An Integrative Healthcare Program for Cancer Patients:

Longitudinal Effects on Emotional Health and Immune Function

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ABSTRACT

Evidence supports potential short-term benefits of integrative healthcare (IH) for cancer patients, which combines conventional Western medicine with adjunctive, complementary treatments; however, the long-term efficacy of IH has not been systematically studied. The current study examined the short- and long-term effectiveness of IH for cancer patients, relative to treatment as usual (TAU), in improving emotional and immune health. Also examined were systematic differences at baseline (i.e., emotional distress, sociodemographic and cancer variables) associated with IH usage. Patients were recruited from a University Medical Center (n = 178) and were eligible to participate irrespective of cancer diagnosis and stage. Patients opted to continue TAU or engage in an IH program. Patients were assessed at three intervals (baseline, 3-month and 12-month follow-up). A subset of the sample (29%; n = 52) was randomized to a blood draw condition. Forty percent of the sample utilized IH services between baseline and 12-month follow-up. Logistic regression analyses revealed patients utilizing IH services (0 = no usage; 1 = 1+ times) presented with higher baseline depression and anxiety. Improvements in health-related quality of life (HRQOL) were evidenced at T2 for IH participants, but were not maintained at T3. Exploratory analyses at T2 revealed psychotherapy contributes to greater reductions in depression and anxiety scores, relative to other services (i.e., massage and acupuncture). Overall, findings offer preliminary but limited support for short-term benefits of IH in improving HRQOL and suggest that integrating psychotherapy and IH may be worth further consideration for mitigating depression and anxiety in cancer patients.

TABLE OF CONTENTS

LIST OF TABLES

TABLE **PAGE**

CHAPTER 1

INTRODUCTION

Depression has been consistently linked to poorer outcomes for cancer patients, and treatment outcome studies have begun to explore the effectiveness of psychosocial interventions for cancer patients, with neuroendocrine and immune mechanisms proposed as potential mechanisms of change for these interventions (Subnis, Starkweather, McCain, & Brown, 2014). The study of these relations in complementary and alternative medicine (CAM) modalities of care for cancer patients is relatively limited, with evidence emerging to suggest the short-term effectiveness of these adjunctive treatments (Baker et al., 2012; Helyer et al., 2006) but lacking in regards to the long-term efficacy of such treatment programs (Barnett & Shale, 2012). This study constitutes a pilot study that aims to determine the long-term effectiveness (i.e., baseline to one-year follow-up) of an integrative healthcare program in improving outcomes for cancer patients, as well as factors associated with integrative healthcare usage in cancer patients across the cancer care continuum.

Depression and inflammation

Depression is the most common psychiatric disorder among cancer patients, with prevalence rates ranging from 10-50% and the highest rates occurring among those diagnosed with pancreatic, oropharyngeal, breast, and lung cancers (Massie, 2004; McDaniel, Musselman, & Nemeroff, 1997; Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008). Depression can be as debilitating as the physical effects of cancer and negatively affects treatment adherence and quality of life (Knopf & Head, 2012; Miller et al., 2008). Moreover, depression is thought to be independently predictive of cancer outcomes, including mortality or low survival rates (Lloyd-Williams, Shiels, Taylor, & Dennis, 2009; Pinquart & Duberstein, 2010; Satin, Linden, &

Philips, 2009). A meta-analysis conducted by Satin et al. (2009) found increased mortality rates among depressed cancer patients, such that mortality was up to 29% higher in patients endorsing depressive symptoms and up to 39% higher among those with a diagnosis of clinical depression, highlighting the detrimental effects of depression on outcomes, particularly if left unaddressed or untreated.

Research strongly supports the notion that cancer patients experience significant cancer-related distress, depression, anxiety, and stress (Croyle & Rowland, 2003; Fann et al., 2008; Massie, 2004), in the first year following their cancer diagnosis (Burgess et al., 2005; Rowland, 1999) and throughout the course of treatment into long-term survivorship (Stanton, Rowland, & Ganz, 2015). Functional impairment is also evident in many cancer patients in several areas, including poorer physical health, increased substance use, and reduced quality of life in areas such as physical/recreational activities, sleep, self-care, interpersonal relationships, and sexual functioning (Burgess et al., 2005; Ciaramella & Poli, 2001; Evans et al., 2005; Fortner, Stepanski, Wang, Kasprowicz, & Durrence, 2002; Lundberg & Passik, 1997). Evidence is accumulating to suggest that depressed and anxious cancer patients experience decreased immune system functioning, more rapid progression of cancer, increased pain, and possibly increased mortality relative to non-depressed patients (Ciaramella & Poli, 2001; Glover et al., 1995; Reddick, Nanda, Campbell, Ryman, & Gaston-Johansson, 2005; Pinquart & Duberstein, 2010; Spiegel & Giese-Davis, 2003). Several pathophysiological mechanisms are thought to underlie the relationship between depression and cancer outcomes, including survival rates, with one of the primary mechanisms of focus being depressogenic effects on cellular immunity.

The close association between cancer and depression is due, in part, to the activation of immuno-inflammatory systems and dysregulation of the hypothalamic-pituitary-adrenal (HPA)

axis (Belmaker & Agam, 2008; Lutgendorf, Sood, & Antoni, 2010). More specifically, depression is thought to down-regulate or impair the immune system, largely via adrenergic and glucocorticoid signaling pathways, and is associated with increased pro-inflammatory cytokine production (Lutgendorf et al., 2010; Miller, Maletic, & Raison, 2009). The stimulation of pro-inflammatory cytokines is a stress response secondary to and triggered by activation of the autonomic nervous system and HPA axis (Lutgendorf et al., 2010), and chronically high levels of circulating pro-inflammatory cytokines have been linked to severe depression (Howren, Lamkin, & Suls, 2009; Raison, Capuron, & Miller, 2006). Depression appears to promote tumor recurrence and progression by suppressing immunity and altering the balance of pro-inflammatory (T-helper 1; TH1) to anti-inflammatory (T-helper 2; TH2) cytokines. This cytokine imbalance creates a tumor microenvironment favoring immunosuppression, angiogenesis (development of tumor vasculature), and cancer cell growth (Lutgendorf et al., 2010; Miller et al., 2009).

In particular, interleukin-6 (IL-6), a pro-inflammatory (TH1) cytokine that acts in synergy with other signaling proteins (e.g., IL-1 and tumor necrosis factor-alpha [TNF-α]), is regarded as an especially important prognostic indicator in cancer patients (Howren et al., 2009; Musselman et al., 2001). IL-6 is one of the most dysregulated cytokines in cancer patients, with high levels predictive of mortality (Seruga, Zhang, Bernstein, & Tannock, 2008) and demonstrating involvement in angiogenesis (Lutgendorf et al., 2010). Clinically depressed cancer patients have significantly higher levels of IL-6 than non-depressed cancer patients and healthy controls (Musselman et al., 2001; Seruga et al., 2008). However, there is relatively limited research comparing cytokine levels in depressed and non-depressed cancer patients to other medically ill populations and healthy controls (Miller et al., 2008), and longitudinal

research examining and more clearly delineating cytokine profiles of these groups throughout treatment and across various disease types and stages is greatly needed.

Howren, Lamkin, & Suls (2009) conducted a quantitative review of the literature that showed IL-6, C-reactive protein (CRP), and IL-1 (to a lesser extent), as positively associated with depression in both clinic- and community-based samples. IL-6 and IL-1 are precursors to CRP, stimulating its production in the liver through the activation of enzymes (Heikkila, Ebrahim, Rumley, Lowe, & Lawlor, 2007). CRP is a non-specific protein and highly sensitive marker of systemic inflammation that has been consistently linked to increased risk for cardiac disease (Howren et al., 2009) and has only recently begun to be explored in relation to cancer outcomes (Heikkila et al., 2007). A study by Heikkila et al. (2007) found elevated levels of circulating CRP and IL-6 to be associated with increased mortality in elderly women with and without cancer, suggesting that these biomarkers may be related to more general comorbidities (e.g., lifestyle, sociodemographic factors, etc.) than to cancer malignancy specifically. In a recent meta-analysis, CRP was found to correlate more strongly with depression, as compared to IL-6, and was theorized to represent more broadly the cumulative effects of a range of inflammatory proteins (Valkanova, Ebmeier, & Allen, 2013). Although relatively few studies have examined CRP and IL-6 simultaneously in the same sample, both of these inflammatory markers are strongly associated with one another (Valkanova et al., 2013), with IL-6 having an established relation to immune functioning in cancer populations (Musselman et al., 2001), despite its lower association with depression across broader community-based samples. As such, studying these biomarkers (CRP and IL-6) in conjunction in the same sample may serve to capture broader and more specific effects on inflammatory processes.

Inflammation is regarded as a key biological mechanism in physical health decline in general and is considered a prognostic indicator of a host of systemic diseases and chronic illnesses (Kiecolt-Glaser, 2010; Miller et al., 2008). It is important to note that inflammation itself is known to produce "sickness behavior" (e.g., pain, fatigue, sleep disturbance) and other behavioral alterations in healthy individuals, cancer patients, and other medically ill patients alike (Ahles & Saykin, 2007; Cleeland, Bennett, & Dantzer, 2003), indicating a complex, bidirectional relationship between inflammation and depression. This bi-directionality is widely acknowledged and is such that: depression triggers inflammatory responses and inflammation triggers behavioral change and depressive symptoms, also referred to as inflammation-based depression (Kiecolt-Glaser, Derry, & Fagundes, 2015; Miller et al., 2008). Both increased pro-inflammatory (TH1) cytokine production and depression severity have been linked to multiple behavioral comorbidities and negative consequences for cancer patients, including increased pain, fatigue, cognitive impairment, drug toxicity and resistance, and tumor malignancy (Lutgendorf et al., 2010; Seruga et al., 2008; Spiegel & Giese-Davis, 2003). Depression itself is associated and often comorbid with a host of health-risk behaviors, such as sleep and appetite disturbances, reduced physical activity (i.e., behavioral deactivation), increased alcohol use, and smoking, all of which have been linked to increased inflammation (Kiecolt-Glaser et al., 2015). For example, sedentary behavior, sleep loss, and diets high in saturated fats have been associated with high levels of circulating pro-inflammatory cytokines (e.g., CRP and Interleukin-6), whereas healthier behaviors (e.g., increased exercise, diets high in fruits and vegetables, and moderate alcohol intake) have been associated with lower levels of inflammatory biomarkers (Kiecolt-Glaser et al., 2015; O'Connor et al., 2009).

