Social support, health, and recurrent breast cancer:

Understanding psychological and biological mechanisms

Dissertation

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Abstract

Prognosis following recurrent breast cancer is poor and associated with high symptom burden. Social support has been suggested as a protective factor that can influence health. The mechanisms by which social support influences health are largely unknown; however, psychological and biological variables are hypothesized to influence this process. The present longitudinal study aimed to confirm whether social support conferred health benefits over time for women with recurrent breast cancer. Further, the study tested if psychological distress and neuroendocrine and immune variables mediated the relationship between social support and health. As an exploratory aim, the study examined whether social support following recurrence was associated with the hazard of all-cause mortality.

Women with recurrent breast cancer were accrued (N=122). Social support was assessed at baseline via structural (Social Network Index) and functional (Perceived Support from Family scale) support measures. Psychological distress, plasma cortisol and norepinephrine, T-cell blastogenic response to the mitogen phytohemagglutinin, and natural killer cell cytotoxicity were assessed at 4 months. Two composite health variables were assessed at 12 months: self-reported, subjective and nurse-assessed, objective ratings of health. Hierarchical multiple linear regression was used to examine whether measures of social support predicted psychological distress and biological variables at 4-months and physical health at 12-months. Multiple imputation followed by
bootstrap mediation was used to obtain point estimates and bias-corrected confidence intervals to examine whether psychological distress and neuroendocrine and immune variables mediated the relationship between social support and health. Cox proportional hazards models were used to determine if high (vs.) low levels of social support at baseline were associated with decreased hazard of all-cause mortality.

Women with greater structural and functional support following recurrence had lower levels of psychological distress at 4 months, and women with lower distress at 4 months experienced better health at 12 months on both subjective and objective measures. Social support indirectly influenced health through its effect on psychological distress. There was no evidence that social support influenced health independent of its effect on distress. Greater levels of social support at recurrence were not associated with decreased hazard of all-cause mortality.

Psychological distress but not neuroendocrine and immune variables mediated the relationship between structural and functional support following recurrence and health at a 1-year follow-up. Clinical implications and future directions are discussed.
Dedication

To my wonderful family, who have served as my ultimate supports throughout this process.
Specifically, to my parents, Jonathan and Cynthia Dorfman: thank you for teaching me to be persistent, tenacious, and most of all, hard working.
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Breast cancer is the most commonly diagnosed cancer in females, with over 230,000 new cases estimated in 2014 (American Cancer Society, 2014). While survival rates have increased (American Cancer Society, 2014), fears of recurrence are common (Simard et al., 2013) with more than 50% of breast cancer survivors experiencing fears of recurrence following completion of adjuvant treatment (Baker, Denniston, Smith, & West, 2005; Jarrett et al., 2013). For some, the fear of recurrence becomes a reality. Approximately 11% of breast cancer survivors will recur within 5 years of completing adjuvant treatment and 20% will recur within 10 years (Brewster et al., 2008). Women diagnosed with recurrence have had a period with no evidence of disease; with the diagnosis of recurrence, they must now cope with the fact that their cancer has returned. For many, the diagnosis of recurrent disease is described as more distressing than the initial diagnosis of breast cancer (Thornton et al., 2014; Warren, 2009). In fact, women with recurrent breast cancer experience greater cancer-specific stress than women with stable disease (Andersen, Shapiro, Farrar, Crespin, & Wells-Digregorio, 2005), and women with recurrence report their disease to have had a greater impact on their lives than both women newly diagnosed with breast cancer and women with stable disease (Hanson Frost et al., 2000).

Prognosis following recurrence is generally poor and associated with high symptom burden (Siddiqi, Given, Given, & Sikorskii, 2009). Women with recurrent breast cancer report
negative physical sequelae, including increased symptoms, signs, illnesses, and toxicities (Andersen, Carpenter, Yang, & Shapiro, 2007; Andersen, et al., 2005; Hanson Frost, et al., 2000; Munkres, Oberst, & Hughes, 1992; Siddiqi, et al., 2009), lower functional status and greater role limitations (Andersen, Carpenter, et al., 2007; Hanson Frost, et al., 2000; Oh et al., 2004), decline in general health perceptions (Northouse et al., 2002; Oh, et al., 2004), increased pain (Butler et al., 2003; Kenne Sarenmalm, Thoren-Jonsson, Gaston-Johansson, & Ohlen, 2009; Mahon & Casperson, 1995; Northouse, et al., 2002), high levels of fatigue (Cleeland et al., 2014; Kenne Sarenmalm, et al., 2009; Mahon & Casperson, 1995), and difficulty sleeping (Cleeland, et al., 2014; Kenne Sarenmalm, et al., 2009). The five-year survival rate for women with recurrence is estimated to be 44% (Giordano et al., 2004). For many, cancer becomes a chronic illness, and the physical and psychological sequelae must be continually addressed for the rest of their lives.

It behooves clinicians to understand factors that might alleviate this experience. Social support has been suggested as a protective factor that can influence one’s physical health (Uchino, Vaughn, Carlisle, & Birmingham, 2012). However, little is known about the impact of social support on the health of women with recurrent breast cancer. The present study aims first to confirm whether social support may confer health benefits for women with recurrent breast cancer. Specifically, the present study examines whether indices of social support predict physical health outcomes for women with recurrence (see Figure 1a). The mechanisms by which social support influences physical health are largely unknown (Feeney & Collins, 2014; Uchino, 2004). While the extant research has confirmed a link between social support and psychological distress, neuroendocrine variables, and immune variables little research has examined the role of these variables in influencing the relationship between social support and physical health. Thus, the present study tests whether psychological distress, neuroendocrine variables, and immune
variables mediate the relationship between social support and physical health for women with recurrent breast cancer (see Figures 1b and 1c).

In the sections that follow, the construct of social support is described along with a review of the literatures examining the relationship between social support and physical health in the general population, in chronic illness populations, and specifically, among cancer survivors. The theoretical and empirical rationale for the conceptualization of biological and psychological processes linking social support to physical health is also reviewed. The overview concludes with a discussion of social support and the aforementioned concepts in the context of cancer, and when available, in the context of recurrent cancer.

I. Social Support

Social support refers to the presence of close others or the resources provided by these individuals (Cohen & Syme, 1985; Ganster & Victor, 1988). Two types of social support are commonly referenced in the literature: structural support and functional support. Structural support refers to the existence of and interconnections within one’s social environment (e.g., family, friends, and the community; Cohen & Syme, 1985; Cohen, 1988; Barerra, 1986; Uchino, 2004). One’s social environment is often described as a network made up of those individuals one has contact with on a regular basis. Measures of structural support may be operationalized as the number of social ties within one’s social network (Uchino, 2004) or as the degree of integration or embeddedness within one’s social network (Barrera, 1986; Cohen, 1988). Individuals who are more integrated within their social network may participate in more community activities and have greater contact with friends and family (Cohen, 2004). Structural support measures are typically viewed as objective measures of social connectedness.
Functional support refers to the resources provided by interpersonal relationships (Cohen, 1988; Cohen & Syme, 1985; Uchino, 2004). For example, functional support can include whether a relationship provides emotional support, informational support, and/or tangible/instrumental support (Cohen, 2004; Cohen & Syme, 1985). Typically, functional support measures assess individuals’ perceptions of the support available or provided to them by members of their social network (Barrera, 1986; Cohen & Syme, 1985; Helgeson, Cohen, & Fritz, 1998) and are described as subjective measures of social support.

i. Physical health, functioning, and symptoms

In general, individuals with higher levels of functional and structural support report better physical health and functioning than those with lower levels of support (Gilbert, Quinn, Goodman, Butler, & Wallace, 2013; Hughes et al., 2014; Jones, Kimberlee, Deave, & Evans, 2013; White, Philogene, Fine, & Sinha, 2009). In a representative sample of over 1,700 older adults in the United States, White and colleagues (2009) found the size of one’s support network to be associated with health, with individuals with smaller networks more likely to describe their health as poor or fair on a self-report assessment of global health status. Women were more likely to report being in very good/excellent health if their support network included a greater variety of sources of support (i.e., friends and community members in addition to family members). Finally, men and women who viewed recent emotional support provided by network members as inadequate were more likely to describe their health as poor or fair when compared to those reporting adequate support. Similar results have been found with other samples, including adolescents (Geckova, van Dijk, Stewart, Groothoff, & Post, 2003), veterans (Ren, Skinner, Lee, & Kazis, 1999), the elderly (Johnson, 1996; Okamoto & Tanaka, 2004; Zunzunegui et al., 2004), community dwelling
individuals (Melchior, Berkman, Niedhammer, Chea, & Goldberg, 2003), and chronic illness populations (Patrick, Morgan, & Charlton, 1986).

A recent meta-analysis of 39 studies examined the relationship between the sociological principle of social capital [e.g., the norms and relationships shaping the quality and quantity of social interactions (The World Bank, 2011); the ability of social networks to foster community and facilitate action though norms like reciprocity and trust (Helliwell & Putnum, 2004; Coleman, 1988)] and physical health (Gilbert, et al., 2013)]. Social capital constructs examined included social support, reciprocity, sense of community, participation, trust, etc. A strong, positive relationship was found. Overall, the effect size for the link between social capital and physical health (i.e., self-reported health and/or mortality) was $OR=1.27$ ($95\% CI=1.21–1.34$); for every one-point increase in social capital, the odds of good health increased by 27%. In the analyses examining the social support system specifically (i.e., an aggregation of measures of structural and functional support), for every one-point increase in social support, individuals' physical health improved by 30% ($OR=1.30; 95\% CI=1.13–1.50$). Sensitivity analyses suggested the estimated effect size ranged from $OR=1.24$ to $1.35$.

The positive relationship between social support and health has been found across other markers of health including functional performance status. Functional performance status refers to the ability of an individual to care for oneself and carry out the normal, day-to-day activities necessary to meet his or her basic needs (e.g., grooming, bathing, driving, etc.) as well as the presence or absence of disability. A systematic review provides support for a relationship between measures of structural support and functional performance status among community dwelling individuals (Stuck et al., 1999). Specifically, individuals who have fewer social contacts, who
engage in fewer community activities, and who have smaller social networks report more limitations in activities of daily living.

Similar results have been found for studies examining measures of functional support. In one study, Seeman and colleagues (1995) followed a cohort of more than 1,000 men and women aged 70-79 for 2.5 years to better understand the link between markers of functional support (i.e., emotional and instrumental support) and functional performance status. In the presence of low levels of instrumental support, individuals reporting greater levels of emotional support experienced improvements in functional performance status over the course of follow-up. The results remained even after controlling for incidence of newly diagnosed medical conditions (e.g., high blood pressure, diabetes, cancer) and hospitalizations. Interestingly, individuals who reported inadequate levels of emotional support at baseline experienced significant improvements in functional performance status if the adequacy of their perceived emotional support increased over the 2.5-year follow-up. This suggests that improvements in functional performance status may result from improvements in perceived support.

While the aforementioned studies followed healthy men and women, studies of chronic illness populations have also reported a significant relationship between social support and functional performance status (Clarke, Frasure-Smith, Lesperance, & Bourassa, 2000; Colantonio, Kasl, Ostfeld, & Berkman, 1993; Weinberger, Tierney, Booher, & Hiner, 1990). For example, in a sample of osteoarthritis patients, univariate analyses revealed that individuals reporting lower levels of functional support (i.e., tangible, belonging, and self-esteem) experienced poorer functional performance status in comparison to those with greater levels of social support (Weinberger, et al., 1990). In multivariate analyses, a linear relationship was found between social
support and functional performance status; tangible support and esteem support were negatively associated with physical disability.

Data from a sample of approximately 3,000 patients with chronic heart failure found those who were less socially integrated at baseline were more likely to have serious functional impairments at the one-year follow-up when compared to those who were more socially integrated (Clarke, et al., 2000). The results remained after controlling for baseline functional performance status and additional measures of health (e.g., deterioration in heart failure, comorbid medical conditions). Similarly, larger social networks have been associated with less impairment in activities of daily living for a sample of elderly stroke patients (Colantonio, et al., 1993). Patients with larger social networks were also less likely to require institutional assistance with activities of daily living (e.g., necessitating placement in skilled nursing facilities) in the 6 weeks following discharge.

Individuals with low levels of social support also report more signs and symptoms of disease. For example, those reporting less structural support (i.e., smaller social networks) may experience more symptoms of physical illness (e.g., edema, cardiac symptoms, pain; Cohen, Teresi and Holmes, 1985; Garcia, Banegas, Perez-Regadera, Cabrera, Rodriguez-Artalejo, 2005) and greater health problems (Bosworth & Schaie, 1997) than those with larger social networks. A recent population-based study of close to 3,600 older adults found that older adults who reported seeing family or friends seldom or never reported greater bodily pain and poorer general health when compared to those seeing close others more often (Garcia, et al., 2005). Interestingly, older adults reporting less frequent contact with close others (i.e., low levels of structural support) experienced similar or worse signs and symptoms of physical health, including vitality, physical
functioning, and subjective reports of general health, as individuals suffering from osteoarthritis, a disabling disease.

A similar relationship has been found with measures of functional support: functional support is negatively associated with signs and symptoms of disease. In a cross-sectional study of hemodialysis patients, those reporting low levels of perceived support experienced greater levels of fatigue than those reporting high levels of perceived support from family ($r=-0.404$), friends ($r=-0.635$), a special person ($r=-0.638$), and overall ($r=-0.643$; Karadag, Kilic, & Metin, 2013). Longitudinal analyses have also provided evidence of this relationship, with functional support predicting signs and symptoms of disease over time. For example, initial levels of functional support (i.e., perceived emotional and instrumental support) were negatively associated with pain at the 3- and 5-year follow-ups for patients with rheumatoid arthritis (Evers, Kraaimaat, Geenen, Jacobs, & Bijlsma, 2003). Similarly, individuals with satisfactory social support at baseline reported fewer HIV-related health symptoms over the next year (e.g., sore throat, skin rash, persistent fatigue, fever, enlarged lymph nodes, yeast infection in mouth or throat, weight loss, etc.) when compared to those who with less satisfactory support (Ashton et al., 2005). Thus, across a variety of chronic illness populations, a negative relationship has been found between measures of functional support and physical symptoms.

ii. **Disease progression**

Disease progression refers to the worsening of disease states, and research suggests that social support may be associated with disease progression (Cohen & Janicki-Deverts, 2009). The majority of research comes from the literatures examining cardiovascular diseases (Seeman, 1996). For example, data from a sample of close to 100 women between the ages of 30 and 65 hospitalized for a cardiac event (i.e., myocardial infarction, unstable angina) found those with lower
levels of emotional support at baseline to experience greater narrowing of the arteries over a 3-year period (mean narrowing=0.15 mm vs. 0.05 mm for those with greater support; Wang, Mittleman, & Orth-Gomer, 2005) indicating greater progression of atherosclerosis. The results remained after controlling for significant health-related factors including alcohol consumption, family history of coronary heart disease, diabetes, hypertension, severity of angina, etc. Similar results were found for measures of structural support, with more socially integrated individuals experiencing less progression (mean narrowing=0.06 mm vs. 0.16 mm).

Additional research has confirmed the link between social support and progression of atherosclerosis (e.g., Angerer et al., 2000), as well as risk for recurrent coronary events (Case, Moss, Case, McDermott, & Eberly, 1992). For example, Case and colleagues (1992) followed over 1,000 men and women for at least 12 months ($M=25$ months) following an acute myocardial infarction. The recurrent cardiac event rate was 19.4% among those living alone at the time of the initial cardiac event; this value is similar to rates of recurrent cardiac events for those with a previous history of myocardial infarction (18.5%) and those with other characteristics known to be associated with post-infarction prognosis, including the New York Heart Association functional class in the month prior to the infarction (21.1%), radionuclide left ventricular ejection fraction (21.3%), frequency of ventricular ectopic complexes (20.0%) and pulmonary congestion (18.5%). Multivariate Cox proportional hazards models revealed that after including each prognostic variable in the model, the Hazard Ratio was 1.54, suggesting that those living alone had a 54% increased hazard of a recurrent cardiac event when compared to those living with at least one other individual.

Social support may also be protective against progression from HIV to AIDS. In a study of 82 HIV-positive men without symptoms of AIDS, Leserman and colleagues (1999) found that, in
univariate analyses, those reporting greater satisfaction with social support had a 40% greater probability of being free of AIDS at the 5.5 year follow-up when compared to those who were less satisfied with their social support. Further, risk of disease progression decreased by 63% for each one-point increase in social support satisfaction \((HR=0.37)\). In multivariate analyses, satisfaction with social support remained significantly associated with decreased risk of AIDS progression \((HR=0.44)\). Two separate groups have reviewed the literature examining the relationship between social support and disease progression among HIV-positive individuals (Ironson & Hayward, 2008; Miller & Cole, 1998). In cross-sectional studies, higher levels of structural and functional support were related to delayed disease progression (Miller & Cole, 1998). In prospective, natural history studies of individuals at more advanced stages of disease, lower levels of social support, in terms of both measures of structural and functional support (e.g., Patterson et al., 1996; Theorell et al., 1995; Solano et al., 1993), were associated with disease progression (Ironson & Hayward, 2008; Miller & Cole, 1998).

iii. Mortality

Finally, the strongest support for the link between social support and physical health comes from research examining the relationship between social support and mortality. In one of the first studies, Berkman and Syme (1979) surveyed close to 7,000 men and women examining the relationship between social support and mortality over the course of 9 years. After taking into account physical health and health behavior indices (e.g., alcohol consumption, smoking, physical activity, etc.), individuals reporting more social ties at baseline were less likely to die by the 9-year follow up. When compared to individuals with a greater number of social contacts, the relative risk of mortality for men and women with the fewest social ties was 2.8 and 2.3, respectively. Since this seminal study, multiple population-based studies have confirmed the link between measures of
structural support and mortality (e.g., Orth-Gomer & Johnson, 1987; Forster & Stoller, 1992; Barger, 2013; Kreibig, Whooley, & Gross, 2014; Menendez-Villava, Gamarra-Mondelo, Alonso-Fachado, Naveira-Castelo, & Montes-Martinez, 2014).

Measures of functional support have less consistently been associated with mortality (Uchino, 2004). The majority of research reporting a significant relationship between the two has been conducted in medical samples or with individuals with health concerns (Barger, 2013; Menendez-Villava, et al., 2014; Penninx et al., 1997). For example, in a nationally representative study of over 30,000 men and women in the United States, measures of social integration (e.g., recent contact with friends or family members, participation in group social activities or religious organizations, etc.) but not functional support (e.g., perceptions of emotional support provided by close others) were significantly and negatively related to mortality (Barger, 2013). However, a subset of analyses was restricted to include only individuals reporting at least one of the following conditions: prior myocardial infarction, stroke, cancer (excluding nonmelanoma skin cancer), or other coronary heart disease. Among those reporting health ailments, high levels of functional support were associated with decreased mortality ($HR=0.65; CI=0.48-0.89$). Thus, the link between functional support and mortality may be greatest for individuals with chronic or acute health conditions, as opposed to healthy individuals.

Data from medical/chronic illness populations have also found a significant relationship between functional support and mortality after controlling for markers of health. For example, Pennix and colleagues (1997) sampled close to 3,000 men and women between the ages of 55 and 85, 66% of whom suffered from a chronic disease (e.g., cancer, cardiac disease, arthritis, etc.). After controlling for the presence of physical health conditions and self-reported perceptions of one’s health, moderate or high levels of functional support (e.g., emotional support) were
significantly associated with reduced risk of mortality (ORs=0.48 and 0.68 respectively) when compared to individuals reporting low levels of support.

Research has examined the link between functional support and mortality in specific disease populations. In a prospective study of individuals surveyed following a myocardial infarction, after controlling for health status, severity of cardiac event, and other measures of behaviors, those lacking emotional support were almost three times as likely to die within 6 months of their first myocardial infarction than those with more emotional support (Berkman, Leo-Summers, & Horwitz, 1992). In a recent meta-analysis, Barth and colleagues (2010) reviewed over 20 prospective studies of individuals with pre-existing coronary heart disease. Similarly, results suggested that low levels of functional support increased one's risk of both cardiac (RR= 1.71) and all-cause mortality (RR=1.59). The results remained after controlling for risk factors of mortality in coronary heart disease patients (HR=1.59). Finally, a recent study examined the relationship between social support and mortality among a sample of men and women with hypertension (Menendez-Villalva, et al., 2014). After controlling for variables that can influence health (e.g., diabetes, age, gender), participants reporting low levels of functional support were at greater risk for mortality from cardiovascular events over the 9-year follow-up (HR=2.6) when compared to those reporting higher levels of functional support.

While both measures of structural and functional support have been associated with mortality—as described above—at present, it is unclear whether one or both forms of support are more closely linked to mortality. The literature has been inconsistent, with some studies finding a negative relationship between social integration, but not functional support, and mortality (Barger, 2013), while others have found one's perceptions of support to be closely linked to mortality (Penninx, et al., 1997). A recent meta-analysis of 148 studies helped to elucidate the link between
social support and mortality. Holt-Lundstad and colleagues (2010) found that, in the omnibus analysis, individuals reporting greater social support (i.e., including both functional and structural measures of support) experienced a 50% decrease in mortality when compared to those reporting insufficient relationships. Importantly, the magnitude of this effect exceeds or is comparable to the magnitude of the effect seen after adjusting for health-relevant behaviors, including quitting smoking and increasing physical activity. However, the results differed depending on the type of social support construct measured. For example, complex measures of social integration (e.g. a single measure that addresses multiple components of social integration like marital status, community involvement, etc.) were associated with a 91% decreased risk of mortality, whereas measures of perceived social support were associated with a 35% decreased risk of mortality.

iv. Summary

The data linking social support to physical health is compelling (see Figure 1a; Uchino, et al., 2012; Taylor, 2007). Specifically, both measures of structural and functional support have been associated with three distinct physical health outcomes among both healthy individuals and chronic illness populations. First, those with higher levels of social support describe better self-reported physical health and fewer signs and symptoms of illness, including lower levels of fatigue and pain and improved functional performance status. Second, higher levels of support are associated with decreased progression of chronic illnesses. Specifically, those with higher levels of support experience slower progression of arteriosclerosis, fewer recurrent cardiac events, and decreased risk of progression from HIV to AIDS. Finally, individuals with high levels of support have a decreased risk of death for both illness-specific and healthy populations. While the protective effect of social support on health has been well confirmed, less is known about the process by which social support is beneficial for our health. While broad theories have attempted to link social
relationships to health (House, Landis, & Umberson, 1988; B.N. Uchino, et al., 2012), it is less clear how, “…our social [supports] get inside our bodies” (Cohen, 2001, pg. 6). The sections that follow outline the hypothesized processes by which social support may be related to health.

II. Understanding the link between social support and health

It has been suggested that, “the mere presence of- or sense of relatedness with another organism may have direct…emotional or neuroendocrinial effects that promote health…” (House, et al., 1988, pgs. 543-544). Our social networks and the presence of close others are thus thought to be protective for one’s health via emotional and biological processes (Berkman & Syme, 1979; Cohen, 1988; Gruenewald & Seeman, 2010; Holt-Lunstad, et al., 2010; Seeman & McEwen, 1996; B.N. Uchino, et al., 2012). Synthesized from the extant literatures (presented below), Figures 1b and 1c hypothesize that psychological processes (e.g., mood, depression), as well as biological processes (i.e., immunologic and neuroendocrine parameters) mediate the relationship between social support and physical health (Cohen & Syme, 1985; Eisenberger & Cole, 2012; Feeney & Collins, 2014; Uchino, Bowen, Carlisle, & Birmingham, 2012; B.N. Uchino, et al., 2012). While a third process related to health behaviors (Uchino, 2004; B.N. Uchino, et al., 2012) has been suggested, one’s health-related practices (e.g., alcohol consumption, cigarette smoking, physical activity, utilization of preventative health services) have not been sufficient to explain the link between measures of social support and health outcomes (Berkman & Syme, 1979; Cohen, 2001; Uchino, Cacioppo, & Kiecolt-Glaser, 1996).

Although theories linking social support to physical health outcomes have been proposed, developers of these models have called for research testing these hypothesized links (Cohen & Janicki-Deverts, 2009; House, et al., 1988; Uchino, 2004; B. N. Uchino, et al., 2012). In fact, experts have deemed theory testing a “priority” (Uchino, 2004). However, few have specifically
tested whether psychological distress and biological variables mediate the hypothesized relationship between social support and physical health outcomes (Cohen & Janicki-Deverts, 2009; Uchino, 2004). Instead, the majority of research has examined the “front end” of the model, i.e., the links between social support and psychological distress or social support and biological variables (Uchino, 2004). While these links are important first steps, they are not sufficient to understand the processes by which social support may affect health. To begin, data are presented describing the known relationship between social support, psychological distress, and biological variables. The section continues by providing information about the limited research examining whether psychological distress and biological variables mediate the relationship between social support and physical health outcomes.

i. The relationship of social support to psychological distress and social support to biological variables

a. Social support and psychological distress

Social support has consistently been associated with psychological distress (e.g., improved quality of life, decreased depressive symptoms, etc.; Antonucci & Akiyama, 1987; Barerra, 1986; Corrigan & Phelan, 2004; Holahan & Moos, 1981; Kawachi & Berkman, 2001; Jensen et al., 2014; Mervin, Byrnes, Shibl, Scuffman, & Cameron, 2014). Specifically, higher levels of functional (e.g., perceived) support have been linked to greater satisfaction with life, as well as decreased depressive symptoms and stress (Jensen et al., 2014; Siedlecki, Salthouse, Oishi, & Jeswani, 2014; B.N. Uchino, et al., 2012). Higher levels of structural support have been linked to improved psychological adjustment (Greenblatt, Becerra, & Serafetinides, 1982; Kogstad, Monness, & Sorensen, 2013) and are thought to be protective against psychological disorders (De
Silva, McKenzie, Harpham, & Huttly, 2005) as well as important for recovery from psychological distress (Kogstad, et al., 2013).

Multiple large-scale, population-based studies have examined the relationship between social support and mental health. In a longitudinal study of over 2,000 members of the general public, a direct relationship was found between social support and mental health; higher levels of social support predicted improvements in psychological symptoms (e.g., symptoms of anxiety and depression) over the course of the 1-year follow-up (Ware, Ware, & Donald, 1981). More recently, a study of over 40,000 men and women in Norway examined the relationship between social support and depressive symptoms. Higher levels of functional support, including emotional and tangible support, were associated with fewer depressive symptoms (Grav, Hellzen, Romild, & Stordal, 2012). The prevalence of depressive symptoms was greatest for individuals with the lowest levels of functional support (e.g., individuals reporting low levels of perceived emotional and tangible support). Thus, social support may affect levels of psychological distress and symptoms of clinically significant psychological illness.

Both the size of one’s social network and one’s perceptions of enacted support may mitigate symptoms associated with psychological disorders. Specifically, individuals diagnosed with clinically significant mental illnesses (e.g., depression, anxiety) that report larger social networks or greater perceived support may experience decreased symptomatology (Holahan & Moos, 1981; Pattison, Llamas, & Hurd, 1979). For example, in a longitudinal study of close to 500 adult males and females, Holahan and Moos (1981) found a negative relationship between the perceived quality of family and work relationships and psychological maladjustment; increased psychiatric symptoms (e.g., affective and somatic symptoms) were associated with reductions in social support over the year long follow-up. Additionally, George and colleagues (1989) examined factors
associated with recovery from depression. In a sample of 150 men and women with depression followed for 6 to 32 months, individuals with smaller social networks and less perceived social support at the initial interview experienced more depressive symptoms at follow-up.

b. Social support and biological variables

i. Immune variables

Social support may be linked to physical health outcomes as a result of its effects on immune variables including functional immunity. Measures of functional immunity examine how certain immune cells (e.g., T-cells, natural killer cells) perform. For example, in the presence of an antigen, T-cells activate and begin to proliferate in order to fight the antigen. One common assessment of functional immunity that has been associated with social support is T-cell proliferative responses to mitogens, including Concanavalin A (ConA; e.g., Kiecolt-Glaser, Dura, Speicher, Trask, & Glaser, 1991) and phytohemagglutinin (PHA; e.g., Baron, Cutrona, Hicklin, Russel, & Lubaroff, 1990; Linn, Linn, & Klimas, 1988; Thomas, Goodwin, & Goodwin, 1985). Mitogens work by inducing the proliferative response, providing an in vitro model of proliferation in response to antigens. Greater proliferation is associated with better immune functioning. Better functional immunity is associated with decreased susceptibility to infectious diseases (Webster Marketon & Glaser, 2008), decreased rates of progression from HIV to AIDS (Hofmann et al., 1987), and decreased morbidity and mortality among older adults (Wikby, Maxson, Olsson, Johansson, & Ferguson, 1998). Further, suppression of the proliferative response may be an indicator of poor prognosis for individuals with cancer (Cheema & Hersh, 1971).

