.004 (.019)	.843	.188 (.343)	.583	-.003 (.028)	.910	.351 (.667)	.598
High Cholesterol	306	.030 (.012)	.011	.410 (.475)	.389	.785 (.526)	.136	.297 (.257)	.247	-.007 (.016)	.659	.724 (.295)	.014	-.016 (.023)	.498	.036 (.522)	.946
Diabetes	404	.037 (.025)	.145	--		-.522 (1.357)	.701	-.784 (.813)	.335	-.018 (.044)	.676	.310 (.628)	.622	-.018 (.094)	.846	-2.154 (1.648)	.191
Obesity	345	.010 (.013)	.456	.462 (.533)	.387	.683 (.591)	.248	-.159 (.302)	.599	.053 (.017)	.002	-.276 (.364)	.448	-.014 (.025)	.566	.150 (.688)	.828
Manifestation Overall	357	-.009 (.015)	.568	-.428 (.763)	.575	.943 (.615)	.125	.317 (.312)	.309	.035 (.017)	.044	-.409 (.432)	.344	.052 (.025)	.039	-.193 (.710)	.786
Angina/CHD	412	.017 (.020)	.378	-.371 (1.056)	.726	1.329 (.754)	.078	-.394 (.477)	.408	.032 (.024)	.184	.418 (.486)	.389	.019 (.036)	.610	-.795 (.876)	.364
Cardiac Arrest/CHF/ Heart Attack	416	.024 (.039)	.536	--		2.640 (1.297)	.042	1.064 (.943)	.259	.018 (.055)	.736	2.876 (1.248)	.021	.095 (.070)	.174	.632 (1.538)	.681
Irregular Heartbeat/ Pacemaker/ Murmur	385	.002 (.017)	.905	-.753 (1.046)	.471	.070 (.821)	.932	.503 (.361)	.164	.050 (.020)	.013	-.626 (.527)	.235	.082 (.030)	.006	-.191 (.830)	.818
Stroke	423	.029 (.038)	.444	--		1.476 (1.421)	.299	.406 (.931)	.663	-.046 (.066)	.485	1.265 (.969)	.192	-.180 (.136)	.184	.611 (1.906)	.748

*Non-Hispanic white=0, Not non-Hispanic white=1 †Women=0, Men=1

Table 17
Post-Hoc Power Analysis for Combined Conditions

Combined Condition N (Event Rate)	Predictor	Odds Ratio	Power Achieved
Risk Overall 215 (.307)	Subjective Stress	1.558	.827
	CES-D	1.018	.052
	Gender	1.350	.510
	Stress*CES-D	.986	.051
	Stress*Gender	1.513	.776
Manifestation Overall 357 (.095)	Subjective Stress	1.373	.420
	CES-D	1.036	.054
	Gender	.664	.626
	Stress*CES-D	1.054	.060
	Stress*Gender	.824	.188

Note. All tests were two-tailed and $\alpha = .05$