In addition, cancer treatment (e.g., chemotherapy, radiation, immunotherapy, hormone therapy, surgery, etc.) activates an immune response and alters the tumor microenvironment, stimulating the production of pro-inflammatory cytokines and producing toxic treatment effects and behavioral comorbidities, such as nausea, fatigue, and depressed mood (Bower et al., 2011; Miller et al., 2008; Seruga et al., 2008; Sridharan & Schoenfeld, 2015). For example, interferon (IFN)-alpha treatment is associated with a high rate of depression, with 30-45% of patients receiving IFN-alpha being diagnosed with depression during the course of immunotherapy (Capuron & Miller, 2004). IFN-alpha is a cytokine with anti-viral properties often delivered as a treatment for cancer and infectious diseases, which effectively highlights another mechanism by which cytokines may induce depression and behavioral changes – specifically, via effects on regional brain activity (Miller et al., 2008). IFN-alpha has been shown to increase blood flow in the dorsal region of the anterior cingulate cortex (dACC), a brain region thought to play an important role in vigilance, with increased activity in this region associated with elevated risk for anxiety and mood disorders ((Miller et al., 2008). Cytokines, such as IL-6 and IFN-alpha, are also thought to affect the synthesis and reuptake of neurotransmitters, such as serotonin, known to play a role in the development of depression (Miller et al., 2008).

In summary, complex bidirectional relationships exist between inflammation and depression, such that elevations in pro-inflammatory cytokines trigger depressive symptoms, and vice versa (i.e., depression increases pro-inflammatory cytokine production), and each induces behavioral changes, or "sickness behaviors" (e.g., behavioral deactivation, appetite disturbance), that in turn cycle back and exert effects on mood and inflammation. There exists a complex constellation of neuroendocrine and immune mechanisms involved in the development and maintenance of depression. For cancer patients, this constellation of interactions is further

complicated by the fact that cancer treatment itself induces inflammation, and thereby depression. Whereas cytokine antagonists, antidepressants, and other anti-inflammatory agents are often employed to curb depressive and other behavioral symptoms (Cleeland et al., 2003; Miller et al., 2008), research on behavioral interventions and its effect on neuroendocrine-immune functioning in cancer patients is in its infancy (Subnis et al., 2011). Although pharmacological interventions are often employed to reduce circulating cytokines in clinically depressed patients (Croyle & Rowland, 2003), pharmacological treatment is generally less effective if psychosocial support is not provided (Knopf & Head, 2012).

Psychosocial interventions

Given the prevalence and impact of depression, anxiety, and chronic stress in cancer patients, the importance of developing and evaluating psychosocial interventions for this population has been highlighted as a pressing need (Fann et al., 2008; Spiegel & Giese-Davis, 2003). The field of behavioral health is poised to make a meaningful contribution to cancer care and mortality via interventions aimed at treating and ameliorating depression, anxiety, and overall emotional distress in this population. In fact, the Institute of Medicine (IOM) indicated psychosocial therapies as essential for patients across the cancer care continuum, including patients of all cancer types and stages, such as late-stage cancers and cancer survivors (Adler & Page, 2008).

There is substantial evidence for the efficacy of psychotherapy in alleviating depression, anxiety, and cancer-specific distress (Costanzo et al., 2011), with multiple meta-analyses confirming the benefits of psychotherapeutic interventions for cancer patients (DiStasio, 2008; Lepore & Coyne, 2006; Lin et al., 2011; Meyer & Mark, 1995; Newell, Sanson-Fisher, & Savolainen, 2002; Sheard & Maguire, 1999; Williams & Dale, 2006). Many studies have found

behavioral interventions, delivered in individual and group formats, to be effective in reducing distress and symptoms of depression, anxiety, pain, and cancer-related fatigue and in improving quality of life and social functioning in cancer patients (Fann et al., 2008; Goodwin et al., 2001; Kissane et al., 2007; Moorey, Greer, Bliss, & Law, 1998; Rehse & Pukrop, 2003; Stanton et al., 2015; Williams & Dale, 2006). However, there also are studies where psychosocial interventions have had only minimal or mixed effects in reducing distress and improving outcomes, such as survival rates, for cancer patients (Antoni et al., 2013; Cunningham et al., 1998; Goodwin et al., 2001; Kissane et al., 2007; Coyne, Lepore, & Palmer, 2006; Mustafa, Carson-Stevens, Gillespie, & Edwards, 2013).

Given the mixed results of treatment outcome studies, at present the general consensus is that some psychosocial interventions, such as cognitive-behavioral therapy, mindfulness-based stress reduction, behavioral activation, problem-solving therapy, and supportive-expressive group therapy, may be effective in reducing depression and anxiety in cancer patients (Fann et al., 2008; Hopko et al., 2011; Hopko, Lejuez, Ryba, Shorter, & Bell, 2016; Williams & Dale, 2006; Newell et al., 2002). However, significant methodological limitations have been indicated in treatment outcome research with cancer patients, including small sample sizes and relatively short follow-up windows (less than 6-months), making it difficult to evaluate the long-term effectiveness of many interventions (Newell et al., 2002). Given the limits of treatment outcome research to date and the prevalence and impact of emotional health issues in the cancer population, studies examining the efficacy of novel treatment approaches for cancer patients are of pressing need.

Complementary Health Approaches

Among novel treatments developed to ameliorate the psychosocial impact of cancer is integrative healthcare (IH), which combines conventional Western medicine with adjunctive, complementary treatments (Deng & Cassileth, 2005a). Within the past two decades, there has been a growing interest among cancer patients and survivors in the use of complementary and alternative medicine (CAM) treatments as adjuvants to standard care to reduce the burden and stress of cancer diagnosis and treatment (Buettner et al., 2006; Cassileth & Chapman, 1996; Fouladbakhsh & Sommel, 2010; Williams & Dale, 2006). CAM is used by up to 80% of cancer patients (Deng & Cassileth, 2005b; Helyer et al., 2006), with estimates varying broadly, in part due to lacking and varying definitions of CAM (Deng & Cassileth, 2005b). The National Center for Complementary and Integrative Health (NCCIH) defines CAM, or "complementary health approaches," as a diverse group of practices and natural products used in conjunction with conventional medicine, whereas the term 'integrative health' denotes the incorporation of complementary approaches into mainstream care (NCCIH, 2016). A recent study found CAM usage to be more prevalent among cancer survivors, irrespective of duration of survivorship, as compared to the general U.S. population (Fouladbakhsh & Stommel, 2008). While the prevalence of CAM services has grown among cancer populations (Fouladbakhsh & Stommel, 2010; Tindle, Davis, Phillips, & Eisenberg, 2005), factors influencing use have not been thoroughly examined (Fouladbakhsh & Stommel, 2008; Yates et al., 2005).

Gender is known to be a particularly strong determinant of CAM usage in the general population in the United States (Barnes, Powell-Griner, McFann, & Nahin, 2004). Women are more likely to use CAM services than men, with recent studies suggesting that this trend is consistent among cancer, as well as non-cancer, populations (Fouladbakhsh & Stommel, 2008,

2010; Yates et al., 2005). Patterns of usage differ slightly by gender, with women having a stronger preference for mind-body practices, such as meditation, relaxation, guided imagery, and yoga, as compared to men (Fouladbakhsh & Stommel, 2008, 2010). This gender disparity is not altogether dissimilar to patterns of use observed in other psychosocial treatment modalities (Rehse & Pukrop, 2003), and has been posited as a reflection of the tendency of women to be more involved in self-care (Fouladbakhsh & Stommel, 2008, 2010). A similarity among men and women in patterns of use appears in their preference for low- or no-cost services (Fouladbakhsh & Sommel, 2010).

There is lesser consensus regarding the influence of other sociodemographic factors (e.g., race/ethnicity, age, socioeconomic status, education level, etc.) on CAM usage, when compared with the wealth of support for gender as a strong correlate of use (Barnes et al., 2005; Fouladbakhsh, Stommel, Given, & Given, 2005). However, some studies have cited White (non-Hispanic) individuals and those of younger age, and of higher income and education as the most common consumers of CAM services in cancer and non-cancer populations alike (Deng & Cassileth, 2005b; Eisenberg et al., 1998; Fouladbakhsh & Stommel, 2008, 2010; Helyer et al., 2006; Rakovitch et al., 2005; Tindle et al., 2005). With regard to race/ethnicity, a national survey of CAM usage in the United States found that Black and Asian adults may be among the highest consumers of CAM services in the general population (Barnes et al., 2004). Similarly, some studies have not found support for race/ethnicity as a predictor of CAM usage in a cancer population (Fouladbakhsh et al., 2005), indicating a need for further exploration in this area.

Age also appears to have a complex relationship with CAM usage, in that prevalence of use peaks in middle age and declines in late-age, in both cancer and non-cancer patients alike (Fouladbakhsh and Stommel, 2008, 2010). Estimates of peak age of CAM use for cancer

survivors, specifically, have ranged from age 34 (Fouladbakhsh and Stommel, 2008) to age 46 (Fouladbakhsh and Stommel, 2010), depending upon the sample. Cancer survivors may initiate complementary services at younger ages and display less steep declines in usage in late age, as compared to the general population (Fouladbakhsh & Stommel, 2008). However, Shen and colleagues (2002) found no support for age as a predictor of CAM usage in late-stage breast cancer patients, nor was support found for income level or marital status. In their sample, higher education remained the only sociodemographic factor associated with increased CAM usage. Mixed results have also been found with regard to the predictive power of marital status in cancer populations. Although Shen et al. (2002) did not find support for marital status, other studies have suggested that married cancer patients, particularly women, may be more likely to use CAM services than those who are single (Helyer, 2006; Wanchai, Armer, & Stewart, 2010). By contrast, other studies have suggested that those who are separated or divorced may be more inclined to use complementary services (Fouladbakhsh et al., 2005). Another study detected similar findings in a sample of cancer survivors, among whom single or widowed individuals were more likely to engage in CAM practices (e.g., yoga, meditation, deep breathing), when compared to those who were married. In this latter study, marital status was thought to be, in part, a reflection of the age distribution of the cancer survivor population, which tended toward an older mean age.