In a review of 81 studies (Uchino, et al., 1996), 19 of which reported on the relationship between functional immunity and social support (e.g., number of confiding relationships, perceived social support, availability of a confidant), higher levels of social support were associated with
better functional immunity, including proliferative responses to PHA and ConA. A subsequent meta-analysis of 9 studies that directly measured the relationship between social support (i.e., both measures of structural and functional support) and functional immunity found the relationship to be reliable \((z=4.38, p=0.000006, \text{fail-safe } n=54.90, r=0.21; \text{Uchino et al., 1996})\). The aforementioned research would suggest that high (vs. low) levels of social support might be health protective due to the relationship between support and immunity.

Further, Natural Killer (NK) cells discriminate between healthy cells and “target cells” including bacteria, viruses, and malignant cells (Vivier, Tomasello, Baratin, Walzer, & Ugolini, 2008). NK cells respond to target cells, lysing (killing) the cells (Uchino, 2006). Consequently, NK cells are important for fighting infections and viruses (Orange & Ballas, 2006; Webster Marketon & Glaser, 2008). NK cells also function to identify and eliminate malignant cells before they can develop into tumors (Orange & Ballas, 2006). NK cell cytotoxicity (NKCC) describes the extent to which NK cells lyse target cells and represents a measure of how well NK cells function. Defects in NKCC are associated with tumorigenesis (Standish et al., 2008). Thus NKCC is an important assessment of functional immunity.

Measures of perceived support (Miyazaki et al., 2003) and reports of loneliness (Kiecolt-Glaser et al., 1984) have been associated with NK cell numbers as well as NK cell activity. Specifically, a positive relationship has been found between perceived support and NK cell numbers (Miyazaki, et al., 2003), with those reporting higher levels of perceived support exhibiting more NK cells. Individuals reporting higher versus lower levels of loneliness have been shown to exhibit significantly lower levels of NK cell activity (Kiecolt-Glaser et al., 1984). Lower levels of social support have also been linked to impaired NKCC among caregivers of chronically ill populations (e.g., cancer patients, individuals with dementia); caregivers with higher levels of
perceived social support experienced a higher percent lysis score than those with lower levels of support (Baron, Cutrona, Hicklin, Russell, & Lubaroff, 1990; Esterling, Kiecolt-Glaser, Bodnar, & Glaser, 1994). Recent work with animal models has confirmed the link between social relationships and NKCC. When compared with normal rats, socially isolated rats exhibited decreased NK cell activity, with isolated rats exhibiting profound impairment (Crucés, Venero, Pereda-Perez, & De la Fuente, 2014).

ii. Neuroendocrine variables

Social support has also been linked to neuroendocrine functioning. The parameters most commonly examined are cortisol and the catecholamines epinephrine and norepinephrine (Uchino, et al., 1996). First, social support has been linked to lower cortisol levels (Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007; Rosal, King, Ma, & Reed, 2004). In a sample of close to 150 men and women, those reporting greater functional support experienced lower levels of salivary cortisol when compared to those reporting lower levels of support in both cross-sectional and longitudinal analyses (Rosal, et al., 2004). Further, in a sample of healthy older adults, individuals reporting greater levels of social integration exhibited more effective regulation of the HPA-axis. Specifically, they experienced greater declines in cortisol over the course of the day in a manner similar to that found in healthy younger individuals (Lai et al., 2012). The beneficial relationship between social support and cortisol is significant; dysregulated cortisol secretion has been linked to physical health problems, including hypertension, diabetes, and heart disease (Otte et al., 2005; Rosmond & Bjorntorp, 2000; Smith et al., 2005). Further, high levels of cortisol have been associated with greater declines in physical functioning (e.g., balance, strength, dexterity) as well as declines in cognitive performance (e.g., naming, memory, abstraction) among older adults (Karlamangla, Singer, McEwen, Rowe, & Seeman, 2002).
While research examining catecholamines has been limited (Uchino, et al., 1996), preliminary analyses suggest that social support may also be linked to lower catecholamine levels. For example, Seeman and colleagues (1994) surveyed close to 800 men and women between the ages of 70 and 79 to examine the relationship between social support and neuroendocrine functioning. Lower levels of urinary norepinephrine and epinephrine were found for men reporting high levels of emotional support. Similarly, among pregnant women with high-risk pregnancies, a negative relationship was found between perceived support from partners and norepinephrine levels (Kemp & Hatmaker, 1989). Those with high levels of support from their partners experienced lower levels of norepinephrine. These results are significant: lower catecholamine levels are beneficial for health outcomes, including cardiovascular functioning (Henry, Stephens, & Ely, 1986; Uchino, 2004). For example, high levels of epinephrine and norepinephrine are associated with abnormal heart rhythms and damage to arteries, as well as increased blood pressure and heart rate (McEwen & Stellar, 1993; Uchino, et al., 1996).

ii. Do psychological distress and biological variables mediate the relationship between social support and physical health outcomes?

At present, over thirty years of research from independent studies and research groups have identified a robust link between social support and physical health. While the mechanisms linking social support to improved physical health are hypothesized to include psychological and biological processes, little direct research has examined the mediating role of psychological distress and biological variables (Cohen & Janicki-Deverts, 2009; House, 2001; Uchino, 2006). Researchers continue to discuss the importance of examining mechanisms contributing to the relationship between social support and health, yet research has lagged.
Limited research suggests the presence of psychological mediators. For example, in a cross-sectional study of two independent samples of adults over the age of 65, Bisconti and Bergeman (1999) found that perceived control over social interactions mediated the relationship between social support (i.e., perceived support from family members, perceived support from friends, and satisfaction with support) and one's perceptions of their physical health. In the presence of high levels of perceived control, the relationship between perceived support from family or friends and health decreased significantly. Further, Shen, McCreary, & Myers (2004) examined mediators of the relationship between social support prior to entering cardiac rehabilitation and physical functioning upon completing rehabilitation among 142 individuals diagnosed with coronary heart disease. Physical functioning was measured via a clinician-rated assessment of the severity of a patient’s illness and risk for a future cardiac event. Depressive symptoms and negative coping responses served as mediators; those with greater support exhibited better physical functioning via fewer depressive symptoms and less engagement in negative coping.

More recently, two large cross-sectional studies have found psychological variables to mediate the relationship between measures of social support and health. Crittenden and colleagues (2014) examined mediators of the relationship between a measure of social integration and pulmonary functioning among more than 1,000 elderly (ages 70-79) men and women. A significant direct effect was found; individuals who were involved in more social roles experienced better lung functioning ($p<0.001$). While biological variables, including urinary epinephrine, norepinephrine, and cortisol were not significant mediators, happiness was a significant mediator (Sobel $t=3.17$, $p=0.001$) accounting for 14% of the association between social integration and lung functioning. Individuals who were more socially integrated experienced better lung functioning via
greater happiness. Further, in a sample of more than 3,000 elderly individuals (ages 65-85), depressed mood was found to mediate the relationship between perceived social support and health-related quality of life (Sobel p < 0.01; Wicke et al., 2014). Greater perceived support was associated with better health-related quality of life through the effect of perceived support on depressive symptoms. The results remained after controlling for a measure of severity of symptoms associated with comorbid health conditions. Thus, recent cross-sectional studies support the role of psychological variables in mediating the relationship between measures of social support and health.

The majority of research examining the role of biological variables has found a direct relationship between social support and neuroendocrine or immune variables (see above). Further, immune and neuroendocrine variables have been associated with physical health outcomes, as described previously. While these associations have led researchers to hypothesize that biological variables may serve as mediators of the relationship between social support and physical health, it appears that research testing whether biological variables directly mediate this relationship has not been conducted (Uchino, 2006). Tumor bearing mouse models provide the best available evidence for the potential mediating role of biological parameters. Wu and colleagues (2000) found that mice raised in groups developed fewer metastases than those raised in isolation. Suppression of NK cells and NKCC was thought to mediate this relationship.

Clearly a handful of studies supporting the role of psychological variables and theories speculating the role of biological variables are not sufficient to confirm whether these variables contribute to the process by which social support influences physical health. Additional research is necessary to further elucidate the role of psychological variables and biological variables in understanding the protective effects of social support for health.
iii. **Summary**

A negative relationship has been found between social support and psychological distress, with those reporting higher levels of both structural and functional support reporting better psychological adjustment and experiencing fewer symptoms of depression and anxiety, as well as less stress. Similarly, higher levels of social support are associated with better functional immunity, as well as lower levels of catecholamines and cortisol. While the direct relationship between social support and psychological distress and biological variables has been confirmed, our understanding of their role as mediators of the relationship between social support and physical health is still in its infancy. As described below, patients with recurrent cancer may be an important population for whom an understanding of the mechanisms linking social support to health may be crucial. The sections that follow describe the rationale for examining these phenomena in recurrent cancer, as well as a review of what is currently known about the effects of social support for this population.

**III. Understanding the effects of social support in the context of recurrent cancer**

According to attachment theory, when one experiences a highly stressful situation, the attachment system is triggered to help protect individuals from harm (Bowlby, 1969; Mikulincer & Shaver, 2007). Distressed individuals may then seek out close others in an attempt to protect themselves and restore their emotional and physical wellbeing to pre-stress levels (Pietromonaco, Uchino, & Dunkel Schetter, 2013). Further, the distress experienced by an individual under stress may signal to others that the individual is in need of assistance, increasing the likelihood that an individual will receive support (Bolger, Foster, Vinokur, & Ng, 1996). Consequently, exposure to stressors can mobilize one’s support network and ensure the provision of support (Barrera, 1986; Bolger, et al., 1996). Responsive support networks can assist individuals under stress with their support needs.
However, the experience of cancer recurrence is qualitatively different than most stressors, including the initial diagnosis of cancer. For some, the experience of recurrence comes years after the initial diagnosis. In the interim, cancer survivors may have lost significant network members or ties to their social network that existed at the initial diagnosis (Thornton, et al., 2014; Wrzus, Hanel, Wagner, & Neyer, 2013). For example, in a qualitative study of women with recurrent breast and gynecologic cancers, women described that, with the passing of time, they had lost friends and family members (e.g., parents, spouses) to disease or death (Thornton, et al., 2014). Additionally, women faced natural shifts in their support systems that occurred as a result of age, including but not limited to retirement from work or the end of parenting responsibilities.

Recurrent cancer is often conceptualized as a chronic stressor. For some women, recurrence becomes their “diabetes,” a disease they must learn to live with and manage for the rest of their lives (Thornton, et al., 2014). The chronic stress of recurrence and associated psychological distress and physical health impairments may increase the support demands placed on network members (Dunkel-Schetter & Skokan, 1990). While one’s support network may mobilize following the diagnosis of cancer, the diagnosis of recurrence may overwhelm some network members and erode their ability to provide adequate support (Arora, Finney Rutten, Gustafson, Moser, & Hawkins, 2007; Bolger, et al., 1996; Brady & Helgeson, 2000; Peters-Golden, 1982). Network members may become overwhelmed by the new and continuing support responsibilities leading to a reduction in the provision of support. Further, the potentially fatal nature of recurrent disease may affect the reactions of members of the support network (Helgeson & Cohen, 1996). Instead of approaching patients, network members may withdraw help or may react to patients inappropriately.
In fact, while patients desire high levels of social support throughout the disease trajectory (Arora, et al., 2007), social support appears to decline after the diagnosis of recurrence. In a study of 54 women with recurrent breast cancer, social functioning significantly declined between the baseline assessment and the follow-up assessment, which occurred 1- to 5-years post-initial diagnosis (Oh, et al., 2004). Further, when compared to the initial diagnosis, the rates of recovery of social functioning have been found to be significantly slower for patients with recurrent disease (Andersen et al., 2008). Thus, women with recurrent breast cancer may not have adequate levels of social support at a time when they may feel an increased need for support (Peters-Golden, 1982). Even if a patient has an adequate number of individuals in her support network at recurrence, patients may perceive the social support available to them to be inadequate. For example, in a study of 100 women with breast cancer, 55 of whom had recurred, those with recurrent disease had higher levels of dissatisfaction with their support than women who had not recurred (Peters-Golden, 1982).

If social support influences health outcomes in recurrent cancer as would be suggested by the extant literatures, and women with recurrent cancer report inadequate levels of support, a greater understanding of the mechanisms by which social support influences health is necessary to aid in the development of targeted interventions. The sections that follow describe the available literatures examining the health benefits of social support, as well as evidence for the hypothesized psychological and biological processes (see Figure 1), described previously, in the context of recurrent cancer. The majority of research examining the role of social support for cancer patients has been conducted among individuals with a first diagnosis of cancer. While this literature may be informative for recurrence patients, the diagnosis of recurrence presents additional challenges (as
described previously). Thus, the sections that follow examine social support in the context of cancer, and when available, information specific to recurrent cancer is provided.

i. Social support and cancer

a. Physical health

Social support has been linked to physical health outcomes for women diagnosed with cancer (Helgeson, et al., 1998). In a systematic review of 16 prospective studies, social support was associated with breast cancer progression (Nausheen, Gidron, Peveler, & Moss-Morris, 2009). The majority of studies conceptualize disease progression in relation to cancer-specific mortality (Nausheen, et al., 2009). Specifically, those with larger social networks and those who were more socially integrated (Funch & Marshall, 1983; Hislop, Waxler, Coldman, Elwood, & Kan, 1987; Kroenke, Kubzansky, Schernhammer, Holmes, & Kawachi, 2006; Vogt, Mullooly, Ernst, Pope, & Hollis, 1992) as well as those with greater levels of perceived support (Ell, Nishimoto, Mediansky, Mantell, & Hamovitch, 1992) were at decreased risk of mortality. The link between social support and mortality in cancer has been replicated in numerous studies (see Falagas et al., 2007 for an additional review). For example, in a recent study, Kroenke and colleagues (2013) followed more than 2,000 women with breast cancer for a median of 10.8 years. When compared to women with larger social networks and greater levels of perceived support, women with smaller social networks and lower levels of perceived support had a higher risk of mortality ($HR=1.61$). The results of a recent meta-analysis further suggest that both structural and functional support may be health protective. Specifically, those with larger social networks and greater perceived social support had a 20% and 15% decrease in relative risk for mortality, respectively (Pinquart & Duberstein, 2010).

Limited research has examined the relationship between social support and progression to recurrent disease and suggests that low levels of social support may be associated with shorter
event-free survival and lower rates of recurrence. For example, a study of over 2,000 breast cancer survivors found that those with greater social wellbeing had a 38% decreased risk of breast cancer recurrence after a median follow-up of 4.8 years (Epplein et al., 2011). Measures of structural support have also been associated with recurrence. Women who were more socially integrated had a longer disease-free interval suggesting that more socially integrated women are less likely to experience recurrence or death (Hislop, et al., 1987).

Social support indices have also been negatively associated with physical health outcomes for women with breast cancer, including pain (Hughes, et al., 2014; Zaza & Baine, 2002), fatigue (Michael, Berkman, Colditz, Holmes, & Kawachi, 2002), physical health-related quality of life (Kroenke, Kwan, et al., 2013; Leung, Pachana, & McLaughlin, 2014), and physical functioning (Kroenke, Kwan, et al., 2013; Michael, et al., 2002). For example, in a study of over 3,000 breast cancer survivors, measures of functional support (e.g., tangible, emotional, and informational support) were associated with poor health (Kroenke, Kwan, et al., 2013). Specifically, after adjusting for important, health-related covariates (e.g., number of comorbid conditions, disease characteristics, treatments, etc.), women who were more socially isolated experienced significant impairments in physical functioning and more breast cancer-specific concerns when compared to women who were socially integrated.

Unlike the literatures examining women with an initial diagnosis of breast cancer, social support has not been reliably linked to decreased risk of mortality from recurrent disease (Lehto, Ojanen, Dyba, Aromaa, & Kellokumpu-Lehtinen, 2006). However, the relationship between social support and mortality as well as other indices of physical health may be strong for individuals with late stage disease. For example, in one study, the relationship between emotional support and survival was strong and significant for women with late stage disease but not for women with early
stage disease (Soler-Vila, Kasl, & Jones, 2003). Additionally, among advanced cancer patients with bone metastases receiving palliative treatment, 68% of whom were diagnosed with breast cancer, social support was correlated with functional performance status (Lam et al., 2013). Individuals reporting less support experienced more limitations in activities of daily living than those with higher levels of support. Similarly, among 132 advanced cancer patients (n=36 breast cancer) undergoing chemotherapy, Zabalegui and colleagues (2011) found social support to be significantly and negatively associated with chemotherapy symptoms; individuals with higher levels of social support experienced fewer chemotherapy symptoms ($r=-0.19$).

Little research has specifically examined the relationship between social support and physical health outcomes in the context of cancer recurrence; however, preliminary data suggests that social support may be beneficial. For example, in a study of 26 women with recurrent breast cancer, Brady and Helgeson (1999) found that women’s perceptions of the emotional support provided by their partner was significantly associated with physical health in both cross-sectional and longitudinal analyses. Women reporting greater levels of support experienced the fewest physical problems (e.g., pain; $r=-0.49$). Additional research is necessary to understand the relationship between social support and health outcomes for women with recurrence.

b. Psychological distress

An extensive literature has examined the relationship between social support and psychological distress in the context of an initial diagnosis of breast cancer. Thus, for brevity, the reader is referred to reviews by Helgeson and Cohen (1996), Mols and colleagues (2005), and Nelles and colleagues (1991), for example. Overall, results suggest a positive relationship between perceived social support and emotional wellbeing (e.g., Kroenke, et al., 2013; Alferi, Carver, Antoni, Weiss, Duran, 2001), and those with larger social networks experience greater emotional
wellbeing (Michael, et al., 2002). Several recent studies have confirmed this relationship among women diagnosed with both early stage (Boinon et al., 2014; Hughes, et al., 2014; McDonough, Sabiston, & Wrosch, 2014) and advanced breast cancer (Applebaum et al., 2014; Hasson-Ohayon, Goldzweig, Dorfman, & Uziely, 2014).

While the majority of research has examined psychological distress in the context of the initial diagnosis of cancer, the diagnosis of recurrence is often associated with increased psychological distress. When compared to newly diagnosed women and those with advanced disease, women with breast cancer recurrence often report higher levels of emotional distress (Mahon & Casperson, 1995; Silberfarb, Maurer, & Crouthamel, 1980). In a study of long-term breast cancer survivors with recurrence (N=54), Oh et al. (2004) found that, when compared to a matched sample of disease free women (N=54), women with recurrence reported declines in emotional wellbeing and greater cancer-specific stress. Similarly, Andersen and colleagues (2005) found that women diagnosed with recurrent breast cancer (N=30) experienced greater levels of cancer-specific stress when compared to disease free women.

In a study of 102 patients with recurrent cancer (n=39 breast), Weisman and Worden (1986) reported that patients became distressed quicker upon the diagnosis of recurrence than at initial diagnosis, and the distress was highest for individuals for whom the recurrence came as a surprise. Women with breast cancer recurrence report impairments in emotional wellbeing, decreased quality of life, and increased cancer-specific stress (Andersen, et al., 2005; Northouse, et al., 2002), as well as feelings of injustice, anger and fear (Chekryn, 1984). Women with breast cancer recurrence also experience more negative appraisals of their illness when compared to other medical populations (Northouse, et al., 2002). For many, the psychological distress experienced at recurrence exceeds that of the initial diagnosis. In a survey of 40 patients with
recurrent cancer (n=14 breast), 78% reported the recurrence diagnosis to be more difficult to adjust to and more emotionally upsetting than the initial diagnosis (Cella, Mahon, & Donovan, 1990). Only 8% of these patients described the initial diagnosis as more emotionally distressing than the diagnosis of recurrence.

Additionally, women with recurrence report high levels of psychiatric morbidity post-recurrence. In one study, Jenkins and colleagues (1991) found a high prevalence of anxiety (27.3%) and depression (31.8%) among women diagnosed with local recurrence. Similarly, Okamura and colleagues (2005) found 22% women with recurrent breast cancer in their sample to meet criteria for an anxiety or mood disorder, with the majority meeting criteria for adjustment disorder (20%). These studies suggest that the emotional response to cancer recurrence may be outside the normative response to life stressors.

A large proportion of research examining social support in recurrent cancer has looked at its relationship to psychological distress. In cross sectional studies of women with recurrent cancer, a negative relationship has been found between social support and psychological distress (Koopman, Hermanson, Diamond, Angell, & Spiegel, 1998; Northouse, Laten, & Reddy, 1995; Northouse, et al., 2002). For example, in a sample of 81 women with recurrent breast cancer, those with greater support experienced less emotional distress (Northouse, et al., 1995). Similarly, Koopman and colleagues (1998) found that women with recurrent or metastatic breast cancer who perceived their support interactions to be aversive experienced greater mood disturbance than those who were more satisfied with their support. Among women from the same sample, those with larger social networks experienced fewer avoidance symptoms (Butler, Koopman, Classen, & Spiegel, 1999). Finally, in a study of recurrent cancer patients, 22% of whom were diagnosed with breast cancer, those with greater perceived support reported fewer depressive symptoms,
decreased stress and better psychological wellbeing than those with less support in univariate analyses (Schulz et al., 1995). In multivariate analyses, perceived support remained negatively associated with both depressive symptoms and psychological wellbeing after controlling for covariates (e.g., physical health indices, medical costs).

While cross-sectional research suggests that social support may be beneficial for women with recurrent cancer, to the best of my knowledge, research has yet to examine the relationship between social support and psychological distress longitudinally for this population of cancer survivors. However, social support has been linked to psychological distress within the context of randomized controlled trials examining the effect of group-based psychotherapy on psychological functioning over time. For example, Classen and colleagues (2001) examined the effect of group-based supportive expressive therapy on emotional distress with women with recurrent or metastatic breast cancer. The goal of supportive-expressive therapy is to create a supportive environment in which group members are encouraged to strengthen relationships, confront problems, and increase meaning in their lives. When compared to women in a control group receiving educational materials only, those receiving the group therapy experienced reductions in cancer-specific stress and total mood disturbance over time. Further, Northouse and colleagues (2005) conducted a prospective, longitudinal, randomized clinical trial examining the effects of a family-focused intervention on psychosocial outcomes for women with recurrent breast cancer. The intervention, delivered to patients and their family caregivers, included components specifically designed to strengthen support received from family members. Women receiving the intervention experienced a significant decrease in hopelessness while women in the control group experienced a significant increase in hopelessness at the 3-month assessment. Although the aforementioned studies suggest that interventions including support components can result in improvements in
psychological variables, additional research is necessary to understand the relationship between social support and psychological distress over time for women with recurrent breast cancer.

c. Biological variables

i. Immune variables

As with other, non-cancer chronic illness populations, social support has been linked to immune variables among cancer patients. Again, the majority of what is known comes the context of an initial diagnosis of cancer rather than recurrent cancer. While the relationship between social support and NKCC has been documented (see below), little is known about the relationship between social support and T-cell proliferation among individuals with cancer. However, the link between social support and T-cell proliferation described previously may be particularly significant for individuals with recurrent cancer because alterations in immune functioning may directly impact the ability of individuals with recurrence to fight the disease (Dunn, Bruce, Ikeda, Old, & Schreiber, 2002; Spiegel & Sephton, 2001; B.N. Uchino, et al., 2012). Among breast cancer patients in particular, reduced proliferative response has been associated with disease progression (Wiltschke et al., 1995). Additional research is necessary to understand the link between social support and T-cell proliferation in the context of recurrent cancer.

As with healthy populations, NK cell activity has been linked to measures of social support among cancer patients. For example, in a sample of 61 women with early stage breast cancer, those reporting high levels of emotional support from an intimate partner or perceiving high levels of support form their physician had greater NKCC (Levy et al., 1990). Social support accounted for almost a third of the variance in NKCC; specifically, support from one’s partner was the greatest predictor of NKCC. Similarly, Lutgendorf and colleagues (2005) found that, among women newly diagnosed with ovarian cancer, greater social support was associated with greater NKCC in tumor
infiltrating lymphocytes. Given that NK cells play an important inhibitory and surveillance role in preventing metastases (Cerwenka & Lanier, 2001) and depressed NK cell activity has been associated with poor prognosis and disease progression in cancer patients (Levy, Herberman, Lippman, D'Angelo, & Lee, 1991; Whiteside & Herberman, 1994), it is plausible that the effect of social support on NK cell activity may mediate the relationship between social support and health outcomes. However, little is known about whether the relationship between social support and NKCC found with women with an initial diagnosis of cancer holds for women with recurrent breast cancer.

ii. Neuroendocrine variables

In the context of cancer, social support has been associated with cortisol levels. For example, in a sample of 108 Chinese breast cancer patients, patients who perceived a higher level of negative support experienced a flatter diurnal cortisol slope when compared to those perceiving less negative support (Ho, Fong, Chan, & Chan, 2013). Typically, the secretion of cortisol peaks soon after waking and decreases throughout the day (Stone et al., 2001). The altered rhythm found for cancer patients with higher levels of negative support may be particularly important considering that anomalous cortisol activity is associated with poor health outcomes including fatigue (Bower et al., 2005) and even mortality (Sephton, Sapolsky, Kraemer, & Spiegel, 2000) for women with breast cancer. Further, among women with advanced breast cancer, a portion of whom had recurred, Turner-Cobb and colleagues (2000) found that women reporting more positive functional support (i.e., appraisal, belonging, and tangible support) experienced lower mean levels of cortisol.

Limited research exists examining the relationship between epinephrine or norepinephrine and social support. The majority of studies examining catecholamines in adult cancer patients have been conducted with women with ovarian cancer. Specifically, low levels of perceived support have
been linked to high levels of intra-tumor norepinephrine (Lutgendorf et al., 2011; Lutgendorf et al., 2009). Among pediatric cancer patients, those with a better family environment (i.e., less family conflict) or more perceived support from friends experienced lower levels of epinephrine and norepinephrine, respectively (Hockenberry-Eaton, Kemp, & Dilorio, 1994). Thus, while data from the general literature, as well as data from other cancer populations has established a negative relationship between social support and epinephrine or norepinephrine, additional research is necessary to confirm or deny these relationships in the context of not only breast cancer, but recurrent breast cancer as well. An examination of catecholamines may be especially relevant for women with recurrent cancer because epinephrine and norepinephrine can increase the invasive potential of cancer cells (Sood et al., 2006).

The sections above presented data linking social support to immune and neuroendocrine variables in the context of cancer. Interestingly, the majority of research has utilized measures of functional support. Consequently, little is known about the effect that the number of contacts or the amount of social integration reported by a patient has on biological variables.

ii. **Mechanisms**

As described previously, social support has been linked to physical health outcomes for cancer patients. However, there is little research examining the mechanisms by which social support influences the health of those with cancer. A review of the literature revealed one study examining the mechanisms linking social support to physical health outcomes for women with recurrent breast cancer. In a study of 189 women surveyed up to 1-month post-recurrence, Northouse and colleagues (2002) found that social support was indirectly related to patients health-related quality of life via hopelessness. Women reporting greater levels of social support experienced less hopelessness, which was associated with better health-related quality of life.
Given the limited research, why might one hypothesize that psychological and biological processes mediate the relationship between social support and health? First, as described above, social support is associated with psychological distress and biological variables in the context of the diagnosis of cancer or the experience of recurrence. Second, psychological distress has been linked to poor health outcomes for cancer patients. For example, in a meta-analysis of 25 studies, patients experiencing depression are at increased risk for mortality ($RR=1.25$; Satin, Linden & Phillips, 2009), and the presence of depressive symptoms has been linked to faster disease progression (Levy, et al., 1991; Spiegel & Giese-Davis, 2003). Similarly, among women with breast cancer, those with low levels of psychological distress have longer recurrence-free and disease-specific survival when compared to those with higher levels of psychological distress (Groenvold et al., 2007). Patients’ psychological distress (e.g., stress, worry, depression, and anxiety) is also frequently described as a significant contributor to fatigue (Peters, Goedendorp, Verhagen, van der Graaf, & Bleijenberg, 2014; Smets, Garssen, Schuster-Uitterhoeve, & de Haes, 1993). Finally, among women undergoing surgery for breast cancer, pre-surgery levels of psychological distress have been associated with post-surgery levels of pain and fatigue; those reporting more emotional distress experienced greater levels of pain and fatigue 1-week post-surgery (Montgomery, Schnur, Erblich, Diefenbach, & Bovbjerg, 2010).

Third, biological variables have been linked to disease-specific mortality, disease progression, and physical symptoms (e.g., Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008; Thornton, Andersen, Crespin, & Carson, 2007). As described previously, among women with metastatic breast cancer, women with abnormal cortisol variation (i.e., flat rhythms) and suppressed NK cell activity experienced earlier mortality (Sephton, Sapolsky, Kraemer, & Speigel, 200). Further, reduced proliferative response to the mitogen PHA has been linked to disease
progression (Wiltschke, et al., 1995) among breast cancer patients. In a sample of women with advanced breast cancer, Thornton and colleagues (2010) found plasma cortisol and epinephrine levels to be significantly associated with levels of pain and fatigue. Finally, administration of norepinephrine and cortisol to ovarian cancer cell lines has been linked to increased in vitro invasive metastatic potential of the cells (Sood, et al., 2006).

The aforementioned research presents direct associations between social support and psychological distress and biological variables, as well as direct associations between psychological distress and biological variables and physical health. Additional research is necessary to confirm or deny the mechanistic role of psychological distress and biological variables in the link between social support and health for recurrent cancer patients.

iii. Summary

As with the general population, in the context of cancer, social support has been associated with decreased rates of mortality, disease progression and physical symptoms (e.g., pain and fatigue). Among women with recurrent disease specifically, social support is positively associated with functional performance status and negatively associated with physical symptoms. Further, higher levels of social support have been linked to lower psychological distress, cancer-specific stress, hopelessness, depressive symptoms and mood disturbance, as well as increased quality of life for women with recurrent cancer.

Little is known about the effect that social support has on immune and neuroendocrine parameters for individuals with recurrent disease. Among patients with newly diagnosed disease, higher levels of social support are associated with greater NKCC while low levels of social support are associated with both dysregulated cortisol secretion and higher mean levels of cortisol. Social
support has also been shown to be negatively associated with catecholamine levels including levels of epinephrine and norepinephrine.

While social support has been directly linked to physical health outcomes, the process by which social support influences physical health is still unknown. It is hypothesized that psychological and biological parameters may mediate the relationship between social support and health. Not only does social support predict psychological distress and biological variables, psychological distress and biological variables predict physical health outcomes. However research specifically examining the role of psychological and biological variables as mediators is lacking. The present study aimed to address this gap in the literature, to better understand the health-protective role of social support for those with breast cancer recurrence.

Patients with recurrent disease are an important population in which to study the effect of social support on physical health outcomes because of the significant link of recurrence to low levels of social support, high levels of psychological distress and physical burden, and the risk of premature death. Additionally, the timing of the recurrence and the fact that recurrence represents the return of disease may present more psychological distress and physical limitations at a time when patients may not have access to the same support network they had when initially diagnosed (Thornton, et al., 2014). The general literature has linked social support and health; thus, it is plausible that with low levels of social support, women with recurrent disease may be vulnerable to poor health outcomes. The present exploratory study hopes to elucidate the relationship between social support and physical health for women with breast cancer recurrence by examining not only the direct relationship between social support and health over time, but also examining the mechanisms by which social support may be related to physical health.
IV. Study Aims and Hypotheses

Research examining the relationship between social support, psychological distress, biological variables, or physical health has been cross-sectional. Cross-sectional data, while informative, does not provide needed information on the sequence of events leading to changes in health (B.N. Uchino, et al., 2012). Further, social factors may not have an immediate, observable impact on psychological, biological, or physiological variables (Miller, Chen, & Cole, 2009). Thus, the present study utilizes a longitudinal design, assessing structural and functional support at baseline, psychological distress and biological variables at 4 months, and physical health at 12 months to measure the relationship between social support and the aforementioned constructs over time.

The longitudinal data that exists with regard to social support in the context of cancer comes from the literature examining the initial diagnosis of cancer. Thus, researchers have called for longitudinal research that examines the social aspects of cancer survivorship (Jarrett, et al., 2013). Due to the qualitatively different experience of recurrence when compared to an initial diagnosis, it is important to examine the effect that social support may have on psychological distress, biological variables, and physical health in women with breast cancer recurrence over time.

i. Main effects

Aim 1: To examine whether measures of both structural and functional support assessed at baseline predict physical health 12 months post-baseline.

Hypothesis 1: Both measures of structural and functional support assessed at baseline will be predictive of subjective and objective ratings of physical health one-year post recurrence. Individuals reporting larger social networks and/or perceiving greater support
from family members at baseline will experience better self-reported, subjective and nurse-assessed, objective ratings of physical health (see Figure 1a).

Aim 2: To examine whether measures of both structural and functional support assessed at baseline predict psychological distress 4 months post-baseline.

Hypothesis 2: Both measures of structural and functional support will be related to psychological distress, with women with greater support at baseline reporting lower levels of psychological distress at the 4-month assessment (see Figure 1b, path a).

Aim 3: To examine whether measures of both structural and functional support assessed at baseline predict biological variables 4 months post-baseline.

Hypothesis 3: Both measures of structural and functional support will be related to biological variables (see Figure 1c, path a). Specifically, women with higher levels of social support at baseline will have a greater proliferative response to the mitogen PHA and greater NKCC. Further, individuals with lower levels of social support at baseline will have higher levels of cortisol and norepinephrine.

ii. Test of Mechanisms

Aim 4: To examine whether psychological distress assessed at 4 months mediates the relationship between baseline levels of social support and self-reported, subjective and nurse-assessed, objective ratings of physical health 12 months post-baseline.

Hypothesis 4: Psychological distress will mediate the relationship between social support and physical health. Social support at baseline will influence physical health at 12 months via psychological distress (see Figure 1b).
**Aim 5:** To examine whether immune and neuroendocrine variables assessed at 4-months mediate the relationship between baseline social support and self-reported, subjective and nurse-assessed, objectives ratings of physical health 12-months post-baseline.

**Hypothesis 5:** Biological variables will mediate the relationship between social support and physical health. Social support at baseline will influence physical health at 12 months via greater proliferative response to the mitogen PHA and NKCC, as well as lower cortisol and norepinephrine levels (see Figure 1c).

iii. **Exploratory aim: Social Support and Survival**

**Aim 6:** To examine whether social support at baseline is associated with the hazard of death.

**Hypothesis 6:** Higher (vs. lower) levels of social support at baseline will be associated with decreased hazard of all-cause mortality among women with recurrent breast cancer.
CHAPTER 2

METHODS

I. Design

A non-experimental, repeated measures design was used, with data available from an archival data set. A total of 122 women with recurrent breast cancer were studied, with 3 assessments occurring over a 12-month period post diagnosis of recurrence. The baseline assessment was completed a median of 10 weeks post-recurrence diagnosis (range 0 to 37 weeks). Follow-up assessments were completed 4- and 12-months following the baseline assessment. Figure 2 provides information about the flow of study participants over the course of the 1-year follow-up.

II. Procedures

i. Eligibility Criteria

Recurrence is classified by the development of metastatic disease in the same area, adjacent to, or distant from the original disease (TMN staging system of the American Joint Committee on Cancer Staging and End Results Reporting; Lenhard, Osteen, & Gansler, 2001). The definition of recurrence excludes the development of second primary tumors (e.g., tumors that did not develop from breast tissue, contralateral breast tumors). Participants were eligible for the present study if they had been diagnosed with the first recurrence of breast cancer, lived within 90 miles of The Ohio State University, were willing and able to provide informed consent, and were
between 21 and 85 years of age. Exclusion criteria included diagnosis of prior or current second primary tumor (e.g., contralateral breast, endometrial), prior or current refusal of cancer treatment, diagnosis of a condition that limits the ability to provide informed consent (e.g., mental retardation, severe or untreated psychiatric disorder, neurological disorders), diagnosis of autoimmunologic or immune-compromising condition or disease (e.g., Rheumatoid arthritis, chronic fatigue syndrome), inability to speak/read English, and significant hearing deficits.

Patients were identified from two psychosocial research studies at The Ohio State University (see below). For both, patients were accrued from the oncology clinics of a National Cancer Institute-designated Comprehensive Cancer Center affiliated with The Ohio State University or were self- or physician-referred patients from the community.

ii. Accrual

a. Randomized controlled trial

The first study was a randomized clinical trial (RCT) for women with newly diagnosed regional breast cancer (Stage II/III; n=227). Women were accrued following surgical treatment, but prior to the start of adjuvant therapies. Women were randomized to a psychologic intervention plus assessment (n=114) or assessment only arms (n=113). Details of the RCT, including procedures for informed consent, accrual and randomization have been published elsewhere (Andersen et al., 2004). Women were followed after completion of the trial, and continued to be assessed every 6 months or annually. Over the course of follow-up, a subset of patients’ breast cancers recurred (n=66). As women recurred, they were approached for accrual to a secondary study on coping with recurrence. Overall, 42 of the 66 (64%) women who recurred were followed post-recurrence.
b. *Longitudinal study of recurrent breast cancer*

New, consecutive cases of recurrent breast cancer were identified from clinic rosters. 102 women were approached; of these women, 80 (78%) agreed to participate. Thus, a total of 122 women from both samples participated.

iii. **Assessment Procedures**

All participants were provided with oral and written informed consent. Following informed consent, women completed face-to-face, structured interviews and questionnaires with a female assessor. Assessments consisted of women's self-reports of structural and functional measures of social support, depressive symptoms, mood disturbance, quality of life and, health. A female research nurse conducted a health assessment with the patient and utilized medical chart inspection and physician consultation as needed. Finally, the research nurse obtained 60mL of blood from participants at each assessment. Assessments were scheduled between 7 and 10am to minimize diurnal variability. All women were reassessed every 4 months for the first year and every 6 months thereafter. For the purpose of the proposed research, data from the baseline, 4 month, and 12 month assessments was used. In appreciation for their time, participants were compensated $50.00-$100.00 per assessment.

III. **Participants**

Table 1 presents sociodemographic, disease/prognostic, and treatment characteristics for the present sample. At baseline, women were on average 55-years old, college educated ($M=14.7$ years, $SD=2.9$), and had an annual family income of over $68K. The majority was Caucasian (92%) and living with a romantic partner (70%), while close to half were employed (47%). At the initial diagnosis, the majority was diagnosed with stage II disease (60%). The average disease free interval was 55 months (median=36, range=5 to 254) and the majority had distant metastases
(68%). The majority of participants with distant disease spread had metastases in their lungs (22% of participants), liver (21%), and/or bone (43%). As treatment typically begins shortly after diagnosis of recurrent disease, 84% had received or were continuing with cancer treatment at the time of the initial assessment (post-surgery=26%, chemotherapy=48%, radiation therapy=21%, hormonal therapy=29%).

Those accrued via the RCT and those accrued via the longitudinal study of recurrent cancer were compared with regard to sociodemographic, disease characteristics, and disease-related variables using Chi-square or ANOVA models as appropriate (see Table 1). Comparisons showed no significant differences on sociodemographic characteristics assessed at baseline (all p values > 0.09). There were no significant differences in characteristics of women’s initial disease, excepting that of stage; women who were accrued via the longitudinal study of recurrent cancer were more likely to have been diagnosed with stage I cancer (30%) than women accrued via the RCT (0%), and women in the RCT were more likely to have been diagnosed with stage II cancer (83% vs. 49%; p<0.01). One of the eligibility criteria for the RCT was diagnosis of stage II or III breast cancer, while women were not selected for the longitudinal study based on stage of initial disease. Thus, it is understandable that the groups would differ with regard to stage of initial disease.

Further, the two groups were similar with regard to characteristics of the recurrence experience although, women in longitudinal study of recurrence (55%) were more likely to be receiving chemotherapy at the baseline assessment than those accrued via the RCT (35%; p<0.05). However, when the sample was restricted to only those alive at the 12-month assessment (n=99; see Table 2), only stage at initial diagnosis significantly differed between the two different accrual avenues.
IV. Missing Data & Sample Size

In the present study, the majority of missing data arose from 3 sources: 1) study drop out; 2) non-compliance with assessments; and, 3) patient death (see Figure 2). Overall, 122 individuals were eligible for the 3 assessments for a total 366 possible assessment points. Of the 122 participants, 120 (98%) were assessed at baseline, 98 (80%) were assessed at the 4-month follow-up, and 82 (67%) were assessed at the 12-month follow-up (see Figure 2). Thus, 300 of 366 (82%) data points are available. Of the missing assessments, 21 of 66 (32%) resulted from patient non-compliance, 16 of 66 (24%) resulted from patient withdrawal (dropout), and 29 of 66 (44%) resulted from patient death.

For the biological measures, rates of missing data are higher than for the self-report and nurse-rated assessments. Of the 122 individuals eligible to complete an assessment at baseline, data on biological measures is available for 75 (61%) individuals at the 4-month assessment. Of the remaining 47 participants, missing data occurred for a variety of reasons. First, a portion of the data was missing by study design. Blood data collection was terminated in May 2006 for the present study. Consequently, 20 participants whose 4-month assessment fell after May 2006 were missing data. Of the remaining participants with missing data, 5 of 27 (19%) dropped from the study and 6 of 27 (22%) died prior to the 4-month assessment. Additionally, 10 of 27 (37%) participants were non-compliant at the 4 month assessment and the remaining 6 of 27 (22%) participants had missing data for other reasons (e.g., difficulties with the blood draw).

For the present study, missing data were imputed for all assessments or data points missing for reasons other than death. By the four-month assessment, 6 participants had died for a total of 116 possible participants. By the 12-month assessment, 23 participants had died for a total of 99 possible participants.
V. Measures

i. Social Support

*Functional Support.* As family ties are an important source of social support and family members are the primary support people for individuals with recurrent cancer (Manne, Pape, Taylor, & Dougherty, 1999; Uchino, et al., 1996), functional support was assessed via The Perceived Support from Family Scale (PSS-FA; Procidano & Heller, 1983). The PSS-FA is a 20-item instrument, which measures the degree to which one perceives that her needs for support are fulfilled by her social network. Participants are asked to rate whether each statement provided (e.g., “I have a deep, sharing relationship with a number of members of my family”) describes the typical support from their family members at the present time. Items are summed and scores range from 0 to 20. Higher scores reflect greater perceived support.

*Structural Support.* The Social Network Index (SNI; Berkman, 1977) is a commonly used measure of social integration that has been shown to predict morbidity and mortality (Berkman & Syme, 1979; Uchino, 2004). The SNI includes items measuring four components: 1) marital status; 2) number of close friends and relatives and frequency of contact with these individuals; 3) church group membership; and 4) membership in other groups (e.g., social, vocational, child-related). Intimate contacts are weighted more heavily than church affiliations and group memberships when calculating a total score. Scores range from 1 to 12, with higher scores representing greater social involvement.

ii. Psychological Distress

*Depressive Symptoms.* The Center for Epidemiological Studies-Depression Scale (CES-D; Radloff, 1977) is a 20-item scale that assesses participants’ depressive symptoms in the past week. Participants are asked to rate how often each statement applied to them in the previous
week on a 4-point scale from 0 ("rarely or none of the time") to 3 ("most or all of the time"). Scores range from 0 to 60, with higher scores representing greater depressive symptoms.

*Negative Mood.* The Profile of Mood States-short form (Shacham, 1983) is a 37-item measure that assesses mood over the past week. Participants are provided a list of adjectives and asked whether each describes how they have been feeling on a 5-point scale from 0 ("not at all") to 4 ("extremely"). The scale is comprised of six mood subscales: 1) Tension-Anxiety; 2) Depression-Dejection; 3) Anger-Hostility; 4) Vigor-Activity; 5) Fatigue-Inertia; and 6) Confusion-Bewilderment. The subscales can be summed to create a measure of Total Mood Disturbance (POMS-TMD). Scores for the POMS-TMD range from -24 to 124 with higher scores representing greater mood disturbance.

*Mental Health-Related Quality of Life.* The Medical Outcomes Study Short form is a 36-item scale that assesses health-related quality of life (SF-36; Ware & Sherbourne, 1992). The SF-36 assesses 8 domains of quality of life: 1) physical functioning; 2) role functioning related to physical health; 3) bodily pain; 4) general health perceptions; 5) vitality; 6) social functioning; 7) role functioning related to emotional health; and 8) mental health. The 8 domains are summarized into two components: Physical Component Summary (PCS; see below for description) and the Mental Component Summary (MCS). The MCS is an aggregation of weighted subscale scores which load most heavily in the mental health component subtracting weighted subscale scores loading more heavily on the physical health component. Scores are transformed to have a mean of 50 and standard deviation of 10 (Ware, Kosinski, & Keller, 1994). Scores range from 0 to 100 with higher scores indicated better mental health-related quality of life.
iii. **Biological Variables**

*Plasma cortisol.* Plasma cortisol determinations were made using the Coat-A-Count RIA (Diagnostic Products Corporation, Los Angeles, CA). Intra-assay variation was 4.3% and inter-assay variation is 5.2%. Sensitivity was 0.2 μg/dl.

*Plasma norepinephrine.* Determinations were made by HPLC with ElectroChemical Detection using Standards and Chemistry [Alumina extraction] purchased from ChromSystems, Munich, Germany (U.S. affiliate Thermo-Alko, Beverly, MA). C-18 Columns were purchased from the Waters Corporation (Waters Corporation, Milford, MA). Intra-assay variation, inter-assay variation, and sensitivity for norepinephrine were 3%, 6%, and 15 pg/ml, respectively.

*Lymphocyte Proliferative Response.* T-cell blastogenic response to the mitogen phytohemaglutinin (PHA) was examined. Detailed descriptions of our standard laboratory procedures have been published elsewhere (Andersen, et al., 2004; Thornton, et al., 2007). Briefly, peripheral blood leukocytes (PBLs) were isolated from 60 mL of venous blood and seeded in triplicate at 0.5 x 10^5/well. PBLs were incubated for 68 hours at 37 degrees Celsius in 96-well-flat-bottom plates, and then labeled or 4 hours with MTS [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt] and phenazine methosulfate to measure proliferative response. Proliferation was determined via optical density of the suspension (Andersen, et al., 2004). Blastogenic response was expressed as the mean of standardized scores of three serial dilutions of PHA at 2.5, 5.0, and 10.0 μg/ml. The composite PHA score was calculated as the average of the z-scores across the three dilutions as described by Carson and colleagues (2004) and Thornton and colleagues (2007).

*Natural Killer Cell Cytotoxicity.* NKCC was examined. PBLs were isolated from 60 mL of venous blood as described previously (Andersen et al., 2004). Briefly, PBLs were suspended in
complete medium and seeded into 96-well v-bottom plates in a volume to allow for effector to
target cell ratios of 100:1, 50:1, 25:1, 12.5:1, 6.25:1, and 3.125:1. The NK-sensitive human myeloid
K562 cell line was used as the target cell against which to test NKCC using a standard chromium
release assay. K562 cells were labeled with chromium-51, washed, and then added to each well.
NKCC is expressed in terms of lytic units. As suggested by Bryant et al., (1992), lytic units were
calculated as the mean of logarithmically transformed specific lysis over all six of the effector to target
ratios. The data was then normalized, converting the lytic units to a logarithmic scale.

iv. **Physical Health**

a. *Nurse-Assessed Physical Health*

*Signs/Symptoms of Illness and Treatment Toxicity.* The Southwest Oncology Group
(SWOG; Moinpour et al., 1989) criteria were used to document the types of and severity of toxicity
reactions from the patients’ cancer treatments and current signs/symptoms. Signs/symptoms were
provided for twenty-two body systems (e.g., hematologic gastrointestinal, neurosensory, pain,
neurologic/neurocentral). Each body system is comprised of 4 to 6 items. A severity rating is
provided for each symptom on a 5-point scale from 0 (“none”) to 4 (“life threatening”), specific to
each item. The average of sign/symptom severity is calculated for each body system as a subscale
score. The average of subscale scores is calculated to obtain an overall toxicity score ranging from
0 to 4 with higher scores indicating greater severity of symptoms. Project nurses with advanced
training in oncology and toxicity screening conducted the assessment. Supporting information was
obtained through consultation with medical staff or chart review as necessary.

*Functional Performance Status.* The Karnofsky Performance Status Scale (Moinpour, et
al., 1989), is the most widely used measure of functional performance status in cancer studies.
The scale ranges from 0 (Dead) to 100 (Normal, no complaints, no evidence of disease). Scores
are provided at 10-point intervals, each containing differential criteria (e.g., 80 = normal activity with effort, some signs/symptoms of disease). Lower scores indicate that the patient is more restricted in her performance of daily and self-care activities.

b. **Self-Reported Physical Health**

*Fatigue.* The Fatigue Symptom Inventory (FSI; Hann et al., 1998) assesses the frequency, severity, daily pattern of fatigue, as well as how much fatigue interferes with daily life. Items are rated using a Likert scale. For example, participants are asked to rate their current level of fatigue on a scale from 0 (“not at all fatigued”) to 10 (“as fatigued as I could be”), as well as how many days they felt fatigued in the past week (from 0 to 7), how much of the day, on average, they felt fatigued from 0 (“none of the day”) to 10 (“the entire day”), and the pattern of fatigue (e.g., fatigue worse in the morning). Further, participants rate the level of interference from fatigue in their lives in the previous week on a scale from 0 (“no interference”) to 10 (“extreme interference”) across a variety of domains, including daily activities (e.g., general level of activity, ability to concentrate, ability to bathe and dress oneself) as well as mood and general enjoyment of life. The Disruption Index is calculated based on 7 items measuring the impact of fatigue on quality of life. Total scores range from 0 to 70 with higher scores indicating greater fatigue.

*Pain.* The Brief Pain Inventory-short form (BPI; Cleeland, 1991; Cleeland & Ryan, 1994) assesses participants’ level of pain over the last 24 hours. Participants are asked whether or not they have experienced pain and the location of the pain. If they have experienced pain, they are asked to rate the severity of the pain at its worst, at its least, on average and currently on a scale from 0 (“no pain”) to 10 (“pain as bad as you can imagine”). Additionally, participants indicate the percentage of relief they have experienced from pain medications from 0% (“no relief”) to 100% (“complete relief”). Finally, participants rate the level of interference from pain in their lives from 0
(“does not interfere”) to 10 (“completely interferes”) across a variety of domains, including daily activities (e.g., general level of activity, walking ability, normal work) as well as mood and general enjoyment of life. The pain interference scale is calculated based on the 7 items measuring the impact of pain on various aspects of daily life. Total scores range from 0 to 70 with higher scores indicating more pain.

*Physical Health-Related Quality of Life.* The Physical Component Summary (PCS; Ware & Sherborne, 1992) of the SF-36 (see above) was used to assess physical health-related quality of life. The PCS is an aggregation of weighted subscale scores which load most heavy on the physical component subtracting weighted subscale scores loading more heavily on the mental health component. As with the MCS, scores are transformed to have a mean of 50 and standard deviation of 10 (Ware, et al., 1994). Scores range from 0 to 100 with higher scores indicated better physical health-related quality of life.

c. *Time to Death*

Whether or not a participant was still living was obtained throughout the course of follow-up via information obtained through medical records and/or death certificates. Following completion of both the RCT and the longitudinal study of recurrence, participants were continuously followed to obtain information on participants’ date of death. For the present study, information about whether or not a participant was still living is current as of March 3, 2014.

VI. Analytic Strategy

i. *Score Calculation*

For ease of analysis and interpretation, composite indices for psychological distress and physical health were calculated. The composite for psychological distress is comprised of depressive symptoms (CES-D), mental health-related quality of life (MCS), and mood (POMS-
Bivariate correlations at the 4-month assessment range from -.769 to .911 (all ps<.001). The correlations suggest a common construct of psychological distress.

Two composite indices for physical health were calculated, the first being participants’ ratings of their health (subjective) and the second being nurse-assessed measures of participants’ health (objective). The composite index for subjective physical health is comprised of pain (BPI), fatigue (FSI-TDI), and physical health-related quality of life (PCS). The composite index for objective physical health is comprised of nurse-rated assessments of signs/symptoms of illness and treatment toxicity (SWOG) and functional performance status (KPS). Bivariate correlations at the 12-month assessment range from -.467 to .596 (all ps<0.001) for subjective health ratings and -.573 (p<0.001) for the objective health ratings, suggesting that the subjective variables and objectives variables may capture distinct, but related measures of health.

Composite scores were calculated in four steps. First, each measure was scored as previously described. Second, each total score was standardized, converted to z-scores. If necessary, the standardized scores were reversed to ensure that all measures within the composite score were scored in the same direction. For example, high scores on the MCS indicate better quality of life, while high scores on the CES-D and POMS-TMD indicate more depressive symptoms or greater mood disturbance. The standardized scores on the MCS were reversed such that higher scores became indicative of greater impairments in mental health-related quality of life. Third, the standardized scores for each measure were summed to obtain a composite total score. Finally, the average of the scales comprising the composite index were obtained. Higher scores on the composite items were indicative of more psychological distress or poorer health.
ii. Hierarchical Multiple Linear Regression

Separate hierarchical multiple linear regression (HMLR) analyses tested aims 1-3. Specifically, aim 1 was tested via four separate regression analyses, two examining whether structural support at baseline predicts the subjective physical health composite variable or objective physical health composite variable at 12 months and two examining whether functional support at baseline predicted the subjective physical health composite or objective physical health composite at 12 months. Aim 2 was tested with two separate HMLR analyses examining whether structural and/or functional support predicted the psychological distress composite variable at 4 months. Finally, aim 3 was tested via 8 HMLR analyses, four for structural support and four for functional support predicting measures of functional immunity (i.e., proliferative response to PHA, NKCC), plasma cortisol levels or plasma norepinephrine levels at 4 months.

For each, the following variables were entered into the HMLR analyses: 1) control variables (if any), and 2) structural or functional support. Classes of control variables were identified conceptually. Control variables considered for inclusion were:

a) baseline levels of the dependent variables for each analysis (e.g., baseline psychological distress composite, baseline cortisol, etc.)

b) additional variables significantly correlated with the dependent variables of interest for each analysis [i.e., sociodemographic variables (i.e., age, education, family income), known prognostic factors (i.e., disease free interval, extent of recurrent disease, and cancer treatments received after recurrence), and whether or not women participated in the intervention arm of the RCT].

Of these possible variables, only one was considered as a covariate if variables were highly correlated with each other ($r>0.4$) to avoid multicollinearity. While controlling for baseline levels of
dependent variables is often recommended for longitudinal analyses, this approach is quite conservative. Thus, for the purposes of the proposed study, analyses were run both with and without controlling for baseline levels of dependent variables to determine if the results differed when the covariates are included in the models.

iii. Mediation analyses

In order to test the process by which social support influences physical health, mediation analyses were conducted. Although the causal steps approach is frequently used in health psychology, testing for mediation using the causal steps approach in conjunction with the Sobel test is conservative. While the causal steps approach and Sobel test are recommended for use with large sample sizes (Fritz & MacKinnon, 2007), the ability to detect mediated effects using this method with smaller sample sizes can be low (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002; Preacher & Hayes, 2004; B.N. Uchino, et al., 2012). As an alternative, bootstrapped mediation has been recommended (Hayes & Scharkow, 2013; B.N. Uchino, et al., 2012) and was used in the present study. Bootstrap mediation analyses can be applied even when the sample size is small or moderate (e.g., N=20-80; Efron & Tibshirani, 1993; Shrout & Bolger, 2002; Preacher & Hayes, 2008), which provides a significant advantage over the traditionally used methods (i.e., the causal steps approach).

Bootstrapped mediation involves repeatedly resampling with replacement from the original data set to obtain multiple bootstrapped samples. It is recommended that one obtain at least 1,000 bootstrapped samples (Preacher & Hayes, 2008; Wu & Jia, 2013). The indirect effect of the independent variable on the dependent variable via the mediating variable is then estimated from each of the bootstrapped data sets to empirically generate a sampling distribution. The sampling distribution is then used to construct confidence intervals and p-values for the indirect effect (Hayes
& Scharkow, 2013; Preacher & Hayes, 2008). If zero is not included in the confidence interval, one can be relatively certain that the indirect effect differs from zero. A bias corrected confidence interval corrects for skew in the population (i.e., the percentage of estimates that are below the parameter estimates of the original sample) and has been recommended as a trustworthy test when power is of importance (Hayes & Scharkow, 2013; Mackinnon, Lockwood, & Williams, 2004; Wang, Zhang, & Tong, 2010).

Aims 4 and 5 were examined separately using bootstrap mediation. As with aims 1-3 (see above), variables considered for inclusion as controls are as follows: 1) baseline levels of the mediator or dependent variable; and 2) variables assessed at baseline that were significantly correlated with the physical health dependent variable of interest for each analysis [i.e., sociodemographic variables (i.e., age, education, family income), known prognostic factors (i.e., disease free interval, extent of recurrent disease, and cancer treatments received after recurrence), and whether or not women participated in the intervention arm of the RCT]. As described previously, controlling for baseline levels of dependent and mediating variables, while a common occurrence in the literature, is a conservative approach. Thus, mediation analyses were run two ways: 1) including baseline levels of dependent and mediating variables, and 2) excluding baseline levels of dependent variables.

iv. Multiple Imputation

A common issue with multivariate, longitudinal research is the presence of missing data. Most previous analyses have employed complete case analyses. However, complete case analysis can eliminate a large amount of data and may bias results if those with missing data differ on the variable of interest from the sample with data (Alison, 2009; Donders, van der Heijden, Stijnen, & Moons, 2006; Schafer, 1999). With the availability of imputation methods, complete case analysis
is no longer deemed acceptable (Little & Rubin, 2002). For missing data, researchers have begun to utilize various imputation methods, which allow the researcher fill-in missing values to maintain the full sample. For example, researchers may utilize mean imputation, which replaces missing values with the mean value obtained from observed cases of the variable, or replace missing values with the last available data point for an individual on the variable in question. However, these methods assume that the value of the missing data is known with certainty, which can result in biased estimates and standard errors (de Goeij et al., 2013; Donders, et al., 2006; He, 2010). Additionally, it is assumed that imputed values are appropriate for each individual at each time point, which may or may not be true (de Goeij, et al., 2013).