Cancer-specific variables, such as cancer type, cancer stage and treatment, may be important determinants of CAM usage (Fouladbakhsh et al., 2005; Yates et al., 2005), with some studies beginning to find support, albeit mixed, for this notion. In regards to cancer type, research suggests that breast cancer patients may be more likely to use complementary health services than patients of other cancer types (Yates et al., 2005; Richardson, Sanders, Palmer,

Greisinger, & Singletary, 2000). Alternately, a study of CAM usage across fourteen European countries revealed the highest prevalence of use among patients with diagnoses of pancreatic, liver, bone/spine, and brain cancer, followed by breast and other cancers (Deng & Cassileth, 2005b; Molassiotis et al., 2005), whereas other studies have found no effect of cancer type on CAM usage (Fouladbakhsh et al., 2005; Fouladbakhsh & Stommel, 2010). With regard to cancer stage, there is some evidence to suggest that early-stage cancer patients may engage in CAM usage at higher rates when compared to late-stage cancer patients (Fouladbakhsh et al., 2005). Relatedly, in cancer survivors, time since diagnosis does not appear to be a significant predictor of CAM usage (Fouladbakhsh & Stommel, 2010). For cancer patients actively in treatment, studies suggest treatment type may be relevant to CAM usage. Patients undergoing radiation therapy appear least likely to supplement conventional medical care with complementary services, whereas patients undergoing cancer surgery, chemotherapy, or a combination of chemo-and radiation therapy are more likely to participate in CAM services by comparison (Fouladbakhsh et al., 2005; Richardson et al., 2000; Yates et al., 2005).

Lastly, physical symptoms and emotional distress have been examined as potential correlates of CAM usage (Astin, 1998). Pain appears to be a particularly strong somatic/physical factor influencing CAM usage in both cancer and non-cancer populations (Astin, 1998; Fouladbakhsh & Stommel, 2008), although there have also been mixed results with regard to the predictive power of pain and overall perceived health status on CAM usage (Fouladbakhsh et al., 2005). Mixed effects have also been detected for the predictive value of emotional distress (i.e., depression, anxiety) on engagement in complementary health approaches in cancer care (Astin, 1998; Fouladbakhsh et al., 2005; Fouladbakhsh & Stommel, 2008). Some studies have reported anxiety, depression and associated symptoms (e.g., fatigue) as of negligible influence over CAM

usage in cancer patients and survivors (Fouladbakhsh & Stommel, 2010; Rakovitch et al., 2005), whereas other studies have found an association between the initiation of CAM services and indicators of emotional distress (i.e., depression, anxiety, lower quality of life; Burstein, Gelber, Guadagnoli, & Weeks, 1999; DiGianni, Garber, Winer, 2002). Despite the higher prevalence of pain and depression in a cancer population, as compared to the general population, these factors may be no more influential in determining use than in the general (non-cancer) population (Fouladbakhsh & Stommel, 2008); in other words, pain and emotional distress may exert a significant and comparable influence in cancer and non-cancer populations alike.

Outcomes associated with CAM usage

Studies have begun to explore and show preliminary support for CAM services, such as yoga, acupuncture, and massage therapy, in reducing depression, anxiety, and distress, and improving overall emotional health and quality of life in cancer patients (Banerjee et al., 2007; Carlson et al., 2000; Hernandez-Reif et al., 2005; Lin et al., 2011; Oh et al., 2010; Rao et al., 2008). There is also some evidence, although insufficient in its totality, for the reduction of other cancer-related symptoms, such as mental confusion, fatigue, pain, and physical symptoms (e.g., hot flashes), following the use of complementary health services and integrative healthcare programs (Baker et al., 2012; Bower et al., 2012; Carlson et al., 2000; Chao et al., 2009; Deng & Cassileth, 2005a). For example, a recent meta-analysis conducted by Lin et al. (2011) provided support for the potential benefits of yoga in improving the emotional health of cancer patients, with those using yoga services showing greater improvements in anxiety, depression, distress, and overall stress, relative to controls and those in supportive group therapy. Similarly, a pilot study on an integrative health intervention offering a wide variety of CAM services (i.e., yoga, touch therapies, meditation, art therapy, homeopathy, etc.) to breast cancer patients found that

patients using the services were often afforded reduced mental and physical fatigue, breast cancer-specific symptoms, and mood disturbance, as well as improved quality of life and immune function (Baker et al., 2012). However, some attention has been called to the limited data on the utility of CAM modalities for reducing cancer-related fatigue (Lin et al., 2011; Poort et al., 2017; Sood et al., 2007) and methodological issues have also been implicated in CAM-related treatment outcome studies, similar to those indicated for other psychosocial interventions (Coyne et al., 2006; Williams & Dale, 2006). Overall, there is some evidence to indicate short-term benefits of IH usage for cancer patients (Baker et al., 2012; Helyer et al., 2006); however, the long-term efficacy of IH has not been systematically studied (Barnett & Shale, 2012).

A recent meta-analysis conducted by Subnis et al., (2014) examined the effects of psychosocial therapies on neuroendocrine-immune functioning in cancer patients, finding the highest degree of support for cognitive-behavioral therapy and CAM therapies. The complementary health approaches employed in the studies reviewed included: yoga, meditation/mind-body skills, massage, and qigong, among others, delivered by a variety of allied healthcare professionals. Of the CAM studies reviewed by Subnis et al. (2014), approximately two-thirds (6/9) revealed significant effects on at least one neuroendocrine or immune outcome measure. For example, an 8-week group mindfulness-based stress reduction (MBSR) intervention, employed with women with early-stage breast cancer and involving breathing techniques, meditation, and mindful yoga, was found to improve quality of life, coping (i.e., increased use of support systems and optimism) and immune functioning, as measured by reductions in cortisol and inflammatory cytokines (IL-4, Il-6, and IL-10), for women who self-selected into the MBSR group relative to those receiving care as usual (Witek-Janusek et al., 2008). Similarly, a randomized controlled trial found Medical Qigong, a group mind-body

intervention with both physical activity and meditation components, to be associated with improved quality of life, mood, and cancer-related fatigue and reduced inflammation, as measured by serum CRP, in a heterogeneous sample of cancer patients. These findings suggest the potential utility of CAM services in boosting immune function in cancer patients, although more investigation is needed in this area, with the emerging nature of this data and associated methodological issues making it difficult to draw conclusions across studies (Subnis et al., 2014).

Consistent with treatment outcome studies using exclusively psychosocial data, most studies employing neuroendocrine or immune outcomes focus narrowly on breast and prostate cancer patients and tend to exclude patients with late-stage cancer or cancer survivors (Adler & Page, 2008; Subnis et al., 2014). In their review, Subnis et al. (2014) indicated the need to explore the effects of psychosocial treatments on immune outcomes in longitudinal studies with varied cancer populations that are more reflective of the cancer care continuum. The lack of standardization in biomarkers has made it difficult to make conclusive remarks regarding the impact of psychosocial therapies on immune functioning (Subnis et al., 2014); however, this issue is not altogether dissimilar to the call for standardized outcome measures in treatment outcome studies more generally (Adler & Page, 2008). In summary, while there is some evidence to suggest the effectiveness of CAM in alleviating distress and reducing inflammation in cancer patients, this body of research is in its relative infancy, and there is a need to explore these effects in longitudinal designs that include more heterogeneous samples of cancer patients to determine the utility and long-term effectiveness of these services across the cancer care continuum.

Present Study

The present study was intended as a pilot study to explore the effectiveness of an integrative healthcare program longitudinally and across the cancer care continuum (i.e., all cancer types and stages). This Integrative Healthcare (IH) program exists within an academic medical center and was designed to provide supportive and integrative therapies for cancer patients and their caregivers during all stages of cancer care, beginning from initial diagnosis and continuing throughout treatment and into survivorship. This IH program provides access to a wide variety of services that include: individual psychotherapy, massage therapy, acupuncture, yoga, reiki, and an 8-week mind-body skills course.

The aims of the current study were two-fold and involved cross-sectional and longitudinal analyses of IH usage in a heterogeneous sample of cancer patients. The primary aims were as follows: (1) to examine systematic differences between the IH usage and TAU group at baseline, in terms of sociodemographic factors (e.g., gender, age, socioeconomic status, marital status, etc.), cancer-specific variables (e.g., cancer type, stage, and treatment), and levels of emotional distress (i.e., depression, anxiety, etc.); and (2) to evaluate the short-term (3-month) and long-term (12-month) effectiveness of an IH program for cancer patients, relative to treatment as usual (TAU), in improving emotional and physical/somatic symptoms, quality of life, and immune system functioning.

Aim 1. Given the lack of consensus regarding socio-demographic and other factors influencing cancer patients' participation in complementary health approaches (Fouladbakhsh et al., 2005; Rakovitch et al., 2005; Wanchai et al., 2010), this study aimed to examine systematic differences between the IH usage and non-IH usage group, in terms of socio-demographic factors, cancer-specific variables, and emotional distress at baseline.

Hypothesis 1a. We hypothesized that participants opting in to the IH usage group would differ socio-demographically, relative to the TAU group, in terms of age, gender, income level, and education, such that those self-selecting into the IH usage group would include a higher proportion of females and be, on average, younger and of higher-income and education, when compared to the TAU group. Given mixed effects for race/ethnicity and marital status, the analyses were exploratory, with no specific direction of effect predicted.

Hypothesis 1b. We hypothesized that participants opting in to the IH usage group would differ in terms of cancer-specific variables, such that those self-selecting into the IH usage group would present, on average, with a higher prevalence of breast cancer, when compared to the TAU group. Due to mixed effects in the literature for treatment-related variables, analyses for treatment type and time since treatment were exploratory, with no specific association predicted.

Hypothesis 1c. We hypothesized that participants opting in to the IH usage group would have more elevated levels of emotional distress at baseline, including higher levels of depression and anxiety and lower health-related quality of life, relative to the TAU group.

Aim 2. Given the need to explore the effectiveness of IH services via longitudinal designs (Baker et al., 2012; Helyer et al., 2006) with the inclusion of a broader range of cancer patients (Subnis et al., 2014), the current study aimed to examine the short-term and long-term efficacy of IH in reducing emotional and physical symptoms and improving immune functioning (i.e., IL-6 and CRP) in a heterogeneous sample of cancer patients.

Hypothesis 2a. We hypothesized that, relative to TAU, participants receiving IH services would show greater reductions in depression, anxiety, and somatic/physical symptoms and greater improvements in quality of life from baseline to 3-month follow-up (short-term) and from baseline to 12-month follow-up (long-term).

Hypothesis 2b. We also hypothesized that, relative to TAU, participants receiving IH services would show greater improvements in immune health, as measured by CRP and IL-6 for a subset of the sample, from baseline to 3-month follow-up (short-term) and from baseline to 12-month follow-up (long-term).

CHAPTER 2

METHOD

Study design

The present study was intended as a pilot study to examine the short-term and long-term effectiveness of an integrative healthcare (IH) program with cancer patients who either opted to use complementary treatments as adjuncts to standard care or who opted to receive treatment as usual (TAU). This study classifies as an open trial with a single group repeated measures design across 12 months. The present study also takes the form of a natural study design in that patients' self-select into the IH program and engage services of their choice. Although patients in the IH program were encouraged to use services as frequently as possible, they were free to choose the relative frequency and duration of use, reflecting naturally occurring patterns of IH usage. No incentives were provided for participation due to lack of funding and use of services (type, frequency, and duration) was determined by the patient and was tracked by the research team. Additionally, all services were provided at set costs, paid by the patient.

Integrative Healthcare Program

The Integrative Healthcare (IH) program under study exists within an academic medical center and cancer institute and was designed to provide supportive and integrative therapies for cancer patients and their caregivers during all stages of cancer care. This IH program includes access to a variety of services that include: psychotherapy, massage therapy, acupuncture, yoga, reiki, and mind-body skills training. A variety of practitioners administer the services, from medically certified massage therapists and acupuncturists to graduate student therapists (under the supervision of a licensed clinical psychologist). It is important to note that mind-body services (i.e., meditation, relaxation, guided imagery, etc.) are generally included in integrative

healthcare programs (NCCIH, 2016), whereas the inclusion of traditional psychotherapy services marks a unique and distinguishing feature of this particular IH program.

The duration, format (individual or group), and cost of services were varied. Psychotherapy was offered individually in 60-minute sessions, whereas massage therapy was offered at various time intervals ranging from 20- to 60-minute sessions. Acupuncture and yoga were offered in both individual and group sessions at varying time intervals (i.e., 30-, 45-, and/or 60-minute sessions). Reiki was available individually (30- or 60-minute sessions), with the option to be received in conjunction with massage or yoga for a reduced price and duration (10-minutes). The mind-body skills course is a 8-week course (8-sessions) that covers strategies for reducing stress, exploring emotions, and increasing mindfulness; this course was offered free-of-charge for cancer patients, whereas all other services were paid services. These services were designed to be affordable, accessible, and competitive with community-based CAM services.

Participants

Participants were 178 adult cancer patients (84% female; 16% male), with a mean age of 58.2 years (SD = 13.3) and a range of 18 to 87 years, recruited from a University Medical Center Cancer Institute. The majority (91%) of the sample was Caucasian, with a mean education level of 15.3 years (SD = 2.9). The most common cancer diagnosis among participants was breast cancer (43%), followed by lung cancer (7%) and multiple instances of cancer (6%). Given the breadth of cancer types included in the present study, cancer types were dichotomized into 'Breast' (43%) and 'Other' (57%) for the purpose of analyses (see Results section for additional information). Half of participants (50%) had lower stage cancers (0-2), and had received chemotherapy (56%) and/or radiation (42%) treatment. The average time since diagnosis was 3.60 years (SD = 5.9).

Forty percent of the participants (n = 71) opted to engage in IH services between baseline and 12-month follow-up, attending IH services an average of 4.31 times (SD = 4.88; median = 3, mode = 1, range: 1 – 29). The most commonly used IH services included massage therapy (17%), followed by psychotherapy (12%) and acupuncture (10%). A subset of the sample (n = 52; 29%) was randomized to a blood draw condition. Of those in the blood draw group, approximately 44% used IH services. A total of 169 participants were eligible for 3-month follow-up at the time of data analysis, and 124 (73%) completed the follow-up data collection (attrition rate = 27%). For 12-month follow-up, 117 participants were eligible for completion at the time of follow-up, with 79 (68%) completing the follow-up data collection (attrition rate = 33%). Baseline characteristics and descriptive statistics of the participants at T2 are displayed in Table 1.

Eligibility criteria for the present study were broad, in that patients ≥ 18 years of age were eligible for inclusion irrespective of cancer type, stage, and treatment status, as well as mental healthcare status (i.e., psychotherapy and/or psychiatry services) and participation in IH services in the community. Patients were excluded from participation if their initiation of IH services at the Cancer Institute occurred prior to the recruitment contact. With regard to IH usage, participants were classified into the IH usage group if they used one or more IH services (any type of service) at the medical center following baseline survey completion. Participants self-selected by opting into (or out of) IH usage, and usage of IH services (type, frequency, and duration) was tallied and tracked on an ongoing basis for each participant in the IH usage group.

Procedure

The Institutional Review Board (IRB) at the University and University Medical Center approved the current study, and all participants were required to complete written informed

consent documents. Participants were recruited in-person at the Cancer Institute, as well as over the telephone. Those recruited in-person were approached in either the outpatient clinic waiting area or within the IH office at the Cancer Institute. Prospective participants for recruitment by telephone were identified via queries through the Tumor Registry Board or through IH records (i.e., newly scheduled participants were identified and contacted either before or at point-of-service). All prospective participants identified through queries were sent an informational packet via postal mail and were informed that study staff would be in contact within two weeks of the mailing to assess interest.

Study participants were asked to complete survey measures at three assessment intervals: baseline (T1; prior to use of IH services), 3-month follow-up (T2), and 12-month follow-up (T3). Participants completed questionnaires in-person, over the telephone, or online. A subset of the sample (approximately 30%) was randomized to a blood draw condition to assess immune system functioning via cytokine plasma levels. Participants were randomly allocated to the blood draw condition using a random number generator and were asked to consent to blood draws at the time of enrollment. Participants were requested to complete the study questionnaires on the same day as the blood draw, when applicable, at each respective time point (i.e., baseline, 3-month, and 12-month follow-up). Blood samples were collected by registered nurses and trained phlebotomists working in the outpatient unit at the Cancer Institute, and all specimens were be sent to a hospital laboratory for analyses. All participants were assigned a Study ID number at study entry used to code survey and biological data.

Measures in the present study assessed basic demographic information and cancer variables, including cancer type and stage, cancer treatment (type, duration, frequency), medications, and previous psychiatric care or psychotherapy. Measures also assessed primary

outcome variables, including depression, anxiety, somatic/physical symptoms, and health-related quality of life. Questions regarding use of community-based IH services were included for a subset of participants. All measures are available in the Appendix.

Measures. ***Demographics.*** Participants completed a demographics questionnaire that assessed basic biographical data including age, gender, race, and socioeconomic status, as well as cancer-related variables, including type, stage, type of treatment and duration. Cancer information was also verified via medical records, when possible, with permission to obtain this information requested in the study consent form.

Emotional Health and Physical Symptoms. The Patient Health Questionnaire (PHQ; Kroenke, Spitzer, & Williams, 2001; Spitzer, Kroenke, & Williams, 1999) was used to assess depression, anxiety, and somatic/physical symptoms at each time point. The PHQ is one of the most commonly administered self-report measures in medical settings (Wittkampf, Naeije, Schene, Huyser, & van Weert, 2007). While there are many different versions of the PHQ, the present study used the PHQ-9 (depression), GAD-7 (anxiety), and PHQ-15 (somatic and physical symptoms), totaling 31 multiple-choice items (see Appendix for measures). These measures have been subject to meta-analytic review, with some evidence to suggest that this triad (i.e., PHQ-9, GAD-7, and PHQ-15) may be an efficient means for detecting and monitoring depressive, anxiety and somatic symptoms in primary care and other medical settings (Kroenke, Spitzer, Williams, & Lowe, 2010).

The PHQ-9 is a 9-item self-report depression screener, asking patients how often in the past two weeks they have been bothered by depressive symptoms, such as "*little interest or pleasure in doing things,*" with responses ranging from 0 ("*Not at all*") to 3 ("*Nearly every day";* Kroenke et al., 2001). Similarly, the GAD-7 is a 7-item self-report anxiety scale that asks

respondents to rate how often they have been bothered by anxious symptoms, such as "*not being able to stop or control worrying,*" within the last two weeks, with responses ranging from 0 ("*Not at all*") to 3 ("*Nearly every day";* Spitzer, Kroenke, Williams, & Lowe, 2006). The PHQ-15 is a 15-item somatic symptom scale that asks respondents to indicate how often they have been bothered by somatic symptoms within the past 4 weeks, with responses ranging from 0 ("*Not bothered at all*") to 2 ("*Bothered a lot*") and symptoms including stomach pain, back pain, headaches, and fainting spells, among others (Kroenke, Spitzer, & Williams, 2002). Cut-off points are similar across all measures, with scores of 5, 10, ≥15 representing mild, moderate, and severe levels of symptom burden (Kroenke et al., 2010). The most commonly recommended cut-off score for sufficient sensitivity and specificity in detecting "clinically significant" symptoms is ≥10 across scales (Kroenke et al., 2010).

The reliability and validity of the PHQ scales is well established (Wittkampf et al., 2007), with the internal reliability of all scales, the PHQ-9 (α = .89; Kroenke et al., 2001), GAD-7 (α = .92; Spitzer et al., 2006), and PHQ-15 (α = .80; Kroenke et al., 2002), resting within the excellent range. The internal consistency of the PHQ scales was comparable in the present study, as follows: PHQ-9 (α = .89), GAD-7 (α = .94), and PHQ-15 (α = .84). The test-retest reliability of the PHQ-9 and GAD-7 is also good to excellent (Kroenke et al., 2001; Spitzer et al., 2006), whereas the test-retest reliability of the PHQ-15 has been less extensively studied and appears to fall within the moderate range (Ravesteijn et al., 2009). Sensitivity to change, a characteristic of measures used to monitor treatment response, has been consistently established for the PHQ-9, whereas evidence is only beginning to emerge for the GAD-7 and PHQ-15 (Kroenke et al., 2010).

Health-related Quality of Life (HRQOL). The Center for Disease Control and Prevention's Health-related Quality of Life measure (CDC-HRQOL-4; also referred to as the Healthy Days measure) was used to assess participants' perceived physical and mental health status. Health-related Quality of Life (HRQOL) is a multi-dimensional concept that includes domains related to physical, mental, emotional and social functioning and goes beyond direct measures of population health by focusing on the impact health status has on quality of life (Moriarty, Zack, & Kobau, 2003). In fact, the CDC- HRQOL-4 measure has been shown to be predictive of morbidity and mortality and healthcare usage, and is often associated with chronic health conditions, health-risk behaviors, and other sociodemographic factors, such as gender and age (Zahran et al., 2005).