Instead, multiple imputation has been recommended (McCleary, 2002). In multiple imputation, multiple sets of plausible replacements for the missing data values are obtained to create multiple, completed data sets (de Goeij, et al., 2013; He, 2010). The missing data values are predicted from not only the known values in the data set, but also the pattern of missing data overall (de Goeij, et al., 2013), creating a prediction model for the missing variables. The imputed data sets are then analyzed using standard statistical procedures to obtain point estimates of parameters for each imputed data set (He, 2010). The results of these analyses are then combined to allow for the calculation of single point estimates of model parameters (Alison, 2009). The number of imputed data sets needed has been questioned in recent years. While some recommend as few as 5 imputed data sets (Alison, 2009), others have called for a much larger number (Graham, Olchowski, & Gilreath, 2007; Wang, et al., 2010). For the present study, 75 imputed data sets were used.

When conducting multiple imputation, all variables included in the model (e.g., see Figures 1a-c), including the dependent variable are utilized to impute the missing values (de Goeij, et al.,
It is also recommended that auxiliary variables be included in the prediction model to impute missing values (Alison, 2009; Enders, 2010). Auxiliary variables need not be variables of interest; however, including auxiliary variables in the prediction model can help to reduce estimation bias, improve the accuracy of the imputations, and restore power lost from having missing data. Candidates for auxiliary variables include variables that are moderately to highly correlated (e.g., $r>0.4$) with the variables of interest included in the model (Alison, 2009; Enders, 2010) and variables that are correlates of missingness (Enders, 2010). The missing at random assumption of multiple imputation is more plausible when variables that are correlates of missingness are included in the imputation model. Further, according to Graham (2009), “Good candidates for auxiliary variables are the same variables used in the analytic model, but measured at different waves” (p. 565). Thus, in the case of longitudinal data, values for variables of interest at time points prior to the time point of interest are good candidates for inclusion in the prediction model to impute missing values.

For the present analyses, a series of independent samples t-tests or chi-square analyses, as appropriate, were used to examine group mean differences or differences in categories of a variable between those having complete or incomplete data on variables of interest (e.g., objective or subjective physical health). A variable was included as an auxiliary variable if it’s value significantly differed between those with and without missing data. Next, bivariate correlations examined whether any additional variables were significantly correlated with the variables of interest. Variables significantly and highly correlated with the variables of interest were included as auxiliary variables for analyses where they were not also used as covariates. Finally, baseline values of mediator variables and the baseline and 4 month values of the subjective and objective physical health composites were included as auxiliary variables in the imputation model.
Multiple imputation procedures (as described above) were used prior to conducting the regression analyses for Aims 1-3. To examine Aims 4 and 5, multiple imputation was used in combination with bootstrap mediation to obtain point estimates and bias corrected confidence intervals using a procedure developed by Wu and Jia (2013). In this procedure, multiple imputation was used to obtain 75 imputed data sets. Next, 1,000 bootstrap samples were drawn from each of the 75 imputed data sets yielding a total of 75,000 bootstrap samples. During the analysis step, point estimates for the indirect effect were obtained for each of the bootstrap samples. Finally, during the mixing step, the 75,000 estimates of the indirect effect were mixed together to approximate the overall point estimate for the indirect effect and calculate the bias corrected confidence interval.

v. Survival Analysis

Aim 6 was examined using Cox proportional hazards models (Cox, 1972) to obtain a multivariate comparison of survival for individuals with high vs. low levels social support at the baseline assessment. Specifically, the purpose of the analyses was to contrast individuals with high vs. low levels of structural or functional support in health outcomes (i.e., all-cause mortality). Thus, a total of 2 models were examined, one for each social support variable of interest. A median split was used to identify those who were high vs. low in each measure of social support.

The following were considered as potential covariates: 1) baseline sociodemographic variables (i.e., age, family income, years of education), 2) disease prognostic factors at recurrence (i.e., disease-free interval, extent of recurrent disease, and type of treatment received after recurrence), and 3) whether or not individuals participated in the intervention. To avoid multicollinearity, the correlation between covariates was examined. If covariates were significantly correlated with each other (e.g., \( r > 0.4 \)), only one was considered as a covariate. A backward
elimination procedure was used to select covariates for the final models as recommended (Clark, Bradburn, Love, & Altman, 2003; Harrell, 2001). Any covariate with $p<0.1$ remained in the final models.

Estimates for hazards ratios and corresponding 95% confidence intervals were obtained for each covariate and for the effect of structural or functional support. Bivariate correlations comparing Schoenfeld residuals to the rank of survival times for individuals experiencing the event of death were examined to test the proportionality assumption (Alison, 2010; Hosmer & Lemeshow, 1999; Kleinbaum & Klein, 2012; Schoenfeld, 1982; Singer & Willett, 2003).
I. Preliminary Analyses

   i. Selection of Control Variables for Aims 1-5

      a. Subjective and Objective Physical Health

      Classes of variables were identified conceptually (i.e., sociodemographic characteristics at baseline, disease/treatment variables, and participation in the intervention arm of the RCT) and then empirical selection was used. Correlational analyses are presented in Table 3. Sociodemographic variables and whether or not a participant received the intervention were not significantly correlated with either the subjective or objective physical health composite variables at 12 months \((p > 0.05)\). Characteristics of the recurrence diagnosis were not significantly correlated with the subjective physical health composite variable. However, extent of recurrent disease \((r=0.275, p=0.015)\) and receipt of surgery at recurrence \((r=-0.241, p=.032)\) were significantly correlated with the objective physical health composite variable. Bivariate correlations between potential covariates were conducted to aid in the selection of covariates for the final models and to reduce the potential for multicollinearity. For models examining objective physical health, extent of recurrent disease was significantly correlated with receipt of surgery \((r=-0.559, p<0.001)\). Thus, extent of recurrent disease was selected as a covariate in the models examining objective physical health as an outcome.
b. Psychological Distress Composite

Neither the sociodemographic variables nor characteristics of recurrence (e.g., extent of recurrent disease, receipt of treatment) considered as covariates were significantly correlated with the psychological distress composite at four months (see Table 4). Additionally, whether or not a participant received the intervention was not significantly associated with the psychological distress composite. Thus, additional covariates were not included in the models examining psychological distress as an outcome.

c. Biological Variables

Correlational analyses showed sociodemographic variables, the extent of recurrent disease, and treatments received at recurrence to be significantly correlated with the neuroendocrine and immune variables at 4 months (see Table 4). Correlated variables were included in the respective endpoint analyses. First, the extent of recurrent disease was significantly correlated with levels of plasma cortisol ($r=-0.351$, $p=0.006$). Second, only age at recurrence diagnosis was significantly correlated with norepinephrine ($r=0.312$, $p=0.016$). Third, receipt of surgery ($r=0.263$, $p=0.048$) and receipt of radiation ($r=-0.282$, $p=0.033$) following the diagnosis of recurrence were significantly correlated with blastogenic response to PHA. Receipt of surgery was not significantly correlated with receipt of radiation ($r=0.078$, $p=0.446$), so both variables were included as control variables in PHA models. Finally, whether or not patients received radiation at recurrence ($r=0.270$, $p=0.044$) was significantly correlated with NKCC and was included as a covariate in the NKCC outcome models.

ii. Selection of auxiliary variables

Auxiliary variables were included in the prediction model to impute missing variables to assist with reducing estimation bias, improving the accuracy of the imputations, and restoring
power lost from having missing data (Alison, 2009; Enders, 2010; Graham, 2009). First, variables were included as auxiliary variables if they were correlates of missingness or correlates of an incomplete variable (Enders, 2010). T-tests revealed that those missing values for the subjective physical health composite variable at 12 months were working more hours per week ($M=16.1$ hours vs. $M=11.1$ hours; $t=1.276$, $p=0.04$) and had a shorter disease-free interval ($M=39.5$ months vs. $M=63.8$ months; $t=-2.230$, $p=0.03$) than those with values. Those with missing values on the distress composite variable at 4 months were more likely to work fewer hours per week ($M=6.5$ hours vs. $M=13.8$ hours; $t=-1.600$, $p<0.01$) and have more positive nodes at the initial diagnosis ($M=5.5$ vs. $M=3.2$ hours; $t=1.228$, $p=0.01$). Chi-squares revealed that those missing data for the psychological distress composite at 4 months were also more likely to have received the intervention than those with complete data ($44.4\%$ vs. $16\%$; $\chi^2=7.195$, $p<0.01$).

As described previously, a portion of data was missing by study design. Blood data collection ended in May 2006; thus, participants assessed after this time period were not eligible for a blood draw and do not have data for the biological variables of interest. Data missing by study design are missing completely at random (Alison, 2009). For the remainder of missing values (i.e. samples were to be drawn but data are missing, e.g., blood draw difficulties), T-tests and chi-square analyses as appropriate were examined.

Under these conditions, first, patients with missing values for cortisol had a higher family income ($M=$86.1K vs. $M=$66.4K; $t=1.229$, $p=0.01$) and were more likely to have received the intervention ($39.1\%$ vs. $15.8\%$; $\chi^2=5.756$, $p=0.02$) than those with complete data. Second, patients missing values for norepinephrine had a higher family income ($M=$88.8K vs. $M=$65.5K; $t=1.459$, $p=0.015$), were working less on average ($M=7.4$ hours vs. $M=14.2$ hours; $t=-1.695$, $p<0.01$), were more likely to have distant metastases as opposed to loco/regional disease ($83.3\%$ vs. $58.9\%$;
and have received the intervention (37.5% vs. 16.0%; \( \chi^2 = 5.029, p = 0.03 \)) than those with complete data. Third, patients with missing data for PHA were significantly more likely to have a higher family income (82.2% vs. 67.3%; \( t = -1.018, p = 0.01 \)) and a shorter disease free interval (\( M = 48.5 \) months vs. \( M = 60.1 \) months; \( t = -1.277, p = 0.05 \)) than patients with complete data. Finally, patients missing values for NKCC had a shorter disease free interval (\( M = 46.6 \) months vs. \( M = 61.0 \) months; \( t = -1.277, p = 0.05 \)) and were more likely to have distant metastases (84.6% vs. 57.7%; \( \chi^2 = 6.035, p = 0.01 \)) compared to patients with complete data. Thus, overall, hours worked per week, family income, number of positive nodes at initial diagnosis, disease-free interval, extent of recurrent disease, and participation in the intervention were included as auxiliary variables in the imputation.

Variables significantly correlated with variables of interest (e.g., mediators, objective physical health composite, subjective physical health composite) that were not selected as covariates due to the potential for multicollinearity or for conceptual reasons were included in the imputation model as auxiliary variables. For example, while receipt of surgery at recurrence was significantly correlated with the objective physical composite variable, it was not included as a covariate due to its close relationship with extent of recurrent disease (\( r = -0.559, p < 0.001 \)); however, it was selected as an auxiliary variable. Additionally, whether or not an individual lived with a romantic partner at the time of recurrence was significantly and highly correlated with both social support measures (SNI: \( r = 0.692, p < 0.001 \); PSS-FA: \( r = 0.256, p = 0.012 \)); thus, it was included as an auxiliary variable to assist with increasing the accuracy of the imputed values for the support variables. Further, baseline values of mediator variables and the baseline and 4 month values of the subjective and objective physical health composites were included as auxiliary variables in the imputation model.
II. Multiple Imputation

As suggested by Enders (2010) and others (UCLA Statistical Consulting Group), the pattern of missing data was explored for the data set including the variables of interest (e.g., social support, biological variables, objective and subjective physical health composite variables, and the psychological distress composite variable), covariates, and auxiliary variables. Examination of the pattern of missing values revealed an arbitrary missing data pattern. Data sets are said to have an arbitrary missing data pattern if missing data occurs in a random fashion for any participant (Dong & Peng, 2013). Thus, a multivariate normal approach via the Markov Chain Monte Carlo (MCMC; Schafer, 1997) method was used to create the 75 imputed data sets using SAS PROC MI. The PROC MI ANALYZE procedure was then used to analyze each of the 75 imputed data sets separately and pool the information into a single result to examine aims 1-3. The MCMC method was also used to create 75 imputed data sets prior to the bootstrap mediation procedure for Aims 4 and 5.

III. Results: Aims 1-5

i. Aim 1: Social support predicting physical health at 12 months

Using a total sample size of 99 participants alive at the 12-month assessment (see Figure 2), hierarchical multiple linear regressions examined whether both structural (SNI) and functional support (PSS-FA) significantly predicted participants’ subjective and nurses’ objective ratings of physical health at the 12 month follow-up based on the two composite measures. The relationship between structural support and subjective physical health at 12 months approached significance ($\beta= -0.052, p=0.082$; see Table 5). Specifically, lower levels of structural support around the time of recurrence were associated with subjective reports of worse health one year later. The model examining structural support accounted for an average of 4.1% of the variance in subjective health
across the 75 imputed data sets (range: 0.8% to 9.9%). Although the pooled result was not significant ($\beta = -0.018$; $p=0.386$), the relationship between functional support and subjective health was in the expected direction, with greater perceived support from family members being associated with better subjective ratings of physical health.

After controlling for baseline levels of subjective health, neither structural nor functional support was significantly associated with subjective health at 12 months ($ps= 0.299$ and $0.829$ respectively; see Table 6). However, baseline subjective health was consistently and positively associated with subjective health at 12 months ($ps<0.01$) suggesting that participants reporting worse health at study entry continued to report worse health at the 12-month follow-up.

Neither structural nor functional support at baseline significantly predicted nurses’ objective ratings of participants’ physical health ($ps=0.246$ and $0.437$, respectively; see Table 7) after controlling for extent of recurrent disease (i.e., loco-regional vs. distant metastases). However, individuals with distant metastases experienced worse health at 12 months ($ps<0.01$). When baseline levels of objective health were included in the models, social support remained a non-significant covariate ($ps >0.555$; see Table 8). However, participants’ baseline objective health was consistently and positively associated with objective health at 12 months ($ps<0.01$) suggesting that participants for whom nurses rated worse health at baseline continued to experience worse health at the 12 month follow-up. Extent of recurrent disease at baseline continued to predict participants’ objective ratings of physical health at 12 months ($ps<0.05$; see Table 8).

ii. **Aim 2: Social support predicting psychological distress at 4 months**

Hierarchical multiple linear regressions examined whether both structural (SNI) and functional support (PSS-FA) significantly predicted participants’ psychological distress at 4-months based on the composite measure of distress. Both structural (SNI: $\beta = -0.099$; $p<0.001$) and
functional (PSS-FA: $\beta = -0.047; p=0.027$) support at baseline were associated with psychological distress at 4 months (see Table 9). Participants who were more integrated within their support networks and those who perceived greater support from their family members following recurrence experienced less psychological distress at 4 months than women reporting less support. The model examining structural support accounted for an average of 12.6% of the variance in psychological distress across the 75 imputed data sets (range: 7.4% to 19.2%) while the model examining functional support accounted for an average of 5.8% of the variance in psychological distress (range: 1.8% to 10.2%).

Structural support, but not functional support ($\beta = -0.025; p=0.147$), remained a significant predictor of psychological distress at 4 months after controlling for baseline levels of distress ($\beta = -0.060; p=0.012$; see Table 10). This suggests that not only were higher levels of structural support at baseline associated with lower levels of psychological distress at 4 months, but structural support was significantly associated with change in psychological distress over the 4 month follow up.

iii. **Aim 3: Social support predicting biological variables at 4 months**

Table 11 presents the results of hierarchical multiple linear regressions examining whether structural and functional support following recurrence predicted plasma cortisol and norepinephrine, blastogenic response to PHA, and NKCC at 4 months. Significant relationships were not found ($ps>0.302$). For the present sample, social support following recurrence was not associated with biological variables at 4 months. Further, social support at baseline was not significantly associated with change in biological variables from baseline to 4 months (see Table 12; $ps>0.150$).
iv. Mediation Analyses

a. Aim 4: Psychological distress as a mediator of the relationship between social support and physical health

Multiple imputation followed by bootstrapped mediation was used to examine whether psychological distress at 4 months was a mediator between social support following recurrence and physical health at 12 months. If the bias corrected confidence interval obtained for each path does not contain zero, than we can conclude that the effect significantly differs from zero. Results are presented in Figure 3 (a through d) and Table 13.

Figures 3a and 3b examine distress as a mediator between structural support and physical health. A significant negative relationship was found between structural support and psychological distress, with individuals reporting greater structural support following recurrence experiencing less distress at 4 months (see Table 13). Further, there was a significant positive relationship between distress at 4 months and both subjective physical health (Point Estimate: 0.524; Bias Corrected CI: 0.327 to 0.730) and objective physical health (Point Estimate: 0.504, Bias Corrected CI: 0.319 to 0.696) at 12 months. Participants reporting greater psychological distress at 4 months had worse physical health at 12-months based on both their own subjective reports and objective nurse reports. As demonstrated by the bias corrected confidence intervals, there was a significant indirect effect of distress at 4 months on the relationship between structural support following recurrence and both subjective (Point Estimate: -0.052, Bias Corrected CI: -0.098 to -0.019) and objective (Point Estimate: -0.051, Bias Corrected CI: -0.094 to -0.019) at 12 months; for the present sample, distress mediates the relationship between structural support and health. There was no evidence that structural support influenced subjective (Point Estimate: 0.005, Bias Corrected CI: -0.049 to
0.056) or objective (Point Estimate: 0.018, Bias Corrected CI: -0.031 to 0.073) physical health independent of its effect on psychological distress.

Distress is presented as a mediator between functional support and physical health in Figures 3c and 3d. As with structural support, functional support following recurrence was significantly and negatively associated with distress at 4 months for both models (see Table 13). Women with greater perceived support from family reported less psychological distress at 4 months than those with less support. Further, distress at 4 month was significantly and positively associated with both subjective (Point Estimate: 0.512, Bias Corrected CI: 0.340 to 0.749) and objective (Point Estimate: 0.489, Bias Corrected CI: 0.303 to 0.677) ratings of health at 12 months. Thus, women reporting more distress at 4 months had worse health at 12 month based on both self and nurse reports of health. Perceived support from family indirectly influenced physical health at 12 months through its effect on psychological distress at 4 months; the bias corrected confidence intervals for both subjective (Point Estimate: -0.023, Bias Corrected CI: -0.053 to -0.003) and objective (Point Estimate: -0.022, Bias Corrected CI: -0.048 to -0.002) physical health at 12 months were entirely below zero. There was no evidence that perceived support from family influenced either subjective (Point Estimate: 0.004, Bias Corrected CI: -0.033 to 0.040) or objective (Point Estimate: 0.007, Bias Corrected CI: -0.029 to 0.045) reports of women's physical health at 12 months independent of its effect on psychological distress at 4 months.

Baseline levels of psychological distress and the subjective or objective physical health composite were included as covariates as appropriate in each model (see Figure 4a through d and Table 14). For models examining the effect of structural support (see Figures 4a and 4b), there were significant negative relationships between structural support and psychological distress and significant positive relationships between psychological distress and both measures of physical
health as demonstrated by the bias corrected confidence intervals (see Table 14). Individuals reporting greater structural support following recurrence reported less distress at 4 months, and individuals reporting greater psychological distress at 4 months experienced worse physical health at 12 months based on both objective and subjective ratings of health. Structural support following recurrence indirectly influenced subjective (Point estimate: -0.024; Bias Corrected Confidence interval: -0.065 to -0.004; see Figure 4a) and objective (Point estimate: -0.022; Bias Corrected Confidence interval: -0.061 to -0.002; see Figure 4b) physical health at 12 months through its effect on psychological distress at 4 months. Consistent with the previous models, there was no direct effect of structural support following recurrence on either subjective or objective reports of women's physical health at 12 months. Thus, structural support following recurrence did not influence physical health at 12 months outside of its effect on psychological distress at 4 months.

After controlling for baseline levels of psychological distress and subjective or objective physical health (see Table 14 and Figures 4c and 4d), functional support no longer predicted psychological distress at 4 months. However, psychological distress at 4 months continued to predict both objective and subjective physical health; individuals reporting greater levels of distress at 4 months experienced worse self-reported and nurse-rated physical health at 12 months. There was no evidence of an indirect effect of functional support on subjective (Point estimate: -0.009; Bias Corrected Confidence interval: -0.030 to 0.003) or objective (Point estimate: -0.008; Bias Corrected Confidence interval: -0.027, 0.002) physical health through psychological distress. Additionally, there was no direct effect of functional support on either subjective or objective physical health measures.
b. **Aim 5: Biological variables as mediators of the relationship between social support and physical health**

Multiple imputation followed by bootstrapped mediation was used to examine whether biological variables—plasma cortisol and norepinephrine, PHA, and NKCC—at 4 months were mediators between social support following recurrence and physical health at 12 months. Results are presented in Figures 5-8 (a through d) and Tables 15-18.

Similar effects were found for all biological variables. Consistent with what was found for the models examining distress as a mediator, there was no direct effect of structural support or functional support following recurrence on either subjective or objective reports of women’s physical health at 12 months as demonstrated by the bias corrected confidence intervals (see Tables 15-18); all bias corrected confidence intervals included zero. Social support following recurrence was not associated with the neuroendocrine or immune variables at 4 months, and there was not a significant relationship between neuroendocrine or immune variables at 4 months and either subjective or objective reports of physical health at 12 months (see Tables 15-18).

Finally, the indirect effects of the neuroendocrine and immune variables on the relationship between structural or functional support following recurrence and subjective or objective physical health at 12 months were not significant. Similar results were found after controlling for baseline levels of the neuroendocrine and immune mediators of interest and subjective or objective physical health for all models (see Tables 19-22 and Figures 9-12). Thus, based on the bias corrected confidence intervals, biological variables at 4 months do not serve as mediators for this sample.

IV. **Results: Aim 6, Survival Analysis**

For the present study, follow up of participant mortality continued until March 3, 2014. The median length of follow-up was 33.6 months from the time of recurrence diagnosis. Of the original
122 participants, 96 participants died of any cause by the end of follow-up. Specifically, 53 died from breast cancer, 6 died from other illnesses, and 37 women died from unknown causes.

i. Univariate Analyses of Survival

Univariate estimates of survival were obtained using the Kaplan-Meier Method (Hosmer & Lemeshow, 1999; Singer & Willett, 2003) to test the null hypothesis that the groups being compared (high vs. low support) have the same survivor function. Curves of high vs. low support based on a median split for each social support variable were compared using the log-rank test.

The number of deaths was similar among those with high versus low levels of structural support (n=49, 83% vs. n=45, 78%, respectively; $\chi^2=0.553, df=1, p=0.457$). Using the Kaplan Meier method, there was no significant difference in survival between groups (see Figure 13; log-rank test: $\chi^2=0.749, df=1, p=0.387$). Thus, we fail to reject the null hypothesis that there is no difference in survival between the two groups. The median time to death among those with high levels of structural support was 33 months ($SD=3.4$ months, 95% CI: 26.0 to 39.3 months) and 37 months ($SD=6.9$ months, 95% CI: 23.3 to 50.5 months) for those with low levels of structural support.

When comparing those with high levels of functional support to those with low levels of functional support, significantly more individuals with high (n=58, 86.6%) levels of functional support died over the course of the follow up than those with low (n=37, 71.2%) levels of support ($\chi^2=4.32, df=1, p=0.038$). Those with higher levels of functional support following recurrence had a significantly shorter time to event than those with lower levels of functional support (see Figure 14; log-rank test: $\chi^2=5.035, df=1, p=0.025$). Unexpectedly, the median time to death among those with high levels of functional support was 29 months ($SD=4.2$ months, 95%, CI: 20.6 to 36.9 months).
and 40 months (SD=8.4 months, 95%, CI: 23.6 to 56.5 months) for those with low levels of functional support.

ii. Selection of Covariates

Bivariate correlations between potential covariates of interest were examined. If covariates were significantly correlated with each other (e.g., r>0.4), only one was considered for inclusion in the final models. The correlations revealed years of education to be significantly and positively correlated with family income (r=0.412, p<.001). Further, extent of recurrent disease was negatively associated with receipt of surgery (r=-0.481, p<.001) such that individuals who did not receive surgery were more likely to have distant metastases. Extent of recurrent disease and years of education were chosen due to their relationship with survival among women with metastatic breast cancer or recurrence (Goldhirsch, Gelber, & Castiglione, 1988; Sprague et al., 2011). Backwards elimination was used to assist with final covariate selection.

iii. Multivariate analyses

Cox proportional hazards analyses were used to conduct multivariate analyses. Departures from the proportional hazards assumption were determined by examining the correlation between Schoenfeld residuals and rank time. Extent of recurrent disease and receipt of hormonal treatment remained as covariates in the model comparing those with high levels of structural support to those with low levels of structural support. The model derived from including the two covariates did not produce evidence of poor fit. When compared to the null model (all covariates equal to zero), the final model represented a significant improvement in model fit ($\chi^2=27.213$, df=3, p<.001). Multivariate analyses confirmed that there was no significant difference in the hazard of death for those with high compared to low levels of structural support. The Wald test statistic is not significant; thus, we cannot conclude that there is a difference between the two
groups in terms of survival (Wald test statistic=0.883, \(HR=0.821\), \(p=0.347\); see Table 23). While there is not a significant difference between groups, the cumulative survival curves (see Figure 15) and hazard ratio suggest that those with less structural support had decreased hazard of all-cause mortality. None of the Schoenfeld residuals were significantly correlated with rank time (all \(ps>0.05\); see Table 24). Thus, it is likely that the proportional hazards assumption is met for all variables included in the model.

Extent of recurrent disease and receipt of hormonal treatment remained in the final model comparing those with high versus low levels of functional support after using backwards elimination to remove covariates with \(p\)-values of 0.1 or less from a series of Cox Proportional Hazards models. The final model produced no evidence of poor fit and represented a significant improvement in model fit \(\chi^2=26.250\), \(df=3\), \(p<.001\) when compared to the null model (all parameter estimates are equal to zero). The hazard of death did not differ significantly for those reporting high versus low levels of functional support following recurrence (Wald test statistic= 1.225, \(HR=0.788\), \(p=0.268\); see Table 25). The hazard ratio for functional support (low vs. high levels of functional support) indicates that those with low levels of functional support following recurrence had 0.788 times the hazard of death of individuals with high levels of functional support following recurrence (21% lower); however the hazard ratio is not significant and the cumulative survival curves are similar for both groups (see Figure 16). After controlling for other covariates in the model, the risk associated with death does not appear to differ based on whether women had high versus low levels of functional support following recurrence. Bivariate correlations comparing Schoenfeld residuals to the rank of survival times for individuals experiencing the event of death were examined and suggest that the proportionality assumption hold for each variable included in the model (see Table 26).
CHAPTER 4
DISCUSSION

The present longitudinal study examined the association between social support (i.e., structural and functional support) and self-reported, subjective and nurse-rated, objective measures of physical health in a sample of women with recurrent breast cancer (see Figure 1a). It was hypothesized that higher levels of structural and functional support following recurrence would confer health benefits over time. The mechanisms by which social support influences physical health are largely unknown; however, it was hypothesized that psychological and biological variables may influence this process (Cohen, Teresi, & Holmes, 1985; Feeney & Collins, 2014; B. N. Uchino, et al., 2012; B. N. Uchino, et al., 2012).

Briefly, regression analyses found social support following the diagnosis of recurrence to predict psychological distress at 4 months; however, social support was not associated with either measure of physical health at 12 months or neuroendocrine or immune variables at 4 months. Multiple imputation followed by bootstrap mediation revealed both structural and functional support to indirectly influence both self-reported, subjective and nurse-rated, objective measures of physical health through the effect of social support on psychological distress. Participants with higher levels of social support at baseline had lower levels of psychological distress at 4 months, and those with lower levels of psychological distress at 4 months experienced better self-reported
and nurse-rated health at 12 months. However, the process by which social support influenced health was not significantly influenced by either the neuroendocrine or immune variables tested in the present study. Finally, in the multivariate analyses, the hazard of all-cause mortality did not significantly differ between those reporting high versus low levels of structural or functional support.

I. **Social support and psychological distress**

As hypothesized, social support following recurrence was associated with psychological distress at 4 months. The results held after controlling for baseline levels of psychological distress suggesting that greater support following recurrence accounted for favorable changes in distress at 4 months. Psychological distress is common among women with recurrent breast cancer (Andersen, et al., 2005; Mahon & Casperson, 1995; Northouse, et al., 2002; Weisman & Worden, 1986). In fact, studies suggest that distress develops more quickly following recurrence (Weisman & Worden, 1986), and for many, the level of distress experienced following recurrence is greater than the level of distress experienced following the initial diagnosis (Cella, et al., 1990; Mahon & Casperson, 1995). Consistent with prior research (Koopman, et al., 1998; Northouse, et al., 1995; Northouse, et al., 2002; Schulz, et al., 1995), the results of the present study suggest that both structural and functional support may be protective against psychological distress for women with recurrent breast cancer. However, much of what is known about the relationship between social support and psychological distress for individuals with recurrent cancer has come from cross-sectional studies. The present study adds to the literature as the first to examine the relationship between social support and psychological distress over time and suggests that higher levels of support following recurrence can have long-term benefits for the psychological wellbeing of women with recurrent breast cancer.
Individuals with higher levels of psychological distress at four months had worse physical health at 12 months as measured by self-reported, subjective and nurse-assessed, objective ratings of participants’ health. Many have argued for distress to be classified as the sixth vital sign in cancer care (Bultz & Carlson, 2006; Howell & Olsen, 2011); along with temperature, blood pressure, respiration, heart rate, and pain, distress is considered to be an important indicator of cancer patients’ health and wellbeing. Thus, it comes as no surprise that individuals with higher levels of distress would experience worse health. In fact, prior research supports this finding from both the general and cancer-specific literatures: psychological distress is a correlate of perceived health status and objective markers of physical health (Andersen, Shelby, & Golden-Kreutz, 2007; Brown, Levy, Rosberger, & Edgar, 2003; Millar, Purushotham, McLatchie, George, & Murray, 2005; Schmitz, Lesage, & Wang, 2009).