The CDC-HRQOL-4 includes questions regarding perceived overall health and estimates of days (in the past 30 days) when physical health, mental health, and other activities (i.e., work, self-care, recreation) were impaired (Moriarty et al., 2003; Zahran et al., 2005). Some example questions include: "*Would you say your health is: Excellent, Very Good, Good, Fair, or Poor?"* and *"Now thinking about your physical health, which includes physical illness and injury, for how many days during the past 30 days was your physical health not good?"* Two additional modules were incorporated for the purpose of this study: the Activity Limitations Module and the Healthy Days Symptom Module, comprising the full set of Healthy Days measures or the CDC-HRQOL-14. The Activity Limitations Module assesses physical, mental, or emotional limitations on daily life and the extent and duration of impairment or health problem. The Healthy Days Symptom Module includes questions regarding days of pain, depressed mood, anxiety, sleeplessness, and vitality (i.e., healthy and full of energy). For the purpose of assessing HRQOL as an outcome variable, the following item was used and reverse-coded for ease of

interpretation: "*Would you say that in general your health is: Excellent, Very Good, Good, Fair, or Poor?"* (reverse coded: 1 = poor to 5 = excellent).

The CDC-HRQOL-4 and associated modules (i.e., full set of Healthy Days measures) have been used in the CDC's Behavioral Risk Surveillance System (BRFSS) for over two decades, a nationwide survey with an emphasis on population health and disease prevention, and have demonstrated good reliability and validity with adults in this context (Moriarty et al., 2003; Zahran et al., 2005). The CDC-HRQOL-4 and full set of Healthy Days measures validly distinguish between disease groups and are regarded as valid and useful measures of health-related quality of life with diverse populations of adults (Moriarty et al., 2003).

Integrative Healthcare Usage. In addition to tracking usage of IH services from patient charts (type, frequency, and duration), a subset of participants were asked to self-report IH usage, including use of services both at the medical center and in the community. These participants were also asked to state reasons for using or not using IH services at the medical center for the purpose of determining potential barriers and improving future studies on IH usage. Self-reported usage was captured for a subset of the sample only, as these items were added partway through the study as a means to capture patterns of use external to our IH program.

Immune functioning. All biospecimens were processed in the university medical center's laboratory following collection in the outpatient clinic at the Cancer Institute. Blood specimens were collected in red top/tiger top serum tubes with a gel-barrier for quantification of CRP. CRP levels were assessed by a latex immunoturbidimetric assay with a standard kit. For IL-6 processing, plasma was separated from cells and processed in a lavender-top (EDTA) tube. IL-6 levels were assessed by enzyme-linked immunoassay (ELISA) with a standard kit. Samples were processed according to standard blood specimen preparation procedures, including

refrigeration at 2-8°C and freezing at -15°C or colder (up to -30°C). Samples were centrifuged at 3500 RPM at room temperature (20-25°C) for 10 minutes.

Data Analytic Plan

Descriptive statistics and correlations among primary study variables were computed using SPSS 22. Attrition analyses were run using cross-tabulation analyses in SPSS 22, with a Pearson Chi-Square test of significance. Binary logistic regression analyses were conducted in SPSS 22 to examine systemic differences between the IH usage and TAU groups at baseline (Aim 1; Sperandei, 2014). A dichotomous IH usage variable (0 = no usage; 1 = 1+ times used) was regressed onto a set of sociodemographic, emotional health, and cancer variables to explore factors associated with engagement in IH services. All sociodemographic and cancer variables were converted to dichotomous variables for the purpose of logistic regression analyses. Bivariate correlations were conducted with dichotomous and/or continuous variables, as per logistic regression analyses.

To determine if IH usage is linked to outcome (criterion) variables (*depression, anxiety, physical/somatic symptoms, quality of life, and immune function*) at 3-month and 12-month follow-up (Aim 2), a series of regression analyses were examined for each outcome variable in SPSS 22, while controlling for baseline scores on the respective outcome measure (Mason & Perreault, 1991). The predictor variable (IH usage) was examined as both a dichotomous variable (0 = no usage; 1 = 1+ times used) and a count variable (i.e., dosage in minutes). For a subset of the sample for which community usage data (dichotomous; yes = 1, no = 0) was collected, regression analyses were run to control for community usage, in addition to baseline levels of outcome variables. Missing data was handled via list-wise deletion, in which a participant's data is excluded from analysis if one or more values are missing. Change in each outcome variable

was determined from two time points: baseline and 3-months, or baseline and 12-months, in an effort to explore short-term and long-term outcomes, respectively. A statistically significant parameter ($p < .05$) indicates that IH usage was predictive of a change in the outcome score, above and beyond the score at baseline, as represented by the following regression equation:

$$Y_{(\text{depression})} = \beta_{(\text{baseline dep})} X_{(\text{IH usage})} + c_{(\text{constant})}$$

Effect sizes were estimated for outcomes data, using Adjusted R^2 values, which represent the proportion of variance in the outcome variable attributable to model predictors. Lastly, a series of t-tests and/or ANOVAs were run in SPSS 22 to further explore effect sizes by group (i.e., IH usage, community usage) and service type (i.e., acupuncture, massage, psychotherapy, etc.) for 3-month outcome analyses. Effect sizes were estimated for exploratory t-tests and ANOVAs using eta-squared values. Eta-squared values represent the proportion of variance in the outcome variable attributable to the predictor variable (Norouzian & Plonsky, 2018; Richardson, 2011).

CHAPTER 3

RESULTS

Preliminary Analyses

Correlations among predictor and outcome variables for logistic and multiple regression models are presented in Tables 2 and 3, respectively. In terms of demographics, gender and ethnicity were not significantly correlated with emotional health variables at T1 (baseline), T2 (3-month follow-up), or T3 (12-month follow-up). Age and income level were associated with T1 (baseline) measures, such that cancer patients of younger age and lower income presented with elevated levels of depression, anxiety (age only), somatic symptoms (income only), and lower HRQOL. Income remained associated with these outcome measures at T2 (3-month) and T3 (12-month), and was uniquely associated with anxiety at T3 (12-month) only. Fewer years of education was associated with lower HRQOL at T1 (baseline) and T2 (3-month), and was marginally association with HRQOL at T3 (12-month). Marital status was not significantly correlated with baseline (T1) outcome variables; however, being unmarried was associated with elevated anxiety and somatic symptoms at T3 (12-month) only.

Cancer-related variables were significantly associated with outcome variables across time points. Cancer type was positively correlated with T1 (baseline) measures, such that breast cancer was associated with fewer somatic symptoms and higher HRQOL at baseline. Cancer stage was significantly associated with T3 (12-month) outcome measures, such that advanced stage cancer was associated with higher levels of T3 depression, anxiety, somatic symptoms, and reduced HRQOL. Cancer stage also showed a positive correlation with T3 (12-month) biomarkers, specifically, IL-6. Cancer treatment (i.e., chemotherapy, radiation, and/or surgery) and years since diagnosis were not correlated with emotional health variables at baseline (T1) or

follow-up (T2 or T3). However, chemotherapy displayed an association with elevations in T3 (12-month) biomarkers, specifically, IL-6.

In terms of IH usage, community usage and composite usage (IH + community usage) were not significantly associated with baseline or outcome variables. However, IH usage (dichotomous; 1 = yes, 0 = no) was correlated with T1 (baseline) depression, such that use of services was associated with increased depression at baseline (prior to use).

Attrition analyses were conducted to assess factors associated with missingness at T2 (3-month; attrition rate = 27%) and T3 (12-month; attrition rate = 33%). Analyses revealed that socio-demographic variables (i.e., gender, age, ethnicity, marital status, income, and years of education) were not significantly associated with attrition at T2 (3-month) or T3 (12-month). With regard to cancer variables, cancer type (dichotomously coded: "Breast" or "Other") was significantly associated with attrition at T2 (3-month), $X^2(1, n = 169) = 10.42, p = .001$, and T3 (12-month), $X^2(1, n = 117) = 17.42, p < .001$, such that those with breast cancer were *less likely* to dropout at follow-up, as compared to those with other forms of cancer. Cancer stage was not significantly associated with attrition at T2 (3-month) or T3 (12-month). Similarly, baseline (T1) depression, anxiety, somatic symptoms, and HRQOL were not predictive of T2 (3-month) or T3 (12-month) attrition. Likewise, scores on emotional health measures at T2 (3-month) were not predictive of attrition at T3 (12-month).

Primary Analyses

Aim 1. ***Factors associated with IH usage***. Results from the logistic regression model are presented in Table 4. Consistent with study hypotheses, baseline depression ($OR = 1.10, p \leq .01$) emerged as a significant predictor of engagement in IH services; for every one-unit increase in depression, there was a 9.5% increase in the odds of using IH services. Baseline anxiety ($OR =$

1.089, $p \leq .01$) was also significantly predictive of engagement in IH services; for every one-unit increase in anxiety, there was an 8.9% increase in the odds of using IH services. Somatic symptoms ($OR = 1.01$, $p = .83$) and HRQOL ($OR = 1.02$, $p = .92$) at baseline (T1) were not predictive of IH engagement. Contrary to expectations, demographics variables (i.e., gender, age, ethnicity, marital status, income, and years of education) were not significant predictors of engagement in IH services. Similarly, cancer-specific variables (i.e., cancer type, cancer treatment, and years since diagnosis) did not emerge as significant predictors of engagement in IH services. Although radiation treatment emerged as a marginal predictor of IH usage in the depression model ($OR = 0.45$, $p = .07$), it did not emerge as a predictive factor in the anxiety model ($OR = 1.41$, $p = .45$), somatic symptoms model ($OR = 0.56$, $p = .15$), or the HRQOL model ($OR = 0.53$, $p = .12$).

Aim 2a. ***Outcomes at 3-month follow-up (T2).*** Results from regression models examining outcomes associated with (a) IH usage (dichotomous; 1 = yes, 0 = no) and (b) IH dosage (in minutes) at T2 (3-month follow-up), while controlling for baseline values of each respective outcome variable, are presented in Table 5. Contrary to expectations, IH usage (dichotomous) and IH dosage (in minutes) did not emerge as significant predictors of depression at T2 (3-month). Similarly, IH usage and IH dosage were not predictive of anxiety or somatic symptoms at T2. With regards to HRQOL, IH usage ($\beta = 0.14$, $p \leq .05$) was found to be a predictor of greater HRQOL at T2, consistent with study hypotheses. However, this finding did not remain for IH dosage (in minutes), which, inconsistent with study hypotheses, was not predictive of T2 HRQOL. When controlling for baseline levels of outcome variables (i.e., depression, anxiety, somatic symptoms, HRQOL), baseline scores were found to be predictive of T2 scores across outcomes measures. (See Table 5 for full results.) As a set, model predictors

explained approximately 38%, 37%, 49%, and 47% of the variance in T2 depression, anxiety, somatic symptoms, and HRQOL, respectively.

For immune outcomes, IH usage (dichotomous) and IH dosage (in minutes) were not predictive of T2 (3-month) levels of C-Reactive Protein (CRP), contrary to study hypotheses. Also, contrary to expectations, IH usage and IH dosage were not predictive of T2 (3-month) levels of Interleukin-6 (IL-6). When controlling for baseline (T1) levels of immune biomarkers, baseline CRP and baseline IL-6 were predictive of T2 levels of CRP and IL-6. (See Table 5 for full results.) As a set, these model predictors accounted for roughly 35% and 56% of the variance in CRP and IL-6, respectively.

Outcome analyses with a subset (n = 76) with community usage data. Results from regression models with a subset of the sample (n = 76) from which community usage data was collected is presented in Table 6; regression models examined outcomes associated with (a) IH usage (dichotomous; 1 = yes, 0 = no) and (b) IH dosage (in minutes), while controlling for community usage (dichotomous; 1 = yes, 0 = no) and baseline values of each respective outcome variable (i.e., depression, anxiety, etc.). Similar to earlier findings and contrary to study hypotheses, IH usage (dichotomous) and IH dosage (in minutes) did not emerge as significant predictors of depression at T2 (3-month follow-up) in the subset. Similarly, IH usage and IH dosage were not predictive of T2 anxiety, nor were usage and dosage predictive of T2 somatic symptoms (See Table 6 for full results). However, consistent with hypotheses, IH usage emerged as a predictor of greater HRQOL at T2 ($\beta = 0.20, p \leq .05$), such that IH usage was predictive of increased HRQOL at 3-month follow-up (T2). This finding did not remain when examined for IH dosage (i.e., usage in minutes), which, inconsistent with study hypotheses, was not predictive of T2 HRQOL. When controlling for community usage (dichotomous; 1 = yes, 0 = no) in the

subset, self-reported community usage was not predictive of T2 depression, T2 anxiety, T2 somatic symptoms, or T2 HRQOL in either model. When controlling for baseline levels of outcome variables, baseline (T1) scores of depression, anxiety, somatic symptoms, and HRQOL were predictive of respective T2 scores across all outcomes measures. As a set, model predictors explained roughly 32%, 32%, 53%, and 38% of the variance in T2 (3-month) depression, anxiety, somatic symptoms, and HRQOL, respectively.

For immune outcomes, contrary to hypotheses, IH usage and IH dosage were not predictive of T2 levels of C-Reactive Protein (CRP) or T2 Interleukin-6 (IL-6). When controlling for community usage (dichotomous; 1 = yes, 0 = no) in the subset, community usage was not predictive of T2 levels of CRP or IL-6. When controlling for baseline levels of biomarkers, baseline CRP was not predictive of T2 levels of CRP; however, baseline levels of IL-6 were predictive of T2 levels of IL-6 in both models. (See Table 6 for full results.) As a set, these model predictors accounted for 38% and 63% of the variance in CRP and IL-6, respectively.

Outcome analyses for IH and community usage examined as a composite variable. Results from regression models examining outcomes associated with composite usage (dichotomous; 1 = yes to either, 0 = participation in neither), while controlling for baseline values of each respective outcome variable (i.e., depression, anxiety, etc.) are presented in Table 7. Similar to prior findings and contrary to study hypotheses, composite usage (IH usage + community usage; dichotomous) did not emerge as a significant predictor of T2 (3-month) depression, T2 anxiety, or T2 somatic symptoms. Also contrary to study hypotheses, and inconsistent with prior findings, composite (combined) usage was not predictive of T2 HRQOL. When controlling for baseline levels of outcome variables (i.e., T1 depression, anxiety, somatic symptoms, HRQOL), baseline (T1) scores were found to be predictive of respective T2 (3-

month) scores across all outcomes measures. (See Table 7 for full results.) As a set, model predictors accounted for 32%, 31%, 53%, and 40% of the variance in T2 (3-month) depression, anxiety, somatic symptoms, and HRQOL, respectively.

For immune outcomes, consistent with hypotheses, composite (combined) usage emerged as a predictor of T2 (3-month) levels of C-Reactive Protein (CRP; $\beta = -0.59$, $p \leq .05$) and Interleukin-6 (IL-6; $\beta = -0.34$, $p \leq .05$), such that increased usage (IH + community usage) was associated with lower levels of circulating CRP and IL-6. When controlling for baseline levels of biomarkers, baseline CRP was not predictive of T2 levels of CRP; however, baseline levels of IL-6 were predictive of T2 (3-month) levels of IL-6. (See Table 7 for full results.) As a set, these model predictors accounted for 65% and 74% of the variance in CRP and IL-6, respectively.

Exploratory analyses. Exploratory analyses by type of IH service revealed a significant effect on mean change scores for depression from T1 (baseline) to T2 (3-month) by type of IH service (i.e., massage, psychotherapy, and acupuncture), $F(3, 45) = 4.93$, $p \leq .01$. Results indicated that participants who engaged in psychotherapy experienced a greater reduction in symptoms of depression from T1 to T2 ($M = -7.71$, $SD = 7.54$), relative to participants engaged in massage therapy ($M = -1.65$, $SD = 3.27$) or acupuncture ($M = -1.50$, $SD = 2.46$) services, with 26.5% of the variance in mean change scores of depression accounted for by IH service type. Similarly, a significant effect on mean change scores for anxiety (T2-T1) by type of IH service was detected, $F(3, 43) = 5.86$, $p \leq .01$, such that participants engaged in psychotherapy experienced a greater reduction in symptoms of anxiety from T1 to T2 ($M = -6.07$, $SD = 5.74$), relative to participants engaged in massage therapy ($M = -0.78$, $SD = 3.95$) or acupuncture ($M = 0.60$, $SD = 2.67$) services. Results revealed that type of service accounted for approximately 31.1% of the variance in mean change scores (T2-T1) for anxiety. No main effect was detected

for type of IH service with respect to mean change scores (T2-T1) for somatic symptoms, $F(3, 45) = 1.67$, $p = .188$, or HRQOL, $F(3, 45) = 0.175$, $p = .913$. There were no difference in mean change scores for somatic symptoms based on participation in massage therapy, psychotherapy, or acupuncture services, nor was there as difference in mean change scores for HRQOL based on participation in massage therapy, psychotherapy, or acupuncture. Of the variance in mean change scores for somatic symptoms and HRQOL, type of service accounted for approximately 10.9% and 1.3%, respectively. (See Table 8 for full results.)

Exploratory analyses of IH usage (dichotomous; 1 = yes, 0 = no) revealed a significant effect on mean change scores for depression from T1 (baseline) to T2 (3-month) by status of IH usage, $t(120) = 2.70$, $p \leq .01$, such that participants who self-selected into IH services experienced greater reductions in depression ($M = -3.58$, $SD = 5.55$) relative to participants who opted into TAU ($M = -0.97$, $SD = 4.90$). IH usage accounted for approximately 5.7% of the variance in mean change scores in depression from T1 to T2. A significant difference in mean change scores (T2-T1) was also detected for HRQOL based on status of IH usage, $t(120) = -2.39$, $p \leq .05$, such that participants who self-selected into IH services were more likely to experience improvements in HRQOL ($M = 0.16$, $SD = 0.95$) as compared to participants who opted into TAU ($M = -0.23$, $SD = 0.79$). Participation in IH usage explained approximately 4.6% of the variance in mean change scores for HRQOL. No main effect was detected for IH usage with respect to mean change scores (T2-T1) for anxiety, $t(116) = 1.29$, $p = .20$, or somatic symptoms, $t(117) = 0.47$, $p = .638$. There was no difference in mean change scores for anxiety or somatic symptoms based on self-selection into IH usage versus TAU. (See Table 9 for full results.) Of the variance in mean change scores for anxiety and somatic symptoms, IH usage accounted for approximately 1.4% and 0.2%, respectively.

Exploratory analyses of community usage (dichotomous; 1 = yes, 0 = no) for a subset of the sample for which this data was available revealed a significant main effect with respect to mean change scores (T2-T1) for anxiety, $t(72) = -2.37$, $p = .02$, such that participants who self-reported community usage were less likely to experience reductions in anxiety ($M = 0.58$, $SD = 4.24$) from T1 to T2, relative to participants who did not report use of services in the community ($M = -1.94$, $SD = 4.32$). Community usage explained approximately 7.2% of the variance in mean change scores in anxiety from T1 to T2. No significant effect was found for community usage with respect to mean change scores (T2-T1) for depression, $t(75) = -1.30$, $p = .20$, somatic symptoms, $t(73) = -1.73$, $p = .09$, or HRQOL, $t(74) = 0.33$, $p = .75$. Based on community usage, there was no difference in mean change scores (T2-T1) for depression, somatic symptoms, or HRQOL. (See Table 10 for full results.) Of the variance in mean change scores for depression, somatic symptoms, and HRQOL, community usage accounted for approximately 2.2%, 3.9%, and 0.1%, respectively.

Aim 2b. ***Outcomes at 12-month follow-up (T3).*** Results from regression models examining outcomes associated with (a) IH usage (dichotomous; 1 = yes, 0 = no) and (b) IH dosage (in minutes) at T3 (12-month follow-up), while controlling for baseline values of each respective outcome variable, are presented in Table 11. Contrary to expectations, IH usage (dichotomous) and IH dosage (in minutes) did not emerge as predictors of T3 (12-month) depression, T3 anxiety, T3 somatic symptoms, or T3 HRQOL. When controlling for baseline levels of outcome variables, baseline (T1) levels of outcomes (i.e., T1 depression, T1 anxiety, T1 somatic symptoms, and T1 HRQOL) were positive predictors of T3 outcomes. (See Table 11 for full results.) As a set, model predictors explained 51%, 36%, 47%, and 42% of the variance in T3 (12-month) depression, anxiety, somatic symptoms, and HRQOL, respectively.

For immune outcomes, contrary to study expectations, IH usage (dichotomous) and IH dosage (in minutes) were not predictive of T3 (12-month) levels of C-Reactive Protein (CRP). Similarly, IH usage (dichotomous) was not predictive of T3 (12-month) levels of Interleukin-6 (IL-6); however, IH dosage (in minutes) was a significant predictor of T3 (12-month) IL-6 (β = -0.58, $p \leq .01$), such that increased dosage in minutes was predictive of lower levels of circulating IL-6 in a subset of the sample. When controlling for baseline levels of biomarkers, baseline levels of IL-6 were significantly predictive of T3 (12-month) levels of IL-6, whereas baseline CRP was not consistently predictive of T3 (12-month) CRP across models. (See Table 11 for full results.) As a set, these model predictors accounted for roughly 17% and 54% of the variance in CRP and IL-6, respectively.