Finally, the results of the present study support the hypothesis that social support exerts an effect on physical health indirectly through psychological distress. While few have studied psychological distress as contributing to the process by which support influences health, the results of the present study are consistent with the limited number of studies examining psychological mediators (Bisconti & Bergeman, 1999; Crittenden, et al., 2014; Shen, et al., 2004; Wicke, et al., 2014) finding social support to indirectly influence physical health through its effect on psychological distress. The present study is the first to examine whether these relationships hold for women with recurrent breast cancer.

Interestingly, after controlling for baseline levels of psychological distress and physical health outcomes, psychological distress remained a significant mediator of the relationships between structural support and both self-reported, subjective and nurse-rated, objective measures of physical health. However, mediation was not found for models examining functional measures of
support after controlling for baseline levels of psychological distress and physical health outcomes. The difference in results may be associated with the different social support constructs assessed in the present study. The Social Network Index (SNI) is a reliable and well-validated measure of network size and integration (Berkman, 1977; Berkman & Breslow, 1983; Berkman & Syme, 1979). When individuals have larger social networks, there may be more individuals available to provide them with social resources, including functional support (Uchino, 2004). Complex measures of social integration like the SNI may tap into more aspects of support than the specific constructs examined by measures of functional support (Uchino, 2004).

Bloom and colleagues (2001) examined the relationship between structural and functional support for women with breast cancer and found that having larger, more integrated social networks provided women with greater access to functional support including emotional and instrumental support (Bloom, Stewart, Johnston, Banks, & Fobair, 2001). A post-hoc regression analysis examined the relationship between structural and functional support in the present study. After controlling for variables significantly correlated with perceived support from family (i.e., whether or not participants received the intervention), the model testing the relationship between structural and functional support was significant \( F(2,92)=25.298, p<0.01 \) and accounted for 34.1% of the variance in functional support. Overall, greater social integration as measured by the SNI was related to greater perceived support from family \( (\beta=0.757, SE=0.117, t=6.462, p<0.01) \). Thus, it is possible that for the current sample, being more integrated in their social networks allowed women better access to support from close others, like family members.

II. Social support and biological variables

In contrast, neither structural nor functional support was significantly associated with the neuroendocrine and immune variables examined in the present study. While post-hoc power
analyses conducted using G* Power (Faul, Erdfelder, Buchner, & Lang, 2009) suggest that the sample size was likely sufficient to detect effects (power ranged from 0.75 to 0.94), social support following recurrence was not associated with neuroendocrine or immune variables after controlling for variables associated with recurrence (e.g., extent of recurrent disease, receipt of surgery, and receipt of radiation). Thus, it appears that social support was not associated with biological variables above and beyond the effect of disease/treatment variables associated with recurrence.

It is possible that the sequelae of advanced disease made it more difficult to detect the effect of social support on neuroendocrine and immune variables in the present study. Patients with advanced cancer have been shown to have alterations in neuroendocrine and immune functioning. For example, the typical circadian patterns of cortisol secretion are altered for women with metastatic breast cancer (Touitou et al., 1995). Women with advanced breast cancer may also have altered immune responses. Research suggests that breast cancer patients exhibit depressed responses to the mitogen PHA with advancing stages of disease (Mandeville, Lamoureux, Legault-Poisson, & Poisson, 1982). Similarly, women with advanced breast cancer have depressed NKCC; in fact, NK cell activity has been shown to be significantly lower for women with advanced breast cancer when compared to health controls (Tsavaris, Kosmas, Vadiaka, Kanelopoulos, & Boulamatsis, 2002) and women with locoregional disease (Konjevic & Spuzic, 1993). It is possible that the relationship between social support and biological variables for women with recurrent breast cancer may not behave as would be expected based on the samples of healthy individuals or other chronic illness populations that have been used to study this relationship in prior research.

The biological variables examined in the present study were not significantly correlated with one another (rs=0.005 to 0.179; ps=0.143 to 0.967) or with the social support variables (ps>0.168; see table 27) at baseline. Some of the non-significant relationships between variables
(e.g., plasma cortisol and norepinephrine, r=0.104, p=0.384) are unexpected (Antoni et al., 2006) and hard to determine. It is possible that this too is a consequence of alterations in immune and neuroendocrine functioning associated with advanced disease.

Ours is not the first to find a non-significant relationship between social support and neuroendocrine and immune variables; the extant literature presents an inconsistent relationship (Segerstrom & Smith, 2012; Uchino, et al., 1996). First, the way in which biological variables are assessed may contribute to the differences in results across studies (Segerstrom & Smith, 2012). For example, cortisol has a consistent diurnal rhythm, peaking soon after waking and decreasing throughout the day (Stone, et al., 2001). Consequently, it may be more difficult to detect a relationship between social support and cortisol during the morning hours (Uchino, et al., 1996). In the present study, blood samples were obtained between 7 and 10am; thus, the timing of the blood draw may have limited our ability to detect effects. Future studies should examine the full range of the diurnal cycle when probing the relationship between social support and cortisol for women with recurrent breast cancer (Uchino, et al., 1996).

Second, momentary arousal, stress, or pain can result in increased activation of the sympathetic nervous system. These momentary changes can create error variance and decrease the reliability of the measurement (Segerstrom & Smith, 2012), which may make it more difficult to detect relationships with social support. Several recommendations have been provided to address these issues. First, procedures that minimize stress, pain, and/or arousal are recommended. For example, single needle sticks can artificially elevate catecholamine levels; thus, if plasma samples are obtained, the use of a catheter with a rest period is preferred over a single needle stick (Uchino, et al., 1996). Second, it is recommended that researchers collect additional, randomly sampled observations of neuroendocrine and immune variables over a short period of time (e.g.,
several days) to minimize error variance and enhance the reliability of the estimates (Segerstrom & Smith, 2012). This may help to ensure that the effects found in studies examining neuroendocrine and immune variables are closer to true findings in the population. In the present study, a single blood draw was obtained at each assessment. Thus, it is possible that the null findings (i.e., lack of relationship with social support) may be an artifact of the methods use.

Third, many social support constructs exist. At present, researchers are still working to understand the ways in which these constructs may differentially affect health. It has been hypothesized that the differences in the types of social support constructs assessed across studies may contribute to the inconsistent relationship between social support and neuroendocrine and immune variables (B.N. Uchino, et al., 2012). The present study examined positive aspects of social support rather than negative aspects of social support. However, threats to social connections in the form of social strain (e.g., greater interpersonal conflict, excessive demands from significant network members, etc.) as well as social disconnection and loneliness may serve as a source of stress leading to chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (Eisenberger & Cole, 2012; Seeman & McEwen, 1996).

For example, Friedman and colleagues (2012) examined the relationship between social strain and cortisol in a community-based sample of more than 1,600 adults. Individuals who had more frequent social strain in relationships with close others (i.e., spouse, family, or close friends) had flatter diurnal cortisol slopes suggesting that these individuals experienced dysregulation of the HPA axis (Friedman, Karlamangla, Almeida, & Seeman, 2012). Similar results have been found for breast cancer patients who perceived a higher level of negative support from network members (Ho, et al., 2013). Social strain, chronic interpersonal stress, and loneliness have also been associated with dysregulation of neuroendocrine and inflammatory systems, including depressed
NK cell response (Steptoe, Owen, Kunz-Ebrecht, & Brydon, 2004) and larger IL-6 responses (Hackett, Hamer, Endrighi, Brydon, & Steptoe, 2012; Miller, Rohleder, & Cole, 2009) in studies of healthy adults. In fact, in one study, the negative relationship between social strain and inflammation was greater than the positive relationship between social support and inflammation (Yang, Schorpp, & Harris, 2014); this relationship was consistent across several measures of inflammation. Thus, the way in which social support was assessed—as a positive characteristic—may have limited the ability of this study to find a significant relationship between social support and neuroendocrine and immune variables.

Finally, while there was a significant indirect effect of psychological distress, neuroendocrine and immune variables did not significantly mediate the relationship between social support and physical health in the present study. Given the complexity of the relationship between social support and health, it is possible that neuroendocrine and immune variables exert their effects at different and multiple points in the process. For example, a recent study of women with early stage breast cancer suggests that inflammation may mediate the relationship between social support and depressive symptoms, such that individuals with low levels of support experienced greater inflammation, and greater inflammation was associated with more depressive symptoms (Hughes, et al., 2014). It has also been theorized that neuroendocrine and immune variables mediate the relationship between psychological distress and physical health variables (Andersen, Kiecolt-Glaser, & Glaser, 1994; Uchino, 2004). In fact, research suggests a direct relationship between psychological distress (e.g., depressive symptoms, mood disturbance) and biological variables including white blood cell counts (Andersen, et al., 1994) and NKCC (Levy, Herberman, Lippman, & d'Angelo, 1987) among individuals with cancer, with individuals with greater psychological distress experiencing impaired immunity. Given the relationship between biological
variables and health (Cerwenka & Lanier, 2001; Sephton, et al., 2000; Sood, et al., 2006; Wiltschke, et al., 1995), it is likely that biological variables may play a role downstream in the path linking social support to health through psychological distress.

III. **Social support and physical health**

The present study failed to confirm the relationship between social support at baseline and physical health at 12 months. This is inconsistent with prior research that has found a strong link between measures of social support and both subjective and objective ratings of health (e.g., Helgeson, 1998; Nausheen et al., 2009; Kroenke et al., 2013, etc.). However, the majority of this research comes from studies of women with an initial diagnosis of cancer. After a thorough search of the literature, only one study had previously examined the relationship between social support and health in women with recurrent breast cancer (Brady & Helgeson, 2000). While a negative relationship was found between emotional support from a partner and informational support from the physician and physical health in both cross-sectional and longitudinal analyses, it is likely that the relationship between support and health is more complex than a clear and linear path given the qualitative differences between recurrent cancer and most stressors.

In fact, although social support did not directly influence health in the present study, structural and functional support indirectly influenced both the self-reported and nurse-rated physical health composites variables through their effects on psychological distress. The presence of a significant indirect effect in the absence of a significant relationship between the independent and dependent variables (see Figure 1; path c) often occurs when the direct effect (path c’) and the mediated effect (ab) have opposite signs, as was found in the present study (see Tables 13 and 14; MacKinnon, 2008; MacKinnon, et al., 2000; MacKinnon et al., 2007). Termed inconsistent mediation, the relationship between the independent variable and dependent variable may in fact
become stronger after adjusting for the mediating variable. Thus, in the present study, adjusting for psychological distress strengthened the relationship between social support following recurrence and the physical health composite variables at 12 months.

IV. Social support and mortality

Neither structural nor functional support assessed following recurrence was significantly associated with the hazard of all-cause mortality in multivariate analyses. While multiple population-based studies have found individuals with higher levels of social support to be at decreased risk for mortality, many of these studies have been conducted with large random samples (e.g., >6,000 participants) of adults (Barger, 2013; Berkman & Syme, 1979; Orth-Gomer & Johnson, 1987). With the present sample size of 122, it is possible that the sample size limited the ability to detect an effect. MedCalc for Windows was used to determine the sample size necessary to achieve significance with the observed effects for the survival analyses (MedCalc Software, 2014). Post-hoc power analyses suggest that sample sizes of 1,587 and 1,634 for analyses examining individuals low vs. high on the SNI and PSS-FA, respectively, would have been required (power $1-\beta=0.8$, $\alpha=0.05$). The sample sizes necessary are significantly larger and more on point with previous research finding significant survival benefits for individuals with high vs. low levels of support.

Further, the majority of studies examining the relationship between social support and mortality in the context of cancer have been conducted with women with early stage breast cancer. These studies have consistently found social support to be related to decreased hazard of mortality (Hislop, et al., 1987; Kroenke, Quesenberry, et al., 2013; Maunsell, Brisson, & Deschenes, 1995). However, the present study examined survival among women with recurrent breast cancer, a condition associated with high symptom burden and poor prognosis. A recent systematic review
examined the relationship between social support and disease progression among cancer patients (Nausheen, et al., 2009). After reviewing the literature, the authors suggest that survival is less affected by social factors for individuals with poor prognosis; instead, disease-related variables may better predict survival. After controlling for extent of recurrent disease in the present analyses, neither structural nor functional support was associated with the hazard of mortality. Instead, extent of recurrent disease was significantly associated with mortality, with individuals with loco/regional disease experiencing a decreased hazard of mortality when compared to those with distant metastases (structural support, $HR=0.302$, $p<0.01$; functional support $HR=0.337$, $p<0.01$). These results are consistent with studies examining the relationship between social support and survival in advanced breast cancer (Butow, Coates, & Dunn, 2000; Ell, et al., 1992).

Unexpectedly, individuals higher in functional support had shorter time to event (i.e., all-cause mortality) than individuals with lower levels of functional support in univariate models. Although the multivariate models were not significant, a similar trend was present with individuals with more structural or functional support following recurrence experiencing an increased hazard of mortality. While these results are counter to much of the extant literature, similar results have been found by others examining the relationship between support and mortality in cancer (Cousson-Gelie, Bruchon-Schweitzer, Dilhuydy, & Jutand, 2007; Lehto, et al., 2006; Villingshoj, Ross, Thomsen, & Johansen, 2006). There are several possible explanations for this finding. First, when individuals are sick, their support needs may increase. According to the support seeking/triage model, individuals with greater disease burden or more physical symptoms should receive and/or seek more support than individuals with fewer symptoms (Barrera, 1986). In fact, in the present study, post hoc analyses revealed that, when compared to individuals with low levels of perceived support from family members, individuals with high levels of support were more likely to have
distant (62.5% vs. 37.5%; \( \chi^2 = 3.312, p = 0.069 \)) disease at recurrence. Thus, the fact that individuals with high rather than low levels of social support experienced an increased hazard of mortality may result from their greater disease burden.

Finally, if support is provided, it may be inappropriate or not well matched to the needs of the individual with recurrence (Thornton, et al., 2014). In the present study, the measures of social support used assessed participants’ perceptions of the amount of support available to them from family members as well as participants’ interconnectedness within their social network. However, these measures do not assess the quality of support and whether or not individuals were satisfied with the support provided by network members. The quality of support received has been associated with health outcomes such that high quality support and greater satisfaction with support is associated fewer health problems (e.g., chronic conditions) and physical symptoms (Vandervoort, 1999; Yang & Schuler, 2009) as well as decreased risk for mortality (Birditt & Antonucci, 2008; Coyne et al., 2001; Kaplan et al., 1994). Thus, while individuals in the present study with high levels of support trended toward an increased hazard of mortality, it is possible that these individuals had poor quality or inadequate support available to them, which was not captured by the support constructs assessed.

V. **Strengths and Limitations of the Current Study**

The present study has several strengths. First, a focus on the process by which social support is associated with physical health is uncommon (e.g., Cohen & Janicki-Deverts, 2009; Uchino, 2004; Uchino et al., 2012); studies have primarily examined the relationship between social support and psychological and biological variables. However, researchers have acknowledged the importance of and called for studies that directly examine the mechanisms linking social support to health outcomes (Cohen & Janicki-Deverts, 2009; House, et al., 1988;
The present study addresses this gap in the literature and is the first of its kind to examine the process by which social support may be related to physical health outcomes among women with recurrent breast cancer, an understudied population of cancer survivors.

Second, the present study uses a superior analytic strategy than has been used in prior studies examining the mechanisms by which social support influences health. The majority of research examining mechanisms uses the causal steps approach to mediation (Baron & Kenny, 1986). In fact, the causal steps approach is the most commonly used method for testing mediation (MacKinnon, Fairchild, & Fritz, 2007); the 1986 description of the causal steps approach has been cited close to 50,000 times since its publication. While the causal steps approach is commonly used, the approach is quite conservative and requires each of four main criteria be satisfied, including the presence of a significant relationship between the independent and dependent variable. The present study failed to find an association between the independent and dependent variables; neither structural nor functional support was associated with either of the two physical health composite variables. Based on the causal steps approach, testing whether psychological distress mediated the relationship between social support and health would not be appropriate because it could be argued there was not an effect to be mediated (Baron & Kenny, 1986; Hayes, 2013; MacKinnon, 2008).

According to Hayes and other prominent mediation experts, the requirement that there be a significant relationship between the independent and dependent variables to probe for mediation is misguided (e.g., Hayes, 2013; MacKinnon, 2008). Instead of using the causal steps approach, testing for mediation using bootstrapping (Hayes, 2009; Preacher & Hayes, 2004) has been recommended (B. N. Uchino, et al., 2012), which loosens the requirements for mediation. As was
found in the present study, mediation can be present in the absence of a significant relationship between the independent and dependent variables (i.e., inconsistent mediation). Had only the causal steps approach been used, the important relationship between social support, psychological distress, and health that was found in the present study might have otherwise been missed.

Finally, the present study uses longitudinal data to examine whether psychological distress, neuroendocrine variables, and immune variables mediate the relationship between social support and health. Longitudinal data is necessary to document temporal precedence: that the independent variable precedes the mediating variable in time and that the mediating variable precedes the dependent variable in time (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001; MacKinnon, et al., 2007). By documenting temporal precedence, one minimizes the potential for reverse causality and establishes an argument against competing orders (Hayes, 2013; MacKinnon, 2008); this increases the probability that the independent variable affects the mediating variable and the mediating variable affects the dependent variable. Cross sectional analyses assume that the effects examined are occurring simultaneously, which is not likely to be the case. The relationships probed during mediation analyses likely take time to unfold such that time must pass for one variable to affect another (Cole & Maxwell, 2003; Gollob & Reichardt, 1991). Thus, longitudinal data may be necessary to see hypothesized effects.

The current study has limitations. The primary one is the sample size: data for the mediation analyses came from 99 women with recurrent breast cancer. While the sample size is larger than most studies of recurrence (e.g., Sarenmalm et al., 2009; Okamura et al., 2005; Cohen, 2002; Bull et al., 1999; Brady & Helgeson, 2000, etc.), a sample size of 99 may not be sufficient to detect the mediation effects examined in the present study. A simulation study by Fritz and MacKinnon (2007) was used to determine whether the sample size available in the present study
would produce adequate power when using the bias corrected bootstrap procedure to test for the presence of mediation. For each simulation, the values of the a, b, and c’ paths (see Figures 1b and 1c) were varied to correspond with criteria for small, small/medium, medium, and large effect sizes (see Figure 17). When compared to the standardized point estimates obtained for the present study, a sample size of more than 368 participants would be necessary to reproduce the observed effects with a power of 0.8 for models examining neuroendocrine and immune variables (see Table 28). Thus, a much larger sample size than was available for the present study would be needed to determine whether these effects were significant.

However, the sample size necessary to reproduce the effects for models examining psychological distress ranged from approximately 53 for models examining structural support to 118 for models examining functional support when models did not include baseline control variables (see Table 28). This is smaller than or only slightly larger than the sample size of 99 available for the aforementioned analyses. After controlling for baseline levels of the mediator and dependent variables, the required sample size to detect effects was approximately 115 for models examining structural support and more than 385 for models examining functional support. This may help to explain why functional support was not found to influence physical health through its effect on psychological distress after controlling for baseline levels of the mediator and dependent variables.

Further, as described above, post-hoc power analyses were conducted in MedCalc (2014) to determine the sample size that would have been required to achieve significance with the observed effects for the survival analyses examining whether high vs. low levels of social support conferred a reduced hazard of all-cause mortality. For the present study, survival analyses were conducted with 122 participants; however, more than 1,500 participants would have been
necessary to achieve significance with the observed effects with a power of 0.8. Thus, the sample size available was not sufficient to detect the desired effects.

Finally, the sample accrued for the present study is homogeneous with respect to race/ethnicity (92% Caucasian), socioeconomic status (mean family income >$68K), and educational attainment (mean >14 years). Thus, the results may not generalize to males, other disease sites, or individuals with fewer socioeconomic resources. However, for the purposes of this study—the first of its kind to examine the process by which social support influences health for women with recurrent breast cancer—the similarity among participants is a strength; by accruing a homogenous sample, we have reduced the within sample variance to maximize the likelihood of finding effects.

VI. Future Directions, Clinical Implications, and Conclusions

Despite the growing interest in understanding the processes by which social support is related to health, much is yet to be learned. The present study provides an important first step by examining hypothesized processes in a sample of women with recurrent breast cancer. While psychological distress was found to mediate the relationship between both structural and functional support and both participants’ subjective and nurses’ objective ratings of participants’ health, it is plausible that other mechanisms may be contributing to this relationship.

An important line of research will likely involve examining proinflammatory cytokines as mediators of the relationship between social support and health. Proinflammatory cytokines [e.g., IL-6, TNF-alpha] assist in the development and proliferation of immune cells and promote inflammatory processes (Jain, Bower, & Irwin, 2012). Inflammation is critical to the body’s ability to respond to infection or injury and assist with recovery (Christian, Deichert, Gouin, Graham, & Kiecolt-Glaser, 2009). In the context of recurrent cancer, proinflammatory cytokines may be an
appropriate target for influencing the process by which social support is related to important health outcomes due to the relationship between proinflammatory cytokines and disease progression. For example, IL-6 has been associated with proliferation of tumor cells (Chopra, Dinh, & Hannigan, 1998), cancer progression (Zhang & Adachi, 1999), and shorter cancer-specific survival (Salgado et al., 2003). Further, TNF-α can activate the immune system to kill tumor cells directly; thus, it has been linked to increased survival time for cancer patients as well as tumor regression (Lejeune et al., 1994; Nakamoto, Inagawa, Takagi, & Soma, 2000).

Social support and inflammation are negatively associated for cancer patients. Studies examining the relationship between social support and inflammation among women with newly diagnosed and advanced cancers (i.e., breast and gynecologic cancers) found that women reporting lower levels of functional support had higher levels of IL-6 over time than those who felt more supported (Costanzo et al., 2005; Hughes, et al., 2014; Lutgendorf, Anderson, Sorosky, Buller, & Lubaroff, 2000). Further, stronger stimulated TNF-α responses have been found for newly diagnosed breast cancer patients who increase their leisure, home, and social activities with friends and family in the year following diagnosis when compared to breast cancer patients who decreased their social involvement during this same time period (Marucha, Crespin, Shelby, & Andersen, 2005). Increased satisfaction with one’s partner was also associated with stronger stimulated TNF-α response. Thus, higher levels of support after the diagnosis of cancer may have a protective effect via the effect of support on inflammation.

Further, while mediation analyses posit causality among variables included in the analyses especially in the presence of temporal precedence, causality cannot be inferred when using nonexperimental data (Kraemer, et al., 2001). To be able to infer causality, a series of experiments are necessary to test whether manipulating the independent variable affects the mediator and
whether manipulating the mediator affects the dependent variable (Spencer, Zanna, & Fong, 2005). These experiments would not have been feasible in the present study. The results suggest that the relationships between social support, psychological distress, and the subjective and objective physical health composite variables are consistent with what we would expect if social support was causally associated with psychological distress and psychological distress was causally associated with physical health. The results of the present study can instead be used to inform experimental work. For example, experimental research can examine whether randomly assigning participants with low levels of support following recurrence to an intervention designed to enhance support improves psychological distress over time and whether improvements in psychological distress associated with the intervention are further associated with physical health at a later time point.

The field will also benefit from additional prospective, longitudinal studies that examine social support in the context of recurrence. Despite their expense, prospective, longitudinal studies allow researchers to better examine the process by which variables influence one another (MacKinnon, 2008). This study design provides more information regarding the temporal precedence of the independent, mediating, and dependent variables and allows for repeated measurement of variables of interest (Hayes, 2013; Kraemer, et al., 2001; MacKinnon, 2008).

Future prospective longitudinal studies should be mindful of the timing of social support assessments. Additional research is necessary to understand whether the amount of support available to women with recurrent breast cancer at different points during the recurrence experience may have a differential impact on psychological distress, neuroendocrine and immune variables, and physical health. For example, it is likely that individuals with lower levels of support following recurrence had lower levels of support prior to recurrence. These individuals may be at
higher risk for poor outcomes. Prospective studies of women with breast cancer have found that, when compared to those who were more socially integrated, those who were socially isolated prior to their cancer diagnosis experienced lower vitality and impairments in physical functioning (Michael, et al., 2002) as well as greater risk of breast cancer-specific and all-cause mortality (Kroenke, et al., 2006). In another study, women who were more socially isolated prior to having a mammogram were more likely to be diagnosed with breast cancer than women who were more socially connected (Fox, Harper, Hyner, & Lyle, 1994). Thus, assessments of support prior to the diagnosis of recurrence may provide important information about the health of patients over time.

Further, literature examining social support in the context of cancer has found a direct relationship between measures of support assessed prior to initiating treatment and psychological, biological, and health outcomes for both newly diagnosed and advanced cancer patients. Specifically, lower levels of support prior to treatment have been linked to increased pain, more depressive symptoms, elevated levels of IL-6, and more advanced disease over time when compared to individuals with more support (Costanzo, et al., 2005; Hughes, et al., 2014; Lutgendorf, et al., 2000). However, less is known about whether social support assessed prior to initiating treatment may have the same effect for women with recurrent breast cancer, though the aforementioned research suggests it might. These studies may provide an important starting point for future research continuing to examine the relationship between social support and health for women with recurrent breast cancer as well as the mechanisms contributing to this relationship.

Finally, while the present study examined two distinct social support constructs, as recommended (Uchino, 2004), and their relation to distress, neuroendocrine and immune variables, and health, other social support constructs exist (Barrera, 1986; Uchino, 2004). For example, measures exist separating perceived support into categories, including emotional support
and instrumental support. Other constructs focus on support received and satisfaction/dissatisfaction with available support as well as negative aspects of support. Future research should examine whether other categories/types of social support result in the same effects seen in the present study. By studying other categories/types of support, we may better identify individuals who can benefit most from an intervention as well as determine additional social support targets to include in interventions for women with recurrent breast cancer.

From a clinical perspective, these findings highlight the importance of longitudinal research to examine the process by which social support may influence health. While cross-sectional research can be useful for understanding the hypothesized relationships between variables, it fails to adequately address the time required for processes to occur (Gollob & Reichardt, 1991). The present study found the relationship between social support and self-reported, subjective and nurse-assessed, objective ratings of participants' physical health at 12 months to occur via the effect of social support on psychological distress in the interim. This longitudinal process suggests that to modify both distress and physical health outcomes, it may be beneficial to directly target the social support needs of women with recurrence in the months following recurrence. The present study also helps to elucidate those for whom an intervention might be most beneficial, and it appears that individuals with low levels of social support following recurrence may be appropriate targets. These results highlight the need to identify women with low levels of support at recurrence and provide them with appropriate interventions.

Women with low levels of support following recurrence may benefit from group-based interventions. Among women with recurrent or metastatic breast cancer, group-based interventions like supportive expressive therapy have been associated with reductions in cancer-specific stress and total mood disturbance over time (Classen, et al., 2001). It will be important for therapists
running groups to work to foster a sense of cohesion among group members. Cohesion refers to the bonding, collaborative working alliance of the group and has consistently been associated with improvement among individuals participating in psychotherapy groups (Burlingame, Fuhriman, & Johnson, 2002). While rarely assessed in the context of interventions for cancer patients, one study found that group cohesion covaried with change in psychological and health variables such that those reporting greater personal involvement with and felt support from the group experienced lower distress and better functional performance status over time (Andersen, Shelby, et al., 2007).

Women may benefit from interventions to assist them with better identifying and utilizing the support available to them by network members. For example, an intervention created by Andersen and colleagues (2009) included components to strengthen the support networks of newly diagnosed women with breast cancer. Participants were provided assistance with identifying network members capable of providing support, matching their support needs with the abilities of those in their network, and learning strategies for assertive communication. When compared to the assessment only arm, women participating in the group-based intervention reported significant increases in perceived support from family members over the course of the study (Andersen, et al., 2004). The effects of the intervention persisted over time. Women in the intervention arm whose breast cancer recurred reported higher levels of perceived support at recurrence than those in the assessment only arm who recurred, and these effects remained over the course of the 12-month follow-up (Andersen et al., 2010). Thus, it is likely that women were able to apply the intervention strategies learned following the initial diagnosis of cancer to their recurrence experience.