Outcome analyses with a subset (n = 36) with community usage data. Results from regression models with a subset of the sample (n = 36) from which community usage data was collected is presented in Table 12; regression models examined outcomes associated with (a) IH usage (dichotomous; 1 = yes, 0 = no) and (b) IH dosage (in minutes) at T3 (12-month follow-up), while controlling for community usage (dichotomous; 1 = yes, 0 = no) and baseline values of each respective outcome variable (i.e., depression, anxiety, etc.). Contrary to expectations, IH usage (dichotomous) and IH dosage (in minutes) were not predictive of T3 (12-month) depression, T3 anxiety, T3 somatic symptoms, and T3 HRQOL. When controlling for community usage (dichotomous; 1 = yes, 0 = no) in the subset, self-reported community usage was not predictive of T3 depression, T3 anxiety, T3 somatic symptoms, or T3 HRQOL. When controlling for baseline levels of outcome variables, baseline (T1) levels of outcomes (i.e., T1 depression, T1 anxiety, T1 somatic symptoms, and T1 HRQOL) were positive predictors of respective T3 (12-month) outcomes. (See Table 12 for full results.) As a set, model predictors

accounted for 48%, 20%, 48%, and 41% of the variance in T3 (12-month) depression, anxiety, somatic symptoms, and HRQOL, respectively, in this subset of the sample.

Outcome analyses for IH and community usage examined as a composite variable.

Results from regression models examining outcomes associated with composite usage (dichotomous; 1 = yes to either, 0 = participation in neither) at T3 (12-month follow-up), while controlling for baseline values of each respective outcome variable (i.e., depression, anxiety, etc.) are presented in Table 13. Contrary to study hypotheses, composite (combined) usage did not emerge as a predictor of T3 (12-month) depression, T3 anxiety, T3 somatic symptoms, or T3 HRQOL. When controlling for baseline levels of outcome variables, baseline (T1) levels of depression, anxiety, somatic symptoms, and HRQOL were found to be positively predictive of respective T3 (12-month) outcomes. (See Table 13 for full results.) As a set, model predictors accounted for 49%, 17%, 45%, and 43% of the variance in T3 (12-month) depression, anxiety, somatic symptoms, and HRQOL, respectively, in the subset.

CHAPTER 4

DISCUSSION

Integrative and holistic care is of growing interest among the general public as well as cancer patients, with rates of usage increasing and the demand for services generating a need for research examining the effectiveness of these interventions (Barnett & Shale, 2012). Research on the efficacy of integrative medicine for improving emotional and physical health outcomes is on the rise; however, much research remains to be conducted in this area. Complementary health approaches, such as yoga, acupuncture, massage therapy, and mind-body approaches, have been demonstrated as efficacious in the short-term with both cancer and non-cancer patients; however, the long-term effectiveness of these interventions remains largely unknown due to a dearth of longitudinal studies (Baker et al., 2012; Barnett & Shale, 2012). Methodological issues notwithstanding, the short-term benefits of integrative programs have been noted to broadly include improvements in depression, anxiety, quality of life, immune function, and physical/somatic symptoms, including those symptoms that occur as a result of cancer treatment, such as pain or neuropathy, fatigue, and hot flashes (e.g., Baker et al., 2012; Barnett & Shale, 2012; Deng & Cassileth, 2005a; Lin et al., 2011; Subnis et al., 2014). The present study explored the short-term (3-month) and long-term (12-month) emotional, physical/somatic, and immune benefits of an integrative healthcare (IH) program for cancer patients, as well as factors influencing engagement in IH services in a cancer care setting.

In terms of factors influencing IH usage, depression and anxiety emerged as significant predictors of engagement in our IH program; cancer patients who elected to participate in our program were more likely to be anxious and depressed, as compared to those who opted for treatment as usual (TAU). All other emotional or physical health variables (i.e., HRQOL,

physical/somatic symptoms) were not significantly associated with engagement in our IH program, nor were socio-demographic or cancer-related variables (e.g., cancer type, cancer treatment). Notably, our findings indicate that depressed and anxious cancer patients may be more likely to seek complementary health approaches to augment standard cancer care, presenting healthcare providers (e.g., oncologists, social workers, psychologists, etc.) with an opportunity to identify, educate, and assist such patients in determining which services would be most likely to complement their care and provide symptom relief (Barnett & Shale, 2012).

Although previous research has been mixed with regard to the predictive power of emotional distress (e.g., Astin, 1998; Fouladbakhsh & Stommel, 2010), our study contributes to the evidence to suggest that depression and anxiety may be amongst the factors driving cancer patients to seek integrative and holistic care. In fact, our findings suggest that depression and anxiety may be predictive of IH usage, above and beyond other factors, such as patient- and treatment -related variables. This marks a deviation from previous research, which has found strong support for gender as a predictor of IH usage and lesser, or more mixed, support for other sociodemographic and cancer-related variables (Barnes et al., 2004; Fouladbakhsh & Stommel, 2008, 2010). These results provide important information about *who* might be seeking integrative care in an oncology setting, pointing toward depression and anxiety as important contributing or motivating factors for engagement in integrative care; however, future research is needed to substantiate this finding and to further understand its implications for the delivery of integrative care in this setting.

With regard to the effectiveness of the intervention, improvements in health-related quality of life (HRQOL) were evidenced for IH participants at T2 (3-month follow-up); however, these gains were not maintained at T3 (12-month follow-up). Contrary to expectations, IH

program participation was not predictive of reductions in depression, anxiety, or somatic symptoms at T2 (3-month) or T3 (12-month). However, exploratory analyses at T2 suggested that those who elected to participate in IH services experienced greater reductions in depression, in addition to improvements in HRQOL, when compared to those engaged in TAU. Although significant reductions in depression were not evidenced when examining outcomes from baseline to T2 (3-month follow-up), it is possible that IH usage may have an effect on depression that we were unable to detect, due to issues of power and/or attrition. As a whole, our findings indicate that IH usage may confer short-term benefits in HRQOL to cancer patients. Exploratory analyses at T2 provided substantiating evidence by suggesting that improvements in HRQOL were not related to any specific service type (e.g, psychotherapy, acupuncture, or massage therapy), but instead may be related more globally to participation in an IH program; or, alternatively, to some other factor not measured here. While we did not find evidence for long-term effects on HRQOL or other emotional health outcomes, it is possible that our study was underpowered to detect an effect, given the smaller sample size at T3 (12-month follow-up).

Of note, the short-term benefits in HRQOL appear to be specific to an IH program embedded within a cancer center, as opposed to IH usage defined more broadly (i.e., IH services provided in the community). That is, improvements in HRQOL were not evidenced when examined according to self-reported use of IH services received in the community, nor were these gains witnessed in those who participated in composite (combined) usage (i.e., community usage in conjunction with our IH program). Thus, our findings imply that short-term benefits in HRQOL for cancer patients may be specific to integrative care offered internally within an oncology setting, as opposed to externally (in the community). It is important to note that community usage data was only available for a subset of the sample and may not be

representative of the range of complementary health services provided in community settings, limiting our ability to draw firm conclusions or comparisons from the data on community (or composite) usage. Additional research is needed to substantiate these findings and to allow for further exploration of the benefits of complementary and integrative health approaches offered within cancer care settings, as compared to those offered externally in the community.

With regard to the clinical meaningfulness of the observed change in HRQOL at T2, it should be noted that the overall magnitude of this change was relatively small; thus, it is difficult to determine how this change in HRQOL would translate to observable changes in the lives of cancer patients. The mechanisms associated with changes in HRQOL with IH usage are also unclear at this time. While it is plausible that cancer patients may experience cognitive or behavioral shifts preceding and/or following participation in an integrative care program in a cancer care center, these pathways are not well delineated in the literature and are in need of further exploration. To increase the clinical meaningfulness of findings, future studies may benefit from using behavioral markers, in addition to self-report measures, to capture changes that occur over time. Such an addition would be especially helpful in ascertaining real-world behavioral changes that may be related to potential improvements in HRQOL and overall wellbeing with IH intervention. Whereas the present study suggests that cancer patients may experience global improvements in HRQOL in the short-term, it does not lend itself to a deeper understanding of the nature of these improvements, as experienced in the lives of cancer patients.

Given our findings regarding *who* is seeking integrative care in a cancer care setting, the lack of impact of our intervention in the short- and long-term on depression and anxiety, as well as on somatic symptoms, indicates an important area of growth. That is, depressed and anxious cancer patients appear to be more inclined to seek integrative care, but do not appear to be

experiencing a significant reduction in depression and anxiety symptoms, nor do their symptoms appear to be worsening, in the course of their care. This finding is suggestive of an opportunity to more thoroughly assess and target depression and anxiety at the outset of participation in an IH program. One way to achieve this end would be to more extensively integrate psychological services with IH programs, which constitutes a vision for the future of holistic care that has recently emerged in the literature (Barnett & Shale, 2012). In fact, a unique feature of the current study is that our IH program offered traditional psychotherapy services alongside complementary health approaches. Whereas most programs offer mind-body and/or relaxation skills, our study is one of the first that we know of to examine traditional psychotherapy services offered as a part of an IH program for cancer patients. Exploratory analyses at T2 also offered support in favor of incorporating mental health care with integrative care to more effectively target depression and anxiety in cancer patients. That is, participants engaged in psychotherapy services in our study experienced greater improvements in depression and anxiety, as compared to those engaged in acupuncture or massage therapy, offering some evidence in support of the potential benefits of traditional mental health services for improving emotional health in an integrative oncology setting. Psychotherapy services may be a valuable component of integrative care in a cancer care setting and may complement integrative programs by effectively mitigating emotional distress (Barnett & Shale 2012). Given the prevalence and negative impact of depression and anxiety on cancer outcomes, including but not limited to mortality, effective psychosocial interventions are an especially pertinent area of development not only for integrative oncology, but also for cancer care more broadly (Knopf & Head, 2012; Spiegel & Giese-Davis, 2003).