Interventions that include women’s network members may also be beneficial. For example, Northouse and colleagues (2005) developed a family focused intervention for women with recurrent breast cancer and their familial caregivers. The intervention included multiple
components (e.g., strategies to improve communication and encourage mutual support and teamwork, assistance with sharing fears and concerns with one another, education about the disease and treatments, symptom management techniques) to assist the patient-caregiver dyad with providing mutual support. Patients receiving the intervention reported less hopelessness and had a less negative view of their illness than patients in the control group. Interestingly, caregivers participating in the intervention had a less negative view of the caregiving experience than those in the control group. Given that caregivers may be patients’ primary sources of support, by improving appraisals of the caregiving experience, caregivers may be better able to provide for the patients and satisfy their role as a support figure.

The aforementioned studies suggest that group- and family-based interventions and interventions that specifically target the support needs of women with cancer are associated with improvements in psychological wellbeing. The present study suggests that psychological distress may indirectly influence the effect of support on health in this population. Thus, it is possible that group- and family-based interventions and interventions that specifically target the support needs of women with recurrence may be beneficial for not only reducing psychological distress but improving health as well.

In conclusion, the present study is the first of its kind to examine the mechanisms by which social support may influence health for women with recurrent breast cancer: a population with high disease burden and poor prognosis. The present longitudinal study adds an important contribution to the literature in that it provides information about the process by which social support may influence health. The theory-based analyses apply advanced statistical methods to answer a research question that was previously unanswered and is consistent with the limited extant literature examining the process by which social support influences health. Overall, the results
suggest that both measures of functional and structural support are negatively associated with psychological distress and social support indirectly influences physical health through its effect on psychological distress. Women with breast cancer recurrence are an understudied population; additional research is necessary to understand the support needs of women with recurrence and the effect of support on health. Further research is warranted to replicate these findings and examine other social support constructs and potential mechanisms (e.g., inflammation) that may influence the relationship between social support and health in this population.
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241*(4865), 540-545.

107


Appendix A: Tables
### Table 1.

**Sociodemographic and Disease Characteristics at Baseline (N=122)**

<table>
<thead>
<tr>
<th></th>
<th>Total (N=122)</th>
<th>RCT (n=42)</th>
<th>Long. Study of Recurrent Cancer (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic Variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>55.1 (11.1)</td>
<td>56.4 (11.1)</td>
<td>54.4 (11.2)</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>92%</td>
<td>98%</td>
<td>89%</td>
</tr>
<tr>
<td>Family Income ($K)</td>
<td>68.3 (58.4)</td>
<td>63.0 (50.2)</td>
<td>71.2 (62.6)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.7 (2.9)</td>
<td>14.9 (3.0)</td>
<td>14.6 (2.8)</td>
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<tr>
<td>Employment Status (% employed)</td>
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<td>45%</td>
<td>48%</td>
</tr>
<tr>
<td>Currently living with a romantic partner (% yes)</td>
<td>70%</td>
<td>71%</td>
<td>70%</td>
</tr>
<tr>
<td><strong>Disease-related variables at Initial Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>20%</td>
<td>0%</td>
<td>30%</td>
</tr>
<tr>
<td>II</td>
<td>60%</td>
<td>83%</td>
<td>49%</td>
</tr>
<tr>
<td>III</td>
<td>20%</td>
<td>17%</td>
<td>21%</td>
</tr>
<tr>
<td>ER/PR status (% positive)</td>
<td>63%</td>
<td>61%</td>
<td>63%</td>
</tr>
<tr>
<td>Number of Positive Nodes</td>
<td>4.0 (6.9)</td>
<td>4.4 (8.1)</td>
<td>3.8 (6.3)</td>
</tr>
<tr>
<td><strong>Disease-related variables at recurrence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since initial diagnosis (months)</td>
<td>57.0 (50.6)</td>
<td>52.6 (39.1)</td>
<td>59.3 (55.6)</td>
</tr>
<tr>
<td>Disease free interval (months)</td>
<td>54.9 (50.0)</td>
<td>51.4 (38.7)</td>
<td>56.7 (55.1)</td>
</tr>
<tr>
<td>Time since recurrence (months)</td>
<td>2.6 (1.5)</td>
<td>2.8 (1.7)</td>
<td>2.5 (1.4)</td>
</tr>
<tr>
<td>Extent of recurrent disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local/Regional</td>
<td>32%</td>
<td>25%</td>
<td>35%</td>
</tr>
<tr>
<td>Distant</td>
<td>68%</td>
<td>75%</td>
<td>65%</td>
</tr>
<tr>
<td>Current cancer treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>16%</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>On treatment</td>
<td>84%</td>
<td>83%</td>
<td>85%</td>
</tr>
<tr>
<td>Chemotherapy (% yes)*</td>
<td>48%</td>
<td>34%</td>
<td>55%</td>
</tr>
<tr>
<td>Surgery (% yes)</td>
<td>26%</td>
<td>24%</td>
<td>28%</td>
</tr>
<tr>
<td>Radiation Therapy (% yes)</td>
<td>21%</td>
<td>24%</td>
<td>19%</td>
</tr>
<tr>
<td>Hormonal Therapy (% yes)</td>
<td>29%</td>
<td>39%</td>
<td>24%</td>
</tr>
</tbody>
</table>

**Notes:** * p<.05, + p<.01
Table 2
Sociodemographic and Disease Characteristics at Baseline (N=99)

<table>
<thead>
<tr>
<th>Sociodemographic Variables</th>
<th>Total (N=99)</th>
<th>RCT (n=37)</th>
<th>Long. Study of Recurrent Cancer (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>54.8 (10.7)</td>
<td>56.0 (10.7)</td>
<td>54.1 (10.8)</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>92%</td>
<td>97%</td>
<td>89%</td>
</tr>
<tr>
<td>Family Income ($K)</td>
<td>71.0 (62.9)</td>
<td>67.3 (52.4)</td>
<td>73.3 (68.8)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.8 (3.0)</td>
<td>15.0 (3.2)</td>
<td>14.7 (2.9)</td>
</tr>
<tr>
<td>Employment Status (% employed)</td>
<td>46%</td>
<td>49%</td>
<td>45%</td>
</tr>
<tr>
<td>Currently living with a romantic partner (% yes)</td>
<td>75%</td>
<td>75%</td>
<td>74%</td>
</tr>
</tbody>
</table>

Disease-related variables at Initial Diagnosis

<table>
<thead>
<tr>
<th>Stage*</th>
<th>Total (%)</th>
<th>RCT (%)</th>
<th>Long. Study of Recurrent Cancer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>21%</td>
<td>0%</td>
<td>34%</td>
</tr>
<tr>
<td>II</td>
<td>61%</td>
<td>83%</td>
<td>48%</td>
</tr>
<tr>
<td>III</td>
<td>17%</td>
<td>17%</td>
<td>18%</td>
</tr>
<tr>
<td>ER/PR status (% positive)</td>
<td>69%</td>
<td>67%</td>
<td>70%</td>
</tr>
</tbody>
</table>

| Number of Positive Nodes  | 3.5 (6.6) | 4.7 (8.6) | 2.9 (5.2)                          |

Disease-related variables at recurrence

| Time since initial diagnosis (months) | 59.3 (50.1) | 55.4 (41.0) | 61.5 (55.8) |
| Disease free interval (months)       | 57.2 (49.4) | 54.3 (40.3) | 58.9 (54.4) |
| Time since recurrence (months)       | 2.7 (1.5)   | 2.8 (1.6)   | 2.6 (1.5)   |

<table>
<thead>
<tr>
<th>Extent of recurrent disease</th>
<th>Local/Regional</th>
<th>Distant</th>
<th>Current cancer treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local/Regional</td>
<td>35%</td>
<td>29%</td>
<td>16%</td>
</tr>
<tr>
<td>Distant</td>
<td>65%</td>
<td>71%</td>
<td>84%</td>
</tr>
<tr>
<td>None</td>
<td>14%</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>On treatment</td>
<td>86%</td>
<td>36%</td>
<td>47%</td>
</tr>
<tr>
<td>Chemotherapy (% yes)</td>
<td>82%</td>
<td>32%</td>
<td>29%</td>
</tr>
<tr>
<td>Surgery (% yes)</td>
<td>53%</td>
<td>16%</td>
<td>19%</td>
</tr>
<tr>
<td>Radiation Therapy (% yes)</td>
<td>32%</td>
<td>26%</td>
<td>32%</td>
</tr>
<tr>
<td>Hormonal Therapy (% yes)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: * p<.05, + p<.01
Table 3
*Correlational analyses for the selection of covariates for analyses examining subjective and objective physical health composite variables as outcomes*

<table>
<thead>
<tr>
<th></th>
<th>Subjective Physical Health Composite (12 Months)</th>
<th>Objective Physical Health Composite (12 Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic Variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.028</td>
<td>0.063</td>
</tr>
<tr>
<td>p</td>
<td>.817</td>
<td>.583</td>
</tr>
<tr>
<td>Family Income</td>
<td>0.019</td>
<td>0.017</td>
</tr>
<tr>
<td>p</td>
<td>.885</td>
<td>.889</td>
</tr>
<tr>
<td>Education</td>
<td>0.004</td>
<td>0.069</td>
</tr>
<tr>
<td>p</td>
<td>.972</td>
<td>.544</td>
</tr>
<tr>
<td><strong>Disease-related variables at recurrence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease free interval (months)</td>
<td>-0.071</td>
<td>0.004</td>
</tr>
<tr>
<td>p</td>
<td>.556</td>
<td>.974</td>
</tr>
<tr>
<td>Extent of Recurrent Disease</td>
<td>0.166</td>
<td>0.275*</td>
</tr>
<tr>
<td>p</td>
<td>.169</td>
<td>.015</td>
</tr>
<tr>
<td>Receipt of Chemotherapy</td>
<td>0.219</td>
<td>0.133</td>
</tr>
<tr>
<td>p</td>
<td>.067</td>
<td>.243</td>
</tr>
<tr>
<td>Receipt of Surgery</td>
<td>-.004</td>
<td>-.241*</td>
</tr>
<tr>
<td>p</td>
<td>.972</td>
<td>.032</td>
</tr>
<tr>
<td>Receipt of Radiation</td>
<td>-0.017</td>
<td>-0.019</td>
</tr>
<tr>
<td>p</td>
<td>.889</td>
<td>.869</td>
</tr>
<tr>
<td>Receipt of Hormonal Therapy</td>
<td>-0.133</td>
<td>-0.087</td>
</tr>
<tr>
<td>p</td>
<td>.268</td>
<td>.447</td>
</tr>
<tr>
<td>Receive the intervention</td>
<td>-0.002</td>
<td>0.001</td>
</tr>
<tr>
<td>p</td>
<td>.983</td>
<td>.994</td>
</tr>
</tbody>
</table>

*Notes: * p<.05, + p<.01
Table 4
Correlational analyses for the selection of covariates for analyses examining psychological distress, neuroendocrine variables, and immune variables as outcomes.

<table>
<thead>
<tr>
<th>Sociodemographic Variables</th>
<th>Psychological Distress (4 months)</th>
<th>Plasma Cortisol (4 months)</th>
<th>Plasma Norepinephrine (4-months)</th>
<th>Response to PHA (4 months)</th>
<th>NKCC (4 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.024</td>
<td>0.032</td>
<td>0.312*</td>
<td>-0.016</td>
<td>-0.035</td>
</tr>
<tr>
<td></td>
<td>p=0.834</td>
<td>p=0.811</td>
<td>p=0.016</td>
<td>p=0.907</td>
<td>p=0.796</td>
</tr>
<tr>
<td>Education</td>
<td>-0.034</td>
<td>0.252</td>
<td>-0.132</td>
<td>0.062</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>p=0.763</td>
<td>p=0.054</td>
<td>p=0.318</td>
<td>p=0.646</td>
<td>p=0.946</td>
</tr>
<tr>
<td>Family Income</td>
<td>-0.137</td>
<td>-0.037</td>
<td>0.133</td>
<td>-0.019</td>
<td>-0.166</td>
</tr>
<tr>
<td></td>
<td>p=0.257</td>
<td>p=0.796</td>
<td>p=0.353</td>
<td>p=0.896</td>
<td>p=0.265</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease-related variables at recurrence</th>
<th>Psychological Distress (4 months)</th>
<th>Plasma Cortisol (4 months)</th>
<th>Plasma Norepinephrine (4-months)</th>
<th>Response to PHA (4 months)</th>
<th>NKCC (4 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Free Interval</td>
<td>-0.055</td>
<td>-0.082</td>
<td>0.191</td>
<td>-0.052</td>
<td>-0.067</td>
</tr>
<tr>
<td></td>
<td>p=0.657</td>
<td>p=0.533</td>
<td>p=0.145</td>
<td>p=0.698</td>
<td>p=0.622</td>
</tr>
<tr>
<td>Extent of Recurrent</td>
<td>-0.022</td>
<td>-0.351*</td>
<td>0.089</td>
<td>-0.250</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>p=0.846</td>
<td>p=0.006</td>
<td>p=0.505</td>
<td>p=0.061</td>
<td>p=0.978</td>
</tr>
<tr>
<td>Receipt of Chemotherapy</td>
<td>0.036</td>
<td>0.000</td>
<td>-0.224</td>
<td>0.014</td>
<td>-0.166</td>
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<tr>
<td></td>
<td>p=0.748</td>
<td>p=0.999</td>
<td>p=0.088</td>
<td>p=0.919</td>
<td>p=0.211</td>
</tr>
<tr>
<td>Receipt of Surgery</td>
<td>0.094</td>
<td>0.225</td>
<td>0.152</td>
<td>0.263*</td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td>p=0.407</td>
<td>p=0.087</td>
<td>p=0.252</td>
<td>p=0.048</td>
<td>p=0.790</td>
</tr>
<tr>
<td>Receipt of Radiation Therapy</td>
<td>-0.135</td>
<td>0.024</td>
<td>0.037</td>
<td>-0.282*</td>
<td>0.270*</td>
</tr>
<tr>
<td></td>
<td>p=0.231</td>
<td>p=0.859</td>
<td>p=0.780</td>
<td>p=0.033</td>
<td>p=0.044</td>
</tr>
<tr>
<td>Receipt of hormonal Therapy</td>
<td>-0.156</td>
<td>0.097</td>
<td>-0.022</td>
<td>-0.013</td>
<td>0.202</td>
</tr>
<tr>
<td></td>
<td>p=0.168</td>
<td>p=0.464</td>
<td>p=0.869</td>
<td>p=0.925</td>
<td>p=0.136</td>
</tr>
<tr>
<td>Receive the intervention</td>
<td>-0.012</td>
<td>0.026</td>
<td>-0.091</td>
<td>0.175</td>
<td>-0.040</td>
</tr>
<tr>
<td></td>
<td>p=0.914</td>
<td>p=0.843</td>
<td>p=0.488</td>
<td>p=0.189</td>
<td>p=0.766</td>
</tr>
</tbody>
</table>

Notes: * p<.05, + p<.01.
Table 5
*Does baseline structural and functional support predict subjective physical health at 12 months?*

<table>
<thead>
<tr>
<th>Predictors</th>
<th>β</th>
<th>t</th>
<th>P-value</th>
<th>Average R²</th>
<th>R² (Min, Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.345</td>
<td>1.44</td>
<td>0.017*</td>
<td>0.041</td>
<td>0.008 to 0.099</td>
</tr>
<tr>
<td>SNI</td>
<td>-0.052</td>
<td>-1.74</td>
<td>0.082</td>
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<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.273</td>
<td>0.78</td>
<td>0.433</td>
<td>0.012</td>
<td>&lt;0.010 to 0.055</td>
</tr>
<tr>
<td>PSS-FA</td>
<td>-0.018</td>
<td>-0.087</td>
<td>0.386</td>
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</table>

*Notes: * p<.05, + p<.01
Table 6
Does structural and functional support predict subjective physical health controlling for baseline ratings of subjective health?

<table>
<thead>
<tr>
<th>Predictors</th>
<th>( \beta )</th>
<th>( t )</th>
<th>P-value</th>
<th>Average R(^2)</th>
<th>( R^2 ) (Min, Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.122</td>
<td>0.56</td>
<td>0.579</td>
<td>0.274</td>
<td>0.147 to 0.390</td>
</tr>
<tr>
<td>Baseline subjective physical health</td>
<td>0.488</td>
<td>4.53</td>
<td>&lt;.0001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNI</td>
<td>-0.029</td>
<td>-1.04</td>
<td>0.299</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.013</td>
<td>-0.04</td>
<td>0.969</td>
<td>0.264</td>
<td>0.151 to 0.383</td>
</tr>
<tr>
<td>Baseline subjective physical health</td>
<td>0.505</td>
<td>4.59</td>
<td>&lt;.0001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS-FA</td>
<td>-0.004</td>
<td>-0.22</td>
<td>0.829</td>
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<td></td>
</tr>
</tbody>
</table>

Notes: * p<.05, + p<.01
Table 7
Does baseline structural and functional support predict objective physical health at 12 months?

<table>
<thead>
<tr>
<th>Predictors</th>
<th>β</th>
<th>t</th>
<th>P-value</th>
<th>Average R²</th>
<th>R² (Min, Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.715</td>
<td>-1.82</td>
<td>0.069</td>
<td>0.100</td>
<td>0.060 to 0.141</td>
</tr>
<tr>
<td>Extent of recurrent disease</td>
<td>0.529</td>
<td>2.72</td>
<td>0.007*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNI</td>
<td>-0.032</td>
<td>-1.16</td>
<td>0.246</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.710</td>
<td>-1.56</td>
<td>0.118</td>
<td>0.093</td>
<td>0.047 to 0.143</td>
</tr>
<tr>
<td>Extent of recurrent disease</td>
<td>0.544</td>
<td>2.79</td>
<td>0.005*</td>
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<td></td>
</tr>
<tr>
<td>PSS-FA</td>
<td>-0.015</td>
<td>-0.78</td>
<td>0.437</td>
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</tr>
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</table>

Notes: * p<.05, + p<.01
Table 8
Does baseline structural and functional support predict objective physical health controlling for baseline ratings of objective health?

<table>
<thead>
<tr>
<th>Predictors</th>
<th>β</th>
<th>t</th>
<th>P-value</th>
<th>Average R²</th>
<th>R² (Min, Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.695</td>
<td>-0.46</td>
<td>0.687</td>
<td>0.387</td>
<td>0.307 to 0.445</td>
</tr>
<tr>
<td>Extent of recurrent disease</td>
<td>0.425</td>
<td>2.56</td>
<td>0.011*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline objective physical health</td>
<td>0.647</td>
<td>6.05</td>
<td>&lt;.0001+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNI</td>
<td>-0.014</td>
<td>-0.59</td>
<td>0.555</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.781</td>
<td>-1.99</td>
<td>0.046*</td>
<td>0.384</td>
<td>0.307 to 0.444</td>
</tr>
<tr>
<td>Extent of recurrent disease</td>
<td>0.428</td>
<td>2.57</td>
<td>0.010*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline objective physical health</td>
<td>0.654</td>
<td>6.06</td>
<td>&lt;.0001+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS-FA</td>
<td>-0.001</td>
<td>-0.06</td>
<td>0.952</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: * p<.05, + p<.01
Table 9
Does baseline structural and functional support predict psychological distress at 4 months?

<table>
<thead>
<tr>
<th>Predictors</th>
<th>β</th>
<th>t</th>
<th>P-value</th>
<th>Average R²</th>
<th>R² (Min, Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.574</td>
<td>2.55</td>
<td>0.011*</td>
<td>0.126</td>
<td>0.074 to 0.192</td>
</tr>
<tr>
<td>SNI</td>
<td>-0.099</td>
<td>-3.39</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.654</td>
<td>1.80</td>
<td>0.071</td>
<td>0.058</td>
<td>0.018 to 0.102</td>
</tr>
<tr>
<td>PSS-FA</td>
<td>-0.047</td>
<td>-2.21</td>
<td>0.027*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: * p<.05, +p<.01
Table 10

*Does baseline structural and functional support predict psychological distress at 4 months after controlling for baseline levels of psychological distress?*

<table>
<thead>
<tr>
<th>Predictors</th>
<th>β</th>
<th>t</th>
<th>P-value</th>
<th>Average R²</th>
<th>R² (Min, Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.241</td>
<td>1.29</td>
<td>0.198</td>
<td>0.508</td>
<td>0.368 to 0.575</td>
</tr>
<tr>
<td>Baseline Distress</td>
<td>0.645</td>
<td>7.61</td>
<td>&lt;.0001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNI</td>
<td>-0.060</td>
<td>-2.51</td>
<td>0.012*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.229</td>
<td>0.77</td>
<td>0.444</td>
<td>0.480</td>
<td>0.334 to 0.556</td>
</tr>
<tr>
<td>Baseline Distress</td>
<td>0.671</td>
<td>7.93</td>
<td>&lt;.0001*</td>
<td></td>
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</tr>
<tr>
<td>PSS-FA</td>
<td>-0.025</td>
<td>-1.45</td>
<td>0.147</td>
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<td></td>
</tr>
</tbody>
</table>

*Notes: * p<.05, + p<.01*
<table>
<thead>
<tr>
<th>Predictors</th>
<th>β</th>
<th>t</th>
<th>P-value</th>
<th>Average R²</th>
<th>R² (Min, Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Cortisol</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>14.560</td>
<td>6.14</td>
<td>&lt;0.001*</td>
<td>0.104</td>
<td>0.020 to 0.210</td>
</tr>
<tr>
<td>Extent of recurrent disease</td>
<td>-2.783</td>
<td>-2.40</td>
<td>0.017*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNI</td>
<td>-0.050</td>
<td>-0.29</td>
<td>0.772</td>
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</tr>
<tr>
<td>Intercept</td>
<td>14.172</td>
<td>5.08</td>
<td>&lt;0.001*</td>
<td>0.103</td>
<td>0.016 to 0.262</td>
</tr>
<tr>
<td>Extent of recurrent disease</td>
<td>-2.770</td>
<td>-2.39</td>
<td>0.017*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS-FA</td>
<td>0.001</td>
<td>0.01</td>
<td>0.994</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2. Norepinephrine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>107.823</td>
<td>0.66</td>
<td>0.507</td>
<td>0.100</td>
<td>0.020 to 0.267</td>
</tr>
<tr>
<td>Age at recurrence</td>
<td>5.955</td>
<td>2.32</td>
<td>0.021*</td>
<td></td>
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<tr>
<td>SNI</td>
<td>7.232</td>
<td>0.90</td>
<td>0.368</td>
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<tr>
<td>Intercept</td>
<td>276.870</td>
<td>1.65</td>
<td>0.099</td>
<td>0.110</td>
<td>0.017 to 0.248</td>
</tr>
<tr>
<td>Age at recurrence</td>
<td>5.726</td>
<td>2.29</td>
<td>0.022*</td>
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<td></td>
</tr>
<tr>
<td>PSS-FA</td>
<td>-6.338</td>
<td>-1.03</td>
<td>0.302</td>
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<td></td>
</tr>
<tr>
<td><strong>3. PHA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.008</td>
<td>0.02</td>
<td>0.983</td>
<td>0.134</td>
<td>0.058 to 0.275</td>
</tr>
<tr>
<td>Receipt of surgery</td>
<td>0.576</td>
<td>1.84</td>
<td>0.066</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receipt of radiation</td>
<td>-0.825</td>
<td>-2.60</td>
<td>0.009*</td>
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</tr>
<tr>
<td>SNI</td>
<td>0.013</td>
<td>0.28</td>
<td>0.783</td>
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</tr>
<tr>
<td>Intercept</td>
<td>-0.433</td>
<td>-0.68</td>
<td>0.499</td>
<td>0.150</td>
<td>0.062 to 0.310</td>
</tr>
<tr>
<td>Receipt of surgery</td>
<td>0.625</td>
<td>1.95</td>
<td>0.052</td>
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<tr>
<td>Receipt of radiation</td>
<td>-0.795</td>
<td>-2.49</td>
<td>0.013*</td>
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<tr>
<td>PSS-FA</td>
<td>0.031</td>
<td>0.91</td>
<td>0.364</td>
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</table>

Continued
Table 11. Continued

<table>
<thead>
<tr>
<th>Predictors</th>
<th>β</th>
<th>t</th>
<th>P-value</th>
<th>Average R²</th>
<th>R² (Min, Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. NKCC</td>
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</tr>
<tr>
<td>Intercept</td>
<td>5.286</td>
<td>8.25</td>
<td>&lt;0.001⁺</td>
<td>0.062</td>
<td>0.008 to 0.152</td>
</tr>
<tr>
<td>Receipt of radiation</td>
<td>0.903</td>
<td>1.57</td>
<td>0.116</td>
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<tr>
<td>SNI</td>
<td>-0.041</td>
<td>-0.51</td>
<td>0.611</td>
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<tr>
<td>Intercept</td>
<td>5.983</td>
<td>5.68</td>
<td>&lt;0.001⁺</td>
<td>0.081</td>
<td>0.005 to 0.216</td>
</tr>
<tr>
<td>Receipt of radiation</td>
<td>0.839</td>
<td>1.45</td>
<td>0.149</td>
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</tr>
<tr>
<td>PSS-FA</td>
<td>-0.059</td>
<td>-1.02</td>
<td>0.308</td>
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<td></td>
</tr>
</tbody>
</table>

Notes: * p<.05, + p<.01
Table 12

Does structural and functional support predict biological variables at 4 months after controlling for levels of biological parameters at baseline?

<table>
<thead>
<tr>
<th>Predictors</th>
<th>β</th>
<th>t</th>
<th>P-value</th>
<th>Average R²</th>
<th>R² (Min, Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Cortisol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>12.843</td>
<td>4.59</td>
<td>&lt;0.001*</td>
<td>0.135</td>
<td>0.020 to 0.235</td>
</tr>
<tr>
<td>Extent of recurrent disease</td>
<td>-2.640</td>
<td>-2.23</td>
<td>0.026*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline cortisol</td>
<td>0.136</td>
<td>1.08</td>
<td>0.279</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNI</td>
<td>-0.031</td>
<td>-0.18</td>
<td>0.854</td>
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</tr>
<tr>
<td>Intercept</td>
<td>12.630</td>
<td>4.02</td>
<td>&lt;0.001*</td>
<td>0.135</td>
<td>0.016 to 0.285</td>
</tr>
<tr>
<td>Extent of recurrent disease</td>
<td>-2.629</td>
<td>-2.23</td>
<td>0.027*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline cortisol</td>
<td>0.138</td>
<td>1.09</td>
<td>0.278</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS-FA</td>
<td>-0.003</td>
<td>-0.02</td>
<td>0.980</td>
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<td></td>
</tr>
<tr>
<td><strong>2. Norepinephrine</strong></td>
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<td></td>
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<tr>
<td>Intercept</td>
<td>-36.464</td>
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<td>0.258</td>
<td>0.091 to 0.387</td>
</tr>
<tr>
<td>Age</td>
<td>4.622</td>
<td>1.87</td>
<td>0.062</td>
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</tr>
<tr>
<td>Baseline norepinephrine</td>
<td>0.412</td>
<td>3.27</td>
<td>0.001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNI</td>
<td>10.842</td>
<td>1.44</td>
<td>0.150</td>
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<tr>
<td>Intercept</td>
<td>160.714</td>
<td>1.00</td>
<td>0.316</td>
<td>0.248</td>
<td>0.105 to 0.361</td>
</tr>
<tr>
<td>Age</td>
<td>4.346</td>
<td>1.78</td>
<td>0.075</td>
<td></td>
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</tr>
<tr>
<td>Baseline norepinephrine</td>
<td>0.381</td>
<td>3.02</td>
<td>0.003*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS-FA</td>
<td>-5.472</td>
<td>-0.95</td>
<td>0.344</td>
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</tbody>
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Continued
### Table 12. Continued

<table>
<thead>
<tr>
<th>Predictors</th>
<th>β</th>
<th>t</th>
<th>P-value</th>
<th>Average R²</th>
<th>R² (Min, Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3. PHA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.037</td>
<td>-0.10</td>
<td>0.921</td>
<td>0.180</td>
<td>0.076 to 0.309</td>
</tr>
<tr>
<td>Receipt of surgery</td>
<td>0.660</td>
<td>2.10</td>
<td>0.036*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receipt of radiation</td>
<td>-0.806</td>
<td>-2.61</td>
<td>0.009*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline PHA</td>
<td>0.252</td>
<td>1.52</td>
<td>0.131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNI</td>
<td>0.014</td>
<td>0.32</td>
<td>0.747</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>-0.573</td>
<td>-0.91</td>
<td>0.362</td>
<td>0.201</td>
<td>0.090 to 0.356</td>
</tr>
<tr>
<td>Receipt of surgery</td>
<td>0.725</td>
<td>2.25</td>
<td>0.025*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receipt of radiation</td>
<td>-0.770</td>
<td>-2.50</td>
<td>0.013*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline PHA</td>
<td>0.273</td>
<td>1.65</td>
<td>0.100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS-FA</td>
<td>0.037</td>
<td>1.11</td>
<td>0.268</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4. NKCC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>4.893</td>
<td>4.65</td>
<td>&lt;0.001*</td>
<td>0.079</td>
<td>0.008 to 0.195</td>
</tr>
<tr>
<td>Receipt of radiation</td>
<td>0.889</td>
<td>1.56</td>
<td>0.119</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline NKCC</td>
<td>0.075</td>
<td>0.54</td>
<td>0.591</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNI</td>
<td>-0.039</td>
<td>-0.49</td>
<td>0.624</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>5.589</td>
<td>4.35</td>
<td>&lt;0.001*</td>
<td>0.097</td>
<td>0.008 to 0.244</td>
</tr>
<tr>
<td>Receipt of radiation</td>
<td>0.824</td>
<td>1.43</td>
<td>0.153</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline NKCC</td>
<td>0.076</td>
<td>0.56</td>
<td>0.577</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS-FA</td>
<td>-0.058</td>
<td>-1.03</td>
<td>0.304</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Notes: * p<.05, + p<.01
Table 13
Summary of models examining distress as a mediator between social support at baseline and physical health at 12 months.

<table>
<thead>
<tr>
<th>Path</th>
<th>Point Estimate</th>
<th>Bootstrap Standard Error</th>
<th>Bias Corrected Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^a)SNI (\rightarrow) Distress (a)</td>
<td>-0.098</td>
<td>0.031</td>
<td>(-0.160, -0.038)*</td>
</tr>
<tr>
<td>Distress (\rightarrow) Subjective Physical Health (b)</td>
<td>0.524</td>
<td>0.102</td>
<td>(0.327, 0.730)*</td>
</tr>
<tr>
<td>SNI (\rightarrow) Subjective Physical Health (Direct Effect)</td>
<td>0.005</td>
<td>0.027</td>
<td>(-0.049, 0.056)</td>
</tr>
<tr>
<td>Indirect Effect (ab path)</td>
<td>-0.052</td>
<td>0.020</td>
<td>(-0.098, -0.019)*</td>
</tr>
<tr>
<td>(^b)SNI (\rightarrow) Distress (a)</td>
<td>-0.100</td>
<td>0.032</td>
<td>(-0.164, -0.038)*</td>
</tr>
<tr>
<td>Distress (\rightarrow) Objective Physical Health (b)</td>
<td>0.504</td>
<td>0.096</td>
<td>(0.319, 0.696)*</td>
</tr>
<tr>
<td>SNI (\rightarrow) Objective Physical Health (Direct Effect)</td>
<td>0.018</td>
<td>0.027</td>
<td>(-0.031, 0.073)</td>
</tr>
<tr>
<td>Indirect Effect (ab path)</td>
<td>-0.051</td>
<td>0.019</td>
<td>(-0.094, -0.019)*</td>
</tr>
<tr>
<td>(^a)PSS-FA (\rightarrow) Distress (a)</td>
<td>-0.046</td>
<td>0.022</td>
<td>(-0.093, -0.003)*</td>
</tr>
<tr>
<td>Distress (\rightarrow) Subjective Physical Health (b)</td>
<td>0.512</td>
<td>0.101</td>
<td>(0.340, 0.749)</td>
</tr>
<tr>
<td>PSS-FA (\rightarrow) Subjective Physical Health (Direct Effect)</td>
<td>0.004</td>
<td>0.018</td>
<td>(-0.033, 0.040)</td>
</tr>
<tr>
<td>Indirect Effect (ab path)</td>
<td>-0.023</td>
<td>0.012</td>
<td>(-0.053, -0.003)*</td>
</tr>
<tr>
<td>(^b)PSS-FA (\rightarrow) Distress (a)</td>
<td>-0.046</td>
<td>0.022</td>
<td>(-0.091, -0.002)*</td>
</tr>
<tr>
<td>Distress (\rightarrow) Objective Physical Health (b)</td>
<td>0.489</td>
<td>0.095</td>
<td>(0.303, 0.677)*</td>
</tr>
<tr>
<td>PSS-FA (\rightarrow) Objective Physical Health (Direct Effect)</td>
<td>0.007</td>
<td>0.019</td>
<td>(-0.029, 0.045)</td>
</tr>
<tr>
<td>Indirect Effect (ab path)</td>
<td>-0.022</td>
<td>0.011</td>
<td>(-0.048, -0.002)*</td>
</tr>
</tbody>
</table>

Notes: * p<.05; \(^a\) No covariates; \(^b\) Model controls for extent of recurrent disease
Table 14
Summary of models examining distress as a mediator between social support at baseline and physical health at 12 months controlling for baseline levels of distress and physical health.

<table>
<thead>
<tr>
<th>Path</th>
<th>Point Estimate</th>
<th>Bootstrap Standard Error</th>
<th>Bias Corrected Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a</strong>SNI → Distress (a)</td>
<td>-0.057</td>
<td>0.024</td>
<td>(-0.105, -0.012)*</td>
</tr>
<tr>
<td>Distress → Subjective Physical Health (b)</td>
<td>0.418</td>
<td>0.147</td>
<td>(0.129, 0.707)*</td>
</tr>
<tr>
<td>SNI → Subjective Physical Health (Direct Effect)</td>
<td>0.004</td>
<td>0.025</td>
<td>(-0.050, 0.051)</td>
</tr>
<tr>
<td>Indirect Effect (ab path)</td>
<td>-0.024</td>
<td>0.014</td>
<td>(-0.065, -0.004)*</td>
</tr>
<tr>
<td><strong>b</strong>SNI → Distress (a)</td>
<td>-0.061</td>
<td>0.024</td>
<td>(-0.110, -0.014)*</td>
</tr>
<tr>
<td>Distress → Objective Physical Health (b)</td>
<td>0.357</td>
<td>0.142</td>
<td>(0.056, 0.620)*</td>
</tr>
<tr>
<td>SNI → Objective Physical Health (Direct Effect)</td>
<td>0.014</td>
<td>0.025</td>
<td>(-0.035, 0.062)</td>
</tr>
<tr>
<td>Indirect Effect (ab path)</td>
<td>-0.022</td>
<td>0.014</td>
<td>(-0.061, -0.002)*</td>
</tr>
<tr>
<td><strong>a</strong>PSS-FA → Distress (a)</td>
<td>-0.022</td>
<td>0.016</td>
<td>(-0.053, 0.011)</td>
</tr>
<tr>
<td>Distress → Subjective Physical Health (b)</td>
<td>0.417</td>
<td>0.145</td>
<td>(0.127, 0.702)*</td>
</tr>
<tr>
<td>PSS-FA → Subjective Physical Health (Direct Effect)</td>
<td>0.005</td>
<td>0.017</td>
<td>(-0.029, 0.038)</td>
</tr>
<tr>
<td>Indirect Effect (ab path)</td>
<td>-0.009</td>
<td>0.008</td>
<td>(-0.030, 0.003)</td>
</tr>
<tr>
<td><strong>b</strong>PSS-FA → Distress (a)</td>
<td>-0.022</td>
<td>0.017</td>
<td>(-0.054, 0.011)</td>
</tr>
<tr>
<td>Distress → Objective Physical Health (b)</td>
<td>0.346</td>
<td>0.137</td>
<td>(0.047, 0.589)*</td>
</tr>
<tr>
<td>PSS-FA → Objective Physical Health (Direct Effect)</td>
<td>0.008</td>
<td>0.016</td>
<td>(-0.025, 0.040)</td>
</tr>
<tr>
<td>Indirect Effect (ab path)</td>
<td>-0.008</td>
<td>0.007</td>
<td>(-0.027, 0.002)</td>
</tr>
</tbody>
</table>

Notes: * p<.05;  
a Model controls for: baseline distress, baseline subjective health composite;  
b Model controls for: baseline distress, baseline objective health, extent of recurrent disease
Table 15
Summary of models examining cortisol as a mediator between social support at baseline and physical health at 12 months.

<table>
<thead>
<tr>
<th>Path</th>
<th>Point Estimate</th>
<th>Bootstrap Standard Error</th>
<th>Bias Corrected Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^a)SNI (\rightarrow) Cortisol (a)</td>
<td>-0.070</td>
<td>0.181</td>
<td>(-0.418, 0.291)</td>
</tr>
<tr>
<td>Cortisol (\rightarrow) Subjective Physical Health (b)</td>
<td>-0.017</td>
<td>0.029</td>
<td>(-0.075, 0.040)</td>
</tr>
<tr>
<td>SNI (\rightarrow) Subjective Physical Health (Direct Effect)</td>
<td>-0.047</td>
<td>0.029</td>
<td>(-0.106, 0.010)</td>
</tr>
<tr>
<td>Indirect Effect (ab path)</td>
<td>0.001</td>
<td>0.007</td>
<td>(-0.007, 0.024)</td>
</tr>
<tr>
<td>(^a)SNI (\rightarrow) Cortisol (a)</td>
<td>-0.055</td>
<td>0.182</td>
<td>(-0.399, 0.314)</td>
</tr>
<tr>
<td>Cortisol (\rightarrow) Objective Physical Health (b)</td>
<td>-0.031</td>
<td>0.032</td>
<td>(-0.089, 0.033)</td>
</tr>
<tr>
<td>SNI (\rightarrow) Objective Physical Health (Direct Effect)</td>
<td>-0.034</td>
<td>0.028</td>
<td>(-0.088, 0.024)</td>
</tr>
<tr>
<td>Indirect Effect (ab path)</td>
<td>0.001</td>
<td>0.008</td>
<td>(-0.013, 0.023)</td>
</tr>
<tr>
<td>(^a)PSS-FA (\rightarrow) Cortisol (a)</td>
<td>-0.021</td>
<td>0.119</td>
<td>(-0.232, 0.236)</td>
</tr>
<tr>
<td>Cortisol (\rightarrow) Subjective Physical Health (b)</td>
<td>-0.016</td>
<td>0.029</td>
<td>(-0.075, 0.043)</td>
</tr>
<tr>
<td>PSS-FA (\rightarrow) Subjective Physical Health (Direct Effect)</td>
<td>-0.022</td>
<td>0.020</td>
<td>(-0.062, 0.018)</td>
</tr>
<tr>
<td>Indirect Effect (ab path)</td>
<td>0.0006</td>
<td>0.004</td>
<td>(-0.005, 0.012)</td>
</tr>
<tr>
<td>(^a)PSS-FA (\rightarrow) Cortisol (a)</td>
<td>-0.006</td>
<td>0.118</td>
<td>(-0.218, 0.251)</td>
</tr>
<tr>
<td>Cortisol (\rightarrow) Objective Physical Health (b)</td>
<td>-0.030</td>
<td>0.032</td>
<td>(-0.089, 0.034)</td>
</tr>
<tr>
<td>PSS-FA (\rightarrow) Objective Physical Health (Direct Effect)</td>
<td>-0.015</td>
<td>0.019</td>
<td>(-0.051, 0.023)</td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>-0.0002</td>
<td>0.005</td>
<td>(-0.014, 0.008)</td>
</tr>
</tbody>
</table>

Notes: * \(p<.05\); \(^a\) Model controls for: extent of recurrent disease
Table 16
Summary of models examining norepinephrine as a mediator between social support at baseline and physical health at 12 months.

<table>
<thead>
<tr>
<th>Path</th>
<th>Point Estimate</th>
<th>Bootstrap Standard Error</th>
<th>Bias Corrected Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^a)SNI \rightarrow \text{Norepinephrine (a)}</td>
<td>6.032</td>
<td>8.667</td>
<td>(-11.848, 22.424)</td>
</tr>
<tr>
<td>\text{Norepinephrine} \rightarrow \text{Subjective Physical Health (b)}</td>
<td>-0.0005</td>
<td>0.0006</td>
<td>(-0.002, 0.0005)</td>
</tr>
<tr>
<td>\text{SNI} \rightarrow \text{Subjective Physical Health (Direct Effect)}</td>
<td>-0.047</td>
<td>0.030</td>
<td>(-0.105, 0.013)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>-0.003</td>
<td>0.007</td>
<td>(-0.030, 0.005)</td>
</tr>
<tr>
<td>(^b)SNI \rightarrow \text{Norepinephrine (a)}</td>
<td>7.045</td>
<td>8.676</td>
<td>(-9.103, 25.291)</td>
</tr>
<tr>
<td>\text{Norepinephrine} \rightarrow \text{Objective Physical Health (b)}</td>
<td>-0.0003</td>
<td>.0006</td>
<td>(-0.002, 0.001)</td>
</tr>
<tr>
<td>\text{SNI} \rightarrow \text{Objective Physical Health (Direct Effect)}</td>
<td>-0.030</td>
<td>0.029</td>
<td>(-0.085, 0.030)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>-0.003</td>
<td>0.008</td>
<td>(-0.043, 0.004)</td>
</tr>
<tr>
<td>(^a)PSS-FA \rightarrow \text{Norepinephrine (a)}</td>
<td>-6.699</td>
<td>6.025</td>
<td>(-17.628, 6.295)</td>
</tr>
<tr>
<td>\text{Norepinephrine} \rightarrow \text{Subjective Physical Health (b)}</td>
<td>-0.0007</td>
<td>0.0006</td>
<td>(-0.002, 0.0004)</td>
</tr>
<tr>
<td>\text{PSS-FA} \rightarrow \text{Subjective Physical Health (Direct Effect)}</td>
<td>-0.025</td>
<td>0.020</td>
<td>(-0.061, 0.017)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.005</td>
<td>0.007</td>
<td>(-0.002, 0.028)</td>
</tr>
<tr>
<td>(^b)PSS-FA \rightarrow \text{Norepinephrine (a)}</td>
<td>-6.731</td>
<td>5.995</td>
<td>(-17.662, 6.288)</td>
</tr>
<tr>
<td>\text{Norepinephrine} \rightarrow \text{Objective Physical Health (b)}</td>
<td>-0.0004</td>
<td>0.0006</td>
<td>(-0.002, 0.001)</td>
</tr>
<tr>
<td>\text{PSS-FA} \rightarrow \text{Objective Physical Health (Direct Effect)}</td>
<td>-0.019</td>
<td>0.020</td>
<td>(-0.006, 0.022)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.002</td>
<td>0.006</td>
<td>(-0.006, 0.023)</td>
</tr>
</tbody>
</table>

Notes: * p<.05; \(^a\) Model controls for: age at recurrence; \(^b\) Model controls for: age at recurrence, extent of recurrent disease.
Table 17
Summary of models examining PHA as a mediator between social support at baseline and physical health at 12 months.

<table>
<thead>
<tr>
<th>Path</th>
<th>Point Estimate</th>
<th>Bootstrap Standard Error</th>
<th>Bias Corrected Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^a)SNI → PHA (a)</td>
<td>0.007</td>
<td>0.049</td>
<td>(-0.092, 0.101)</td>
</tr>
<tr>
<td>PHA → Subjective Physical Health (b)</td>
<td>0.215</td>
<td>0.114</td>
<td>(-0.011, 0.447)</td>
</tr>
<tr>
<td>SNI → Subjective Physical Health (Direct Effect)</td>
<td>-0.047</td>
<td>0.030</td>
<td>(-0.107, 0.012)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.002</td>
<td>0.012</td>
<td>(-0.019, 0.034)</td>
</tr>
<tr>
<td>(^b)SNI → PHA (a)</td>
<td>0.012</td>
<td>0.049</td>
<td>(-0.090, 0.103)</td>
</tr>
<tr>
<td>PHA → Objective Physical Health (b)</td>
<td>0.210</td>
<td>0.105</td>
<td>(-0.003, 0.410)</td>
</tr>
<tr>
<td>SNI → Objective Physical Health (Direct Effect)</td>
<td>-0.035</td>
<td>0.029</td>
<td>(-0.090, 0.023)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.003</td>
<td>0.011</td>
<td>(-0.016, 0.031)</td>
</tr>
<tr>
<td>(^a)PSS-FA → PHA (a)</td>
<td>0.032</td>
<td>0.037</td>
<td>(-0.046, 0.101)</td>
</tr>
<tr>
<td>PHA → Subjective Physical Health (b)</td>
<td>0.231</td>
<td>0.119</td>
<td>(-0.007, 0.469)</td>
</tr>
<tr>
<td>PSS-FA → Subjective Physical Health (Direct Effect)</td>
<td>-0.030</td>
<td>0.022</td>
<td>(-0.074, 0.011)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.008</td>
<td>0.010</td>
<td>(-0.005, 0.040)</td>
</tr>
<tr>
<td>(^b)PSS-FA → PHA (a)</td>
<td>0.025</td>
<td>0.037</td>
<td>(-0.054, 0.091)</td>
</tr>
<tr>
<td>PHA → Objective Physical Health (b)</td>
<td>0.217</td>
<td>0.109</td>
<td>(-0.006, 0.421)</td>
</tr>
<tr>
<td>PSS-FA → Objective Physical Health (Direct Effect)</td>
<td>-0.023</td>
<td>0.019</td>
<td>(-0.058, 0.017)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.006</td>
<td>0.009</td>
<td>(-0.007, 0.032)</td>
</tr>
</tbody>
</table>

Notes: * p<.05; \(^a\) Model controls for: receipt of receipt of surgery at recurrence, receipt of radiation at recurrence; \(^b\) Model controls for extent of recurrent disease, receipt of radiation at recurrence.
Table 18
Summary of models examining NKCC as a mediator between social support at baseline and physical health at 12 months.

<table>
<thead>
<tr>
<th>Path</th>
<th>Point Estimate</th>
<th>Bootstrap Standard Error</th>
<th>Bias Corrected Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNI → NKCC (a)</td>
<td>-0.052</td>
<td>0.082</td>
<td>(-0.213, 0.110)</td>
</tr>
<tr>
<td>NKCC → Subjective Physical Health (b)</td>
<td>-0.087</td>
<td>0.071</td>
<td>(-0.224, 0.054)</td>
</tr>
<tr>
<td>SNI → Subjective Physical Health (Direct Effect)</td>
<td>-0.051</td>
<td>0.030</td>
<td>(-0.110, 0.007)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.005</td>
<td>0.010</td>
<td>(-0.006, 0.040)</td>
</tr>
<tr>
<td>SNI → NKCC (a)</td>
<td>-0.055</td>
<td>0.084</td>
<td>(-0.224, 0.108)</td>
</tr>
<tr>
<td>NKCC → Objective Physical Health (b)</td>
<td>-0.046</td>
<td>0.077</td>
<td>(-0.195, 0.108)</td>
</tr>
<tr>
<td>SNI → Objective Physical Health (Direct Effect)</td>
<td>-0.033</td>
<td>0.028</td>
<td>(-0.088, 0.023)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.002</td>
<td>0.008</td>
<td>(-0.009, 0.030)</td>
</tr>
<tr>
<td>PSS-FA → NKCC (a)</td>
<td>-0.062</td>
<td>0.058</td>
<td>(-0.177, 0.048)</td>
</tr>
<tr>
<td>PHA → Subjective Physical Health (b)</td>
<td>-0.087</td>
<td>0.074</td>
<td>(-0.237, 0.059)</td>
</tr>
<tr>
<td>PSS-FA → Subjective Physical Health (Direct Effect)</td>
<td>-0.025</td>
<td>0.020</td>
<td>(-0.064, 0.015)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.006</td>
<td>0.008</td>
<td>(-0.003, 0.037)</td>
</tr>
<tr>
<td>PSS-FA → NKCC (a)</td>
<td>-0.063</td>
<td>0.057</td>
<td>(-0.175, 0.053)</td>
</tr>
<tr>
<td>PHA → Objective Physical Health (b)</td>
<td>-0.049</td>
<td>0.080</td>
<td>(-0.200, 0.109)</td>
</tr>
<tr>
<td>PSS-FA → Objective Physical Health (Direct Effect)</td>
<td>-0.019</td>
<td>0.020</td>
<td>(-0.056, 0.023)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.002</td>
<td>0.007</td>
<td>(-0.007, 0.027)</td>
</tr>
</tbody>
</table>

Notes: * p<.05; a Model controls for: receipt of radiation; b Model controls for receipt of radiation, extent of recurrent disease
Table 19
Summary of models examining cortisol as a mediator between social support at baseline and physical health at 12 months controlling for baseline levels of cortisol and physical health.

<table>
<thead>
<tr>
<th>Path</th>
<th>Point Estimate</th>
<th>Bootstrap Standard Error</th>
<th>Bias Corrected Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>^aSNI → Cortisol (a)</td>
<td>-0.048</td>
<td>0.187</td>
<td>(-0.417, 0.315)</td>
</tr>
<tr>
<td>Cortisol → Subjective Physical Health (b)</td>
<td>-0.028</td>
<td>0.024</td>
<td>(-0.072, 0.022)</td>
</tr>
<tr>
<td>SNI → Subjective Physical Health (Direct Effect)</td>
<td>-0.020</td>
<td>0.025</td>
<td>(-0.072, 0.027)</td>
</tr>
<tr>
<td>Indirect Effect (ab path)</td>
<td>0.001</td>
<td>0.007</td>
<td>(-0.008, 0.025)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Path</th>
<th>Point Estimate</th>
<th>Bootstrap Standard Error</th>
<th>Bias Corrected Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>^aSNI → Cortisol (a)</td>
<td>-0.036</td>
<td>0.181</td>
<td>(-0.382, 0.181)</td>
</tr>
<tr>
<td>Cortisol → Objective Physical Health (b)</td>
<td>-0.037</td>
<td>0.023</td>
<td>(-0.081, 0.007)</td>
</tr>
<tr>
<td>SNI → Objective Physical Health (Direct Effect)</td>
<td>-0.011</td>
<td>0.025</td>
<td>(-0.061, 0.038)</td>
</tr>
<tr>
<td>Indirect Effect (ab path)</td>
<td>0.001</td>
<td>0.008</td>
<td>(-0.014, 0.020)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Path</th>
<th>Point Estimate</th>
<th>Bootstrap Standard Error</th>
<th>Bias Corrected Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>^aPSS-FA → Cortisol (a)</td>
<td>-0.023</td>
<td>0.117</td>
<td>(-0.233, 0.227)</td>
</tr>
<tr>
<td>Cortisol → Subjective Physical Health (b)</td>
<td>-0.027</td>
<td>0.024</td>
<td>(-0.071, 0.023)</td>
</tr>
<tr>
<td>PSS-FA → Subjective Physical Health (Direct Effect)</td>
<td>-0.011</td>
<td>0.018</td>
<td>(-0.047, 0.027)</td>
</tr>
<tr>
<td>Indirect Effect (ab path)</td>
<td>0.0009</td>
<td>0.004</td>
<td>(-0.005, 0.013)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Path</th>
<th>Point Estimate</th>
<th>Bootstrap Standard Error</th>
<th>Bias Corrected Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>^aPSS-FA → Cortisol (a)</td>
<td>-0.009</td>
<td>0.116</td>
<td>(-0.223, 0.240)</td>
</tr>
<tr>
<td>Cortisol → Objective Physical Health (b)</td>
<td>-0.037</td>
<td>0.023</td>
<td>(-0.081, 0.008)</td>
</tr>
<tr>
<td>PSS-FA → Objective Physical Health (Direct Effect)</td>
<td>-0.003</td>
<td>0.017</td>
<td>(-0.037, 0.029)</td>
</tr>
<tr>
<td>Indirect Effect</td>
<td>0.0004</td>
<td>0.005</td>
<td>(-0.009, 0.012)</td>
</tr>
</tbody>
</table>

Notes: ^a p<.05; * Model controls for: extent of recurrent disease, baseline subjective health, and baseline cortisol
Table 20
Summary of models examining norepinephrine as a mediator between social support at baseline and physical health at 12 months controlling for baseline norepinephrine and physical health.

<table>
<thead>
<tr>
<th>Path</th>
<th>Point Estimate</th>
<th>Bootstrap Standard Error</th>
<th>Bias Corrected Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>aSNI→ Norepinephrine (a)</td>
<td>9.744</td>
<td>8.560</td>
<td>(-7.660, 26.140)</td>
</tr>
<tr>
<td>Norepinephrine→ Subjective Physical Health (b)</td>
<td>-0.0006</td>
<td>0.0006</td>
<td>(-0.002, 0.0006)</td>
</tr>
<tr>
<td>SNI→ Subjective Physical Health (Direct Effect)</td>
<td>-0.017</td>
<td>0.028</td>
<td>(-0.074, 0.036)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>-0.005</td>
<td>0.008</td>
<td>(-0.034, 0.005)</td>
</tr>
</tbody>
</table>

| bSNI→ Norepinephrine (a) | 11.997 | 8.430 | (-3.367, 29.865) |
| Norepinephrine→ Objective Physical Health (b) | -0.0003 | 0.0006 | (-0.001, 0.0007) |
| SNI→ Objective Physical Health (Direct Effect) | -0.014 | 0.027 | (-0.066, 0.040) |
| Indirect Effect (ab) | -0.005 | 0.009 | (-0.042, 0.004) |

| aPSS-FA→ Norepinephrine (a) | -6.114 | 5.925 | (-16.999, 4.699) |
| Norepinephrine→ Subjective Physical Health (b) | -0.0006 | 0.0006 | (-0.002, 0.0005) |
| PSS-FA→ Subjective Physical Health (Direct Effect) | -0.012 | 0.018 | (-0.047, 0.024) |
| Indirect Effect (ab) | 0.004 | 0.006 | (-0.002, 0.027) |

| bPSS-FA→ Norepinephrine (a) | -5.499 | 5.847 | (-16.593, 5.650) |
| Norepinephrine→ Objective Physical Health (b) | -0.0004 | 0.0006 | (-0.002, 0.0007) |
| PSS-FA→ Objective Physical Health (Direct Effect) | -0.004 | 0.017 | (-0.037, 0.032) |
| Indirect Effect (ab) | 0.002 | 0.005 | (-0.003, 0.024) |

Notes: * p<.05; a Model controls for: age at recurrence, baseline norepinephrine, baseline subjective health; b Model controls for: age at recurrence, extent of recurrent disease, baseline norepinephrine, baseline objective health
### Table 21

Summary of models examining PHA as a mediator between social support at baseline and physical health at 12 months controlling for baseline PHA and physical health.

<table>
<thead>
<tr>
<th>Path</th>
<th>Estimate</th>
<th>Bootstrap Standard Error</th>
<th>Bias Corrected Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>^a^SNI→ PHA (a)</td>
<td>0.027</td>
<td>0.048</td>
<td>(-0.070, 0.119)</td>
</tr>
<tr>
<td>PHA→ Subjective Physical Health (b)</td>
<td>0.111</td>
<td>0.109</td>
<td>(-0.102, 0.333)</td>
</tr>
<tr>
<td>SNI→ Subjective Physical Health (Direct Effect)</td>
<td>-0.020</td>
<td>0.027</td>
<td>(-0.077, 0.030)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.003</td>
<td>0.008</td>
<td>(-0.006, 0.033)</td>
</tr>
<tr>
<td>^b^SNI→ PHA (a)</td>
<td>0.030</td>
<td>0.047</td>
<td>(-0.070, 0.115)</td>
</tr>
<tr>
<td>PHA→ Objective Physical Health (b)</td>
<td>0.015</td>
<td>0.106</td>
<td>(-0.186, 0.228)</td>
</tr>
<tr>
<td>SNI→ Objective Physical Health (Direct Effect)</td>
<td>-0.013</td>
<td>0.027</td>
<td>(-0.067, 0.040)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.0008</td>
<td>0.006</td>
<td>(-0.007, 0.021)</td>
</tr>
<tr>
<td>^a^PSS-FA→ PHA (a)</td>
<td>0.052</td>
<td>0.036</td>
<td>(-0.021, 0.122)</td>
</tr>
<tr>
<td>PHA→ Subjective Physical Health (b)</td>
<td>0.116</td>
<td>0.115</td>
<td>(-0.104, 0.354)</td>
</tr>
<tr>
<td>PSS-FA→ Subjective Physical Health (Direct Effect)</td>
<td>-0.008</td>
<td>0.020</td>
<td>(-0.050, 0.029)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.007</td>
<td>0.009</td>
<td>(-0.003, 0.037)</td>
</tr>
<tr>
<td>^b^PSS-FA→ PHA (a)</td>
<td>0.045</td>
<td>0.034</td>
<td>(-0.029, 0.107)</td>
</tr>
<tr>
<td>PHA→ Objective Physical Health (b)</td>
<td>0.011</td>
<td>0.108</td>
<td>(-0.189, 0.233)</td>
</tr>
<tr>
<td>PSS-FA→ Objective Physical Health (Direct Effect)</td>
<td>0.0003</td>
<td>0.018</td>
<td>(-0.036, 0.036)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.001</td>
<td>0.006</td>
<td>(-0.007, 0.022)</td>
</tr>
</tbody>
</table>

Notes: ^a^ p<.05; ^a^ Model controls for receipt of surgery at recurrence, receipt of radiation at recurrence, baseline PHA, baseline subjective health; ^b^ Model controls for: receipt of radiation at recurrence, extent of recurrent disease, baseline PHA, baseline subjective health
Table 22
Summary of models examining NKCC as a mediator between social support at baseline and physical health at 12 months controlling for baseline levels of NKCC and physical health.

<table>
<thead>
<tr>
<th>Path</th>
<th>Point Estimate</th>
<th>Bootstrap Standard Error</th>
<th>Bias Corrected Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>aSNI → NKCC (a)</td>
<td>-0.065</td>
<td>0.084</td>
<td>(-0.228, 0.103)</td>
</tr>
<tr>
<td>NKCC → Subjective Physical Health (b)</td>
<td>-0.053</td>
<td>0.061</td>
<td>(-0.180, 0.060)</td>
</tr>
<tr>
<td>SNI → Subjective Physical Health (Direct Effect)</td>
<td>-0.027</td>
<td>0.027</td>
<td>(-0.082, 0.026)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.004</td>
<td>0.008</td>
<td>(-0.004, 0.032)</td>
</tr>
<tr>
<td>aPSS-FA → NKCC (a)</td>
<td>-0.070</td>
<td>0.057</td>
<td>(-0.181, 0.043)</td>
</tr>
<tr>
<td>PHA → Subjective Physical Health (b)</td>
<td>-0.051</td>
<td>0.064</td>
<td>(-0.184, 0.071)</td>
</tr>
<tr>
<td>PSS-FA → Subjective Physical Health (Direct Effect)</td>
<td>-0.010</td>
<td>0.017</td>
<td>(-0.046, 0.023)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.004</td>
<td>0.007</td>
<td>(-0.003, 0.029)</td>
</tr>
<tr>
<td>bSNI → NKCC (a)</td>
<td>-0.057</td>
<td>0.085</td>
<td>(-0.227, 0.105)</td>
</tr>
<tr>
<td>NKCC → Objective Physical Health (b)</td>
<td>-0.032</td>
<td>0.062</td>
<td>(-0.162, 0.082)</td>
</tr>
<tr>
<td>SNI → Objective Physical Health (Direct Effect)</td>
<td>-0.013</td>
<td>0.027</td>
<td>(-0.065, 0.039)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.001</td>
<td>0.007</td>
<td>(-0.007, 0.023)</td>
</tr>
<tr>
<td>bPSS-FA → NKCC (a)</td>
<td>-0.065</td>
<td>0.056</td>
<td>(-0.176, 0.048)</td>
</tr>
<tr>
<td>PHA → Objective Physical Health (b)</td>
<td>-0.035</td>
<td>0.064</td>
<td>(-0.170, 0.082)</td>
</tr>
<tr>
<td>PSS-FA → Objective Physical Health (Direct Effect)</td>
<td>-0.005</td>
<td>0.017</td>
<td>(-0.039, 0.029)</td>
</tr>
<tr>
<td>Indirect Effect (ab)</td>
<td>0.002</td>
<td>0.006</td>
<td>(-0.005, 0.023)</td>
</tr>
</tbody>
</table>

Notes: * p<.05; a Model controls for: receipt of radiation at recurrence, baseline NKCC, baseline subjective health; b Model controls for: receipt of radiation at recurrence, extent of recurrent disease, baseline NKCC, baseline objective health.
Table 23
Application of the Cox Proportional Hazards Method examining structural support using extent of recurrent disease and receipt of hormonal treatment as covariates.

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>Wald Statistic</th>
<th>df</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural support (low vs. high)</td>
<td>-0.198</td>
<td>0.211</td>
<td>0.883</td>
<td>1</td>
<td>0.821</td>
<td>0.543 to 1.240</td>
<td>0.347</td>
</tr>
<tr>
<td>Extent of recurrent disease (loco/regional vs. distant)</td>
<td>-1.198</td>
<td>0.257</td>
<td>21.792</td>
<td>1</td>
<td>0.302</td>
<td>0.182 to 0.499</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Receipt of hormonal treatment (no vs. yes)</td>
<td>0.402</td>
<td>0.235</td>
<td>2.921</td>
<td>1</td>
<td>1.495</td>
<td>0.943 to 2.370</td>
<td>0.087</td>
</tr>
</tbody>
</table>

*Notes: * p<.05; Total number of events = 94; Reference groups: higher levels of support, distant disease and having received hormonal therapy
Table 24
Correlation between Schoenfeld residuals and rank time for the event of death for each covariate in the model examining structural support.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural support (low vs. high)</td>
<td>-0.223</td>
<td>0.280</td>
</tr>
<tr>
<td>Extent of recurrent disease</td>
<td>0.044</td>
<td>0.673</td>
</tr>
<tr>
<td>Receipt of Hormonal Treatment</td>
<td>-0.110</td>
<td>0.289</td>
</tr>
</tbody>
</table>

Notes: * p<.05
Table 25
Application of the Cox Proportional Hazards Method examining functional support using extent of recurrent disease and receipt of hormonal treatment as covariates.

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>Wald Statistic</th>
<th>df</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional Support (low vs. high)</td>
<td>-.239</td>
<td>0.216</td>
<td>1.225</td>
<td>1</td>
<td>0.788</td>
<td>0.516 to 1.202</td>
<td>0.268</td>
</tr>
<tr>
<td>Extent of recurrent disease (loco/regional vs. distant)</td>
<td>-1.088</td>
<td>0.255</td>
<td>18.160</td>
<td>1</td>
<td>0.337</td>
<td>0.204 to 0.556</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Receipt of hormonal treatment (no vs. yes)</td>
<td>0.412</td>
<td>0.234</td>
<td>3.102</td>
<td>1</td>
<td>1.509</td>
<td>0.955 to 1.287</td>
<td>0.078</td>
</tr>
</tbody>
</table>

* Notes: * p<.05; Total number of events = 95; Reference groups: higher levels of support, distant disease and having received hormonal therapy.
Table 26  
Correlation between Schoenfeld residuals and rank time for the event of death for each covariate in the model examining functional support.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional support (low vs. high)</td>
<td>0.018</td>
<td>0.863</td>
</tr>
<tr>
<td>Extent of recurrent disease</td>
<td>0.056</td>
<td>0.589</td>
</tr>
<tr>
<td>Receipt of Hormonal Therapy</td>
<td>0.030</td>
<td>0.775</td>
</tr>
</tbody>
</table>

Notes: * p<0.05
Table 27

*Correlation between biological and social support variables at baseline.*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cortisol</td>
<td>-----</td>
<td>-----</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Norepinephrine</td>
<td>0.104</td>
<td>-----</td>
<td>p=0.384</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. PHA</td>
<td>-0.009</td>
<td>-0.115</td>
<td>p=0.939</td>
<td>p=0.342</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. NKCC</td>
<td>0.172</td>
<td>0.179</td>
<td>0.005</td>
<td>p=0.157</td>
<td>p=0.143</td>
<td>p=0.967</td>
</tr>
<tr>
<td>5. PSS-FA</td>
<td>0.042</td>
<td>-0.005</td>
<td>-0.128</td>
<td>-0.021</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. SNI</td>
<td>-0.095</td>
<td>-0.161</td>
<td>-0.031</td>
<td>-0.091</td>
<td>0.532</td>
<td></td>
</tr>
</tbody>
</table>

*Notes: * p<.05, + p<.01*
Table 28

Required Sample Sizes for Mediation Analyses based on standardized path estimates using table from Fritz and Mackinnon (2007).

<table>
<thead>
<tr>
<th>Model</th>
<th>Standardized Point Estimate for a</th>
<th>Standardized Point Estimate for b</th>
<th>Approximate sample size necessary for $\beta=0.80$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediator: Psychological Distress</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS-FA $\rightarrow$ distress $\rightarrow$ subjective</td>
<td>-0.236</td>
<td>0.587</td>
<td>118</td>
</tr>
<tr>
<td>PSS-FA $\rightarrow$ distress $\rightarrow$ subjective (with baseline controls)</td>
<td>-0.117</td>
<td>0.468</td>
<td>400</td>
</tr>
<tr>
<td>SNI $\rightarrow$ distress $\rightarrow$ subjective</td>
<td>-0.369</td>
<td>0.589</td>
<td>53</td>
</tr>
<tr>
<td>SNI $\rightarrow$ distress $\rightarrow$ subjective (with baseline controls)</td>
<td>-0.213</td>
<td>0.470</td>
<td>115</td>
</tr>
<tr>
<td>PSS-FA $\rightarrow$ distress $\rightarrow$ objective</td>
<td>-0.240</td>
<td>0.511</td>
<td>118</td>
</tr>
<tr>
<td>PSS-FA $\rightarrow$ distress $\rightarrow$ objective (with baseline controls)</td>
<td>-0.116</td>
<td>0.361</td>
<td>400</td>
</tr>
<tr>
<td>SNI $\rightarrow$ distress $\rightarrow$ objective</td>
<td>-0.376</td>
<td>0.527</td>
<td>53</td>
</tr>
<tr>
<td>SNI $\rightarrow$ distress $\rightarrow$ objective (with baseline controls)</td>
<td>-0.227</td>
<td>0.373</td>
<td>115</td>
</tr>
<tr>
<td>Mediator: Cortisol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS-FA $\rightarrow$ cortisol $\rightarrow$ subjective</td>
<td>-0.027</td>
<td>-0.095</td>
<td>&gt;462</td>
</tr>
<tr>
<td>PSS-FA $\rightarrow$ cortisol $\rightarrow$ subjective (with baseline controls)</td>
<td>-0.031</td>
<td>-0.147</td>
<td>&gt;462</td>
</tr>
<tr>
<td>SNI $\rightarrow$ cortisol $\rightarrow$ subjective</td>
<td>-0.046</td>
<td>-0.102</td>
<td>&gt;462</td>
</tr>
<tr>
<td>SNI $\rightarrow$ cortisol $\rightarrow$ subjective (with baseline controls)</td>
<td>-0.031</td>
<td>-0.148</td>
<td>&gt;462</td>
</tr>
<tr>
<td>PSS-FA $\rightarrow$ cortisol $\rightarrow$ objective</td>
<td>-0.002</td>
<td>-0.140</td>
<td>&gt;462</td>
</tr>
<tr>
<td>PSS-FA $\rightarrow$ cortisol $\rightarrow$ objective (with baseline controls)</td>
<td>-0.007</td>
<td>-0.174</td>
<td>&gt;462</td>
</tr>
<tr>
<td>SNI $\rightarrow$ cortisol $\rightarrow$ objective</td>
<td>-0.046</td>
<td>-0.147</td>
<td>&gt;462</td>
</tr>
<tr>
<td>SNI $\rightarrow$ cortisol $\rightarrow$ objective (with baseline controls)</td>
<td>-0.029</td>
<td>-0.177</td>
<td>&gt;462</td>
</tr>
<tr>
<td>Mediator: Norepinephrine (NE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS-FA $\rightarrow$ NE $\rightarrow$ subjective</td>
<td>-0.159</td>
<td>-0.175</td>
<td>462</td>
</tr>
<tr>
<td>PSS-FA $\rightarrow$ NE $\rightarrow$ subjective (with baseline controls)</td>
<td>-0.145</td>
<td>-0.159</td>
<td>462</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Model</th>
<th>Standardized Point Estimate for ( a )</th>
<th>Standardized Point Estimate for ( b )</th>
<th>Approximate sample size necessary for ( \beta=0.80 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNI→NE→ subjective</td>
<td>0.102</td>
<td>-0.137</td>
<td>&gt;462</td>
</tr>
<tr>
<td>SNI→ NE→ subjective (with baseline controls)</td>
<td>0.164</td>
<td>-0.134</td>
<td>462</td>
</tr>
<tr>
<td>PSS-FA → NE→ objective</td>
<td>-0.160</td>
<td>-0.094</td>
<td>&gt;462</td>
</tr>
<tr>
<td>PSS-FA → NE→ objective (with baseline controls)</td>
<td>-0.133</td>
<td>-0.094</td>
<td>&gt;462</td>
</tr>
<tr>
<td>SNI→ NE→ objective</td>
<td>0.119</td>
<td>-0.066</td>
<td>&gt; 462</td>
</tr>
<tr>
<td>SNI→NE→ objective (with baseline controls)</td>
<td>0.202</td>
<td>-0.080</td>
<td>&gt;368</td>
</tr>
</tbody>
</table>

**Mediator: Blastogenic response to phytohemagglutinin (PHA)**

<table>
<thead>
<tr>
<th>Model</th>
<th>Standardized Point Estimate for ( a )</th>
<th>Standardized Point Estimate for ( b )</th>
<th>Approximate sample size necessary for ( \beta=0.80 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSS-FA → PHA → subjective</td>
<td>0.140</td>
<td>0.310</td>
<td>400</td>
</tr>
<tr>
<td>PSS-FA → PHA → subjective (with baseline controls)</td>
<td>0.232</td>
<td>0.155</td>
<td>368</td>
</tr>
<tr>
<td>SNI→ PHA → subjective</td>
<td>0.022</td>
<td>0.289</td>
<td>&gt;377</td>
</tr>
<tr>
<td>SNI → PHA → subjective (with baseline controls)</td>
<td>0.084</td>
<td>0.149</td>
<td>&gt;462</td>
</tr>
<tr>
<td>PSS-FA → PHA→ objective</td>
<td>0.112</td>
<td>0.136</td>
<td>&gt;462</td>
</tr>
<tr>
<td>PSS-FA → PHA→ objective (with baseline controls)</td>
<td>0.198</td>
<td>0.014</td>
<td>&gt;462</td>
</tr>
<tr>
<td>SNI → PHA → objective</td>
<td>0.039</td>
<td>0.262</td>
<td>&gt;377</td>
</tr>
<tr>
<td>SNI → PHA → objective (with baseline controls)</td>
<td>0.095</td>
<td>0.019</td>
<td>&gt;462</td>
</tr>
</tbody>
</table>

**Mediator: Natural Killer Cell Cytotoxicity (NKCC)**

<table>
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<tr>
<th>Model</th>
<th>Standardized Point Estimate for ( a )</th>
<th>Standardized Point Estimate for ( b )</th>
<th>Approximate sample size necessary for ( \beta=0.80 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSS-FA → NKCC → subjective</td>
<td>-0.183</td>
<td>-0.175</td>
<td>462</td>
</tr>
<tr>
<td>PSS-FA → NKCC →subjective (with baseline controls)</td>
<td>-0.206</td>
<td>-0.101</td>
<td>368</td>
</tr>
<tr>
<td>SNI→ NKCC → subjective</td>
<td>-0.109</td>
<td>-0.173</td>
<td>462</td>
</tr>
<tr>
<td>SNI→ NKCC → subjective (with baseline controls)</td>
<td>-0.135</td>
<td>-0.107</td>
<td>&gt;462</td>
</tr>
<tr>
<td>PSS-FA → NKCC → objective</td>
<td>-0.119</td>
<td>-0.092</td>
<td>&gt;462</td>
</tr>
<tr>
<td>PSS-FA → NKCC→objective (with baseline controls)</td>
<td>-0.192</td>
<td>-0.066</td>
<td>&gt;462</td>
</tr>
<tr>
<td>SNI→NKCC→ objective</td>
<td>-0.115</td>
<td>-0.085</td>
<td>&gt;462</td>
</tr>
<tr>
<td>SNI→ NKCC → objective (with baseline controls)</td>
<td>-0.119</td>
<td>-0.061</td>
<td>&gt;462</td>
</tr>
</tbody>
</table>
Appendix B: Figures
Figure 1. Theoretical framework depicting the link between social support and physical health and the processes by which social support and health are hypothesized to be related.

a. *Aim1: Social support predicts physical health outcomes*
b. **Aims 2 and 4: Psychological Distress**

- **Psychological Distress**
  - 4 months
  - (e.g., depressive symptoms, mood disturbance, mental health-related quality of life)

- **Social Support**
  - Baseline
  - Structural or Functional

- **Physical Health Outcomes**
  - 12 months
  - (e.g., self- and nurse-reported)

---

Continued
c. **Aims 3 and 5: Neuroendocrine and Immune Variables**

Figure 1. Continued
Figure 2. Participant assessment status at each study time point.

Baseline
Total completed (120/122)

Dropped: 0
Non-compliant: 2
Terminated: 0

4 months
Total completed (98/111)

Dropped: 5
Non-compliant: 13
Terminated: 6

12 months
Total completed (82/88)

Dropped: 6
Non-compliant: 6
Terminated: 17
Figure 3. Models examining psychological distress as a mediator between social support following recurrence and physical health at 12 months (B, Bootstrap Standard Error). Note: * p<.05.

a)

Distress Composite (4 months)

-0.098 (0.031)*

SNI (Baseline)

0.005 (0.027)

Subjective Physical Health (12 months)

0.524 (0.102)*

ab path: -0.052 (0.020)*

b)

Distress Composite (4 months)

-0.100 (0.032)*

SNI (Baseline)

0.018 (0.027)

Objective Physical Health (12 months)

0.504 (0.096)*

ab path: -0.051 (0.019)*

Continued
Figure 3. Continued

c)

Distress Composite (4 months)

-0.046 (0.022)*

PSS-FA (Baseline)

0.004 (0.018)

Subjective Physical Health (12 months)

0.512 (0.101)*

ab path: -0.023 (0.012)*

d)

Distress Composite (4 months)

-0.046 (0.022)*

PSS-FA (Baseline)

0.007 (0.019)

Objective Physical Health (12 months)

0.489 (0.095)*

ab path: -0.022 (0.011)*
Figure 4. Models examining psychological distress as a mediator between social support following recurrence and physical health at 12 months after controlling for baseline levels of distress and physical health (B, Bootstrap Standard Error). Note: * p<.05.

a) 

```
Distress Composite (4 months) | 0.004 (0.025)  
SNI (Baseline) --|-- Subjective Physical Health (12 months)
-0.057 (0.024)*  
```

ab path: -0.024 (0.014)*

b) 

```
Distress Composite (4 months) | 0.014 (0.025)  
SNI (Baseline) --|-- Objective Physical Health (12 months)
-0.061 (0.024)*  
```

ab path: -0.022 (0.014)*

Continued

162
Figure 4. Continued

c)

Dotted lines indicate significant pathways.

\[ \text{Distress Composite (4 months)} \]
\[ \text{PSS-FA (Baseline)} \]
\[ 0.005 (0.017) \]
\[ \text{Subjective Physical Health (12 months)} \]
\[ 0.417 (0.145)^* \]
\[ -0.022 (0.016) \]
\[ \text{ab path: } -0.009 (0.008) \]

d)

Dotted lines indicate significant pathways.

\[ \text{Distress Composite (4 months)} \]
\[ \text{PSS-FA (Baseline)} \]
\[ 0.008 (0.016) \]
\[ \text{Objective Physical Health (12 months)} \]
\[ 0.346 (0.137)^* \]
\[ -0.022 (0.017) \]
\[ \text{ab path: } -0.008 (0.007) \]
Figure 5. Models examining cortisol as a mediator between social support following recurrence and physical health at 12 months (B, Bootstrap Standard Error). Note: * p<.05.

a) Cortisol (4 months)

SNI (Baseline) → Cortisol (4 months) → Subjective Physical Health (12 months)

ab path: 0.001 (0.007)

b) Cortisol (4 months)

SNI (Baseline) → Cortisol (4 months) → Objective Physical Health (12 months)

ab path: 0.001 (0.008)

Continued
Figure 5. Continued

c) 

\[ \text{Cortisol (4 months)} \]
\[ \text{PSS-FA (Baseline)} \] 
\[ \text{Subjective Physical Health (12 months)} \]

-0.021 (0.119) 
-0.016 (0.029) 
-0.022 (0.020)

ab path: 0.0006 (0.004)

d) 

\[ \text{Cortisol (4 months)} \]
\[ \text{PSS-FA (Baseline)} \] 
\[ \text{Objective Physical Health (12 months)} \]

-0.006 (0.118) 
-0.030 (0.032) 
-0.015 (0.019)

ab path: -0.0002 (0.005)
Figure 6. Models examining norepinephrine as a mediator between social support following recurrence and physical health at 12 months (B, Bootstrap Standard Error). Note: * p<.05.

a)

Norepinephrine (4 months)  
SNI (Baseline)  
Subjective Physical Health (12 months)

-0.0005 (0.0006)  
-0.047 (0.030)

ab path: -0.003 (0.007)

b)

Norepinephrine (4 months)  
SNI (Baseline)  
Objective Physical Health (12 month)

-0.0003 (0.0006)  
-0.030 (0.029)

ab path: -0.003 (0.008)

Continued
Figure 6. Continued

c) Norepinephrine (4 months)

PSS-FA (Baseline) → Subjective Physical Health (12 months)

-6.699 (6.025) → -0.025 (0.020)

ab path: 0.005 (0.007)

d) Norepinephrine (4 months)

PSS-FA (Baseline) → Objective Physical Health (12 month)

-6.731 (5.995) → -0.019 (0.020)

ab path: 0.002 (0.006)
Figure 7. Models Examining PHA as a mediator between social support following recurrence and physical health at 12 months (β, Bootstrap Standard Error). Note: * p<.05.

a)

Subjective Physical Health (12 months)

SNI (Baseline)

-0.047 (0.030)

PHA (4 months)

0.007 (0.049)

0.215 (0.114)

ab path: 0.002 (0.012)

b)

Objective Physical Health (12 months)

SNI (Baseline)

-0.035 (0.029)

PHA (4 months)

0.012 (0.049)

0.210 (0.105)

ab path: 0.003 (0.011)

Continued
Figure 7. Continued

(c) PHA (4 months)

0.032 (0.037)  

PSS-FA (Baseline) 

Subjective Physical Health (12 months)

-0.030 (0.022)

ab path: 0.008 (0.010)

(d) PHA (4 months)

0.025 (0.037)  

PSS-FA (Baseline) 

Objective Physical Health (12 months)

-0.023 (0.019)

ab path: 0.006 (0.009)
Figure 8. Models examining NKCC as a mediator between social support following recurrence and physical health at 12 months (B, Bootstrap Standard Error). Note: * p<.05.

a)

b)

Continued
Figure 8. Continued

c)

\[ \text{NKCC (4 months)} \]

\[ \text{Subjective Physical Health (12 months)} \]

\[ \text{PSS-FA (Baseline)} \]

\(-0.062 (0.058)\)

\(-0.087 (0.074)\)

\(-0.025 (0.020)\)

ab path: 0.006 (0.008)

d)

\[ \text{NKCC (4 months)} \]

\[ \text{Objective Physical Health (12 month)} \]

\[ \text{PSS-FA (Baseline)} \]

\(-0.063 (0.057)\)

\(-0.049 (0.080)\)

\(-0.019 (0.020)\)

ab path: 0.002 (0.007)
Figure 9. Models examining cortisol as a mediator between social support following recurrence and physical health at 12 months controlling for baseline cortisol and physical health (B, Bootstrap Standard Error). Note: * p<.05.

a)  
- Cortisol (4 months)  
  -0.048 (0.187)  
- SNI (Baseline)  
  -0.020 (0.025)  
- Subjective Physical Health (12 months)  
  -0.028 (0.024)  
ab path: 0.001 (0.007)

b)  
- Cortisol (4 months)  
  -0.036 (0.181)  
- SNI (Baseline)  
  -0.011 (0.025)  
- Objective Physical Health (12 months)  
  -0.037 (0.023)  
ab path: 0.001 (0.008)  

Continued
Figure 9. Continued

c)  

![Diagram c)](attachment:diagram.png)

-0.023 (0.117)  
-0.027 (0.024)  
-0.011 (0.018)  

ab path: 0.0004 (0.005)

d)  

![Diagram d)](attachment:diagram.png)

-0.009 (0.116)  
-0.037 (0.023)  
-0.003 (0.017)  

ab path: 0.0004 (0.005)
Figure 10. Models examining norepinephrine as a mediator between social support following recurrence and physical health at 12 months controlling for baseline norepinephrine and physical health (B, Bootstrap Standard Error). Note: * p<.05.

a)

![Diagram a]

- Norepinephrine (4 months)
- SNI (Baseline)
- Subjective Physical Health (12 months)

b)

![Diagram b]

- Norepinephrine (4 months)
- SNI (Baseline)
- Objective Physical Health (12 months)

ab path: -0.005 (0.009)

Continued
Figure 10. Continued

c) Norepinephrine (4 months)

-6.114 (5.925)

PSS-FA (Baseline)

-0.012 (0.018)

Subjective Physical Health (12 months)

-0.0006 (0.0006)

ab path: 0.004 (0.006)

d) Norepinephrine (4 months)

-5.499 (5.847)

PSS-FA (Baseline)

-0.004 (0.017)

Objective Physical Health (12 months)

-0.0004 (0.0006)

ab path: 0.002 (0.005)
Figure 11. Models examining PHA as a mediator between social support following recurrence and physical health at 12 months controlling for baseline PHA and physical health (B, Bootstrap Standard Error). Note: * p<.05.

a)

```
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<th>PHA</th>
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<tbody>
<tr>
<td></td>
<td>(4 months)</td>
</tr>
<tr>
<td></td>
<td>0.027 (0.048)</td>
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<tr>
<td>SNI (Baseline)</td>
<td>0.111 (0.109)</td>
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<tr>
<td></td>
<td>-0.020 (0.027)</td>
</tr>
<tr>
<td>Subjective Physical Health (12 months)</td>
<td></td>
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</table>

ab path: 0.003 (0.008)
```

b)

```
<table>
<thead>
<tr>
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<th>PHA</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(4 months)</td>
</tr>
<tr>
<td></td>
<td>0.030 (0.047)</td>
</tr>
<tr>
<td>SNI (Baseline)</td>
<td>0.015 (0.106)</td>
</tr>
<tr>
<td></td>
<td>-0.013 (0.027)</td>
</tr>
<tr>
<td>Objective Physical Health (12 month)</td>
<td></td>
</tr>
</tbody>
</table>

ab path: 0.0008 (0.006)
```

Continued
Figure 11. Continued

c)

![Diagram c)](image)

Subjective Physical Health (12 months) = 0.008 (0.020) - PSS-FA (Baseline) - 0.006 (0.009)

Objective Physical Health (12 months) = 0.045 (0.034) + PSS-FA (Baseline) + 0.003 (0.018)

PSS-FA (Baseline) = -0.008 (0.020) + PHA (4 months) - 0.006 (0.009)

PHA (4 months) = 0.052 (0.036) + Subjective Physical Health (12 months) + 0.001 (0.006)

0.116 (0.115) = 0.011 (0.108) + Objective Physical Health (12 month) + 0.001 (0.006)

d)

Subjective Physical Health (12 months) = 0.008 (0.020) - PSS-FA (Baseline) - 0.006 (0.009)

Objective Physical Health (12 months) = 0.045 (0.034) + PSS-FA (Baseline) + 0.003 (0.018)

PSS-FA (Baseline) = -0.008 (0.020) + PHA (4 months) - 0.006 (0.009)

PHA (4 months) = 0.052 (0.036) + Subjective Physical Health (12 months) + 0.001 (0.006)

0.116 (0.115) = 0.011 (0.108) + Objective Physical Health (12 month) + 0.001 (0.006)
Figure 12. Models examining NKCC as a mediator between social support following recurrence and physical health at 12 months controlling for baseline NKCC and physical health (B, Bootstrap Standard Error). Note: * p<.05.

a)

NKCC (4 months)

SNI (Baseline)

Subjective Physical Health (12 months)

-0.065 (0.084)

-0.027 (0.027)

ab path: 0.004 (0.008)

b)

NKCC (4 months)

SNI (Baseline)

Objective Physical Health (12 month)

-0.057 (0.084)

-0.013 (0.026)

ab path: 0.001 (0.007)

Continued
Figure 12. Continued

c)

PSS-FA (Baseline) → NKCC (4 months) → Subjective Physical Health (12 months)

ab path: 0.004 (0.007)

-0.070 (0.057) → -0.051 (0.064)

0.010 (0.017)

d)

PSS-FA (Baseline) → NKCC (4 months) → Objective Physical Health (12 months)

ab path: 0.002 (0.006)

-0.065 (0.056) → -0.035 (0.064)

-0.005 (0.017)
Figure 13. Graph of the survival functions for the event of death comparing those with high levels of structural support (green line) to those with low levels of structural support (blue line) following recurrence. Total number of events: 94.
Figure 14. Graph of the survival functions for the event of death comparing those with high levels of functional support (green line) to those with low levels of functional support (blue line) following recurrence. Total number of events: 95.
Figure 15. Graph of the survival functions from the Cox Proportional Hazards Model for the event of death comparing those reporting high levels of structural support (green line) with those reporting low levels of structural support (blue line). Total number of events: 94.
Figure 16. Graph of the survival functions from the Cox Proportional Hazards Model for the event of death comparing those reporting high levels of functional support (green line) with those reporting low levels of functional support (blue line). Total number of events: 95.
Figure 17. Empirical estimates of sample sizes needed for 0.8 power obtained from Fritz & MacKinnon (2007)

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<th>Test</th>
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<th>SM</th>
<th>SL</th>
<th>HS</th>
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<td>BK (c' = .59)</td>
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<tr>
<td>Bias-corrected bootstrap</td>
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<td>385</td>
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<td>71</td>
<td>53</td>
<td>396</td>
<td>115</td>
<td>54</td>
<td>34</td>
</tr>
</tbody>
</table>

Note. All sample sizes have been rounded up to the next whole number. In the condition labels, the first letter refers to the size of the α path, and the second letter refers to the size of the β path; S = 0.14, H = 0.26, M = 0.39, and L = 0.59 (e.g., condition SM is the condition with α = 0.14 and β = 0.39). All results, except for those for Baron and Kenny’s (1986) test (BK), have been collapsed across r' conditions.