With regard to immune outcomes, limited evidence emerged to support improvements in immune health following engagement in our IH program. That is, IH usage was not predictive of

improvements in immune functioning at T2, although a unique effect was detected at T3. Specifically, IH dosage (in minutes) emerged as predictive of T3 (12-month) levels of IL-6, with increased minutes of exposure to IH services associated with lower levels of circulating IL-6. Although this finding is promising, it should be interpreted with caution due to the small sample size (n = 14) of the subset allocated to the blood draw condition at T3. Another interesting finding regarding immune functioning emerged at T2 (3-month) when combining IH usage (dichotomous) with self-reported community usage to form a composite variable (dichotomous). Although neither IH usage nor community usage were independently predictive of improvements in immune health, composite usage emerged as a predictor of lower levels of circulating IL-6 and CRP at T2, suggesting that combined usage (i.e., community usage in conjunction with our IH program) may confer unique physical health benefits to cancer patients. This finding is notable and warrants more systematic exploration, given limitations associated with a current sample (i.e., subset only) and inconsistent results regarding composite usage across models. Nonetheless, our study lends some support to the evidence in support of improved immune functioning for cancer patients engaged in integrative care (see Subnis et al., 2014), albeit limited and inconsistent in nature. Very few studies have examined CRP as an immune outcome for cancer patients, with IL-6 being more consistently linked to immune functioning in cancer populations comparatively (Musselman et al., 2001). Given the overall limited effect detected for immune outcomes in the current sample, it is difficult to determine whether CRP is as reliable of an outcome measure as IL-6, although some inconsistencies were observed (i.e., slightly lesser effect detected for CRP, by comparison).

Overall, our study contributes to the body of evidence in support of the short-term benefits of integrative healthcare for cancer patients. Specifically, our findings lend support to

the notion of improved health-related quality of life (HRQOL) following participation in an IH program embedded within a cancer center. Finally, our data provide some clues regarding *who* is seeking integrative care in a cancer setting and subsequent areas of improvement for integrative programs. While depressed and anxious cancer patients were more inclined to seek integrative services in our study, they did not appear to be experiencing significant symptom improvement in this area. These findings suggest that cancer patients engaged in IH may be more likely to experience global benefits to overall health, as opposed to improvements in depressive, anxious, or somatic symptoms. Thus, cancer patients may benefit from a more extensive incorporation of psychological and integrative healthcare services to improve depressive and anxious symptomology, as well as overall emotional health and wellbeing. Our study is the first that we know of to explore traditional psychotherapy services offered within an integrative program at a cancer care center. We hope our data motivate future research on the integration of psychological services and CAM, as growing public interest and demand for holistic care is likely to only increase the need for further integration of care (Barnett & Shale, 2012).

Limitations and Future Directions

Although this study has its inherent strengths, it is not without its limitations. The present study was intended as a pilot study and employed a longitudinal, open-trial (non-controlled) design, allowing participants to self-select into services of their choosing. While this design approximates usage in a natural (real-world) setting, it does not lend itself to systematic exploration of the benefits of IH usage. Thus, future research would benefit from employing an experimental design, such as a randomized controlled trial (RCT), more conducive to systematically exploring outcomes associated with IH usage and controlling for potential confounds. Further, given the nature of the study design, the findings do not allow for causal

inferences regarding the effect of IH usage on emotional and immune health outcomes, nor do the findings reveal specific mechanisms by which IH usage may improve outcomes, namely health-related quality of life (HRQOL). However, the findings allow for tentative conclusions about the relationship between IH usage and improvements in HRQOL in cancer patients utilizing services offered within a cancer care setting; future longitudinal controlled trials would be better suited to explore causality and potential casual mechanisms within this context. An additional limitation stemming from our open-trial design pertains to the uncontrolled nature of frequency of IH use. In the current sample, frequency of use among those who self-selected into the IH usage group was relatively low, with 40% of the sample using services and frequency of use ranging from 1 to 29 times, with an average of 4.31 IH encounters. The low rate of use in the current sample, in conjunction with the uncontrolled nature of the design, may have limited our ability to detect an effect. Future randomized controlled trials (RCTs) would allow for a greater degree of control over frequency of use and dosage effects in order to determine the unique contribution of integrative care to improvements in emotional and immune functioning.

An additional limitation of the current study relates to attrition; it is important to note that those who did not complete follow-up data collection may differ from those who completed one or both of the follow-ups (e.g., mortality, severity of diagnosis, emotional distress, etc.). In particular, attrition is an especially salient issue for our blood-draw condition, which was limited to a subset of the sample (30%), rendering immune results more susceptible to the effects of attrition due to a smaller sample size. In addition, immune results may also be impacted by rates of use, with only 44% of the blood draw group using services, as well as by the broad range of cancer diagnoses and treatments captured in the current sample. Cancer treatment is known to exert an effect on immune functioning (e.g., see Miller et al., 2008); thus, examining effects of

IH usage on immune functioning with a sample spanning the cancer care continuum may have introduced a wealth of potential confounds, or noise, rendering interpretation particularly problematic. Thus, immune results should be interpreted with extreme caution. Future studies would benefit from employing a controlled design (e.g., RCT) with a more robust sample, wherein cancer variables, such as type, stage and treatment, are more systematically controlled in order to more clearly distinguish effects on immune functioning.

Furthermore, data on community usage of IH services was collected only for a subset of the sample (43% of the overall sample), as noted previously, and was limited to self-report data. As such, findings with regard to community usage may be limited in their generalizability, as the full range of community services and relative benefits may not be accurately represented by the subset. Future studies should examine community usage more systematically from the outset to capture the effects alone and/or in conjunction with integrative oncology programs. Understanding the prevalence of community use may also be of interest to healthcare providers (i.e., oncologists, nurses, psychologists, etc.), who have the responsibility of informing cancer patients of the unique benefits and potential contraindications of integrative services for overall emotional health and wellbeing (Deng & Cassileth, 2005a; Barnett & Shale, 2012).

To some extent, our study may have been limited in its power to detect effects, due to issues of design (open-trial) and relatedly, dosage and attrition, as discussed above. It is important to note that our findings are suggestive of fewer overall benefits to emotional health, with benefits limited primarily to HRQOL, as compared to previous research on integrative programs indicating improvements in a broader range of outcomes, including depression, anxiety, and physical/somatic symptoms (e.g., see Baker et al., 2012; Deng & Cassileth, 2005a). Additionally, issues of power may also be pertinent to our long-term (12-month) analyses and

those using only a subset of the sample, namely our immune and community usage analyses. Although T3 (12-month) findings were mostly consistent with those at T2 (3-month), with some exceptions, we may have been limited in our ability to detect long-term effects due to sample size. Lastly, our study may have been limited in its ability to detect change in physical/somatic symptoms, due lesser-established test-retest reliability and sensitivity to change for the PHQ-15 measure (Kroenke et al., 2010; Ravesteijn et al., 2009), which assesses a broad range of physical/somatic symptoms. Future studies may benefit from using a more sensitive or specific measure, targeting specific physical/somatic symptoms, such as cancer-related pain or fatigue, to elucidate potential change in these symptoms over time.

Despite its limitations, the current study has several strengths, including its longitudinal design and inclusion of patients spanning the cancer care continuum. While this study was intended as a pilot study and employed a non-controlled design, it effectively captures natural patterns of usage that reflect what might be expected in a real-world integrated oncology setting. Taken as a whole, our findings suggest that integrative care, offered as an adjunct to standard cancer care, may confer short-term benefits to cancer patients, particularly with regard to health-related QOL. Our study presently offers limited evidence in support of the long-term benefits of integrative care. Our findings also suggest that depressed and anxious cancer patients may be more inclined to seek integrative care but may not be maximally benefitting from IH intervention. Our findings provide some evidence to suggest that the incorporation of psychology services with integrative care may increase overall efficacy with regard to the alleviation of depressive and anxiety symptoms in cancer patients. Future researchers and clinicians should continue to investigate the ways in which integrative care may be further integrated with

psychological services to more readily assess, target, and mitigate emotional distress in cancer patients.

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APPENDIX

Table A-1.
Baseline characteristics and descriptive statistics of participants

		By self-selection at T2	
	Full sample (*n = 178*)	IH usage (*n = 61*)	Control (*n = 108*)
Gender, *n (%)*			
Female	149 (84%)	52 (85%)	90 (83%)
Male	29 (16%)	9 (15%)	18 (17%)
Age, *M (SD)*	58.2 (13.3)	56.9 (12.7)	58.1 (13.5)
Range	18 – 87		
Ethnicity, *n (%)*			
Caucasian	162 (91%)	57 (95%)	96 (89%)
Other	15 (8%)	3 (5%)	12 (11%)
Marital Status, *n (%)*			
Married	97 (55%)	40 (67%)	50 (47%)
Not Married	79 (44%)	20 (33%)	57 (53%)
Income, *n (%)*			
Below 50K	95 (53%)	30 (51%)	63 (59%)
Above 50K	79 (44%)	29 (49%)	43 (41%)
Years of Education, *M (SD)*	15.3 (2.9)	15.4 (2.8)	15.3 (3.0)
Range	10 - 26		
Cancer Type, *n (%)*			
Breast	76 (43%)	26 (43%)	46 (43%)
Other	102 (57%)	35 (57%)	62 (57%)
Cancer Stage, *n (%)*			
Stage 0-1	58 (33%)	19 (28%)	36 (37%)
Stage 2	30 (17%)	10 (20%)	18 (19%)
Stage 3	42 (24%)	16 (31%)	23 (24%)
Stage 4	27 (15%)	6 (12%)	20 (21%)
Chemotherapy, *n (%)*	100 (56%)	35 (60%)	59 (63%)
Radiation, *n (%)*	74 (42%)	30 (52%)	37 (39%)
Surgery, *n (%)*	68 (38%)	27 (47%)	37 (39%)
Years since Dx, *M (SD)*	3.60 (5.9)	3.76 (5.9)	3.14 (5.1)
Range	0 – 30		
Baseline depress, *M (SD)*	8.00 (6.4)	9.75 (6.8)	7.11 (6.0)
Baseline anx, *M (SD)*	6.18 (6.0)	7.52 (6.3)	5.45 (5.7)
Baseline somatic, *M (SD)*	9.06 (5.3)	9.43 (4.5)	9.03 (5.8)
Baseline QoL, *M (SD)*	3.04 (1.1)	2.98 (1.2)	3.04 (1.1)

Table A-2.

Correlations among Predictor Variables and IH usage

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Gender	-																
2. Age	-.07	-															
3. Ethnicity	-.03	-.09	-														
4. Marital Status	-.25**	.02	-.05	-													
5. Income	-.12	.10	-.10	.37**	-												
6. Years of Education	-.09	-.03	.08	.01	.16*	-											
7. Cancer Type	-.38**	-.01	.02	-.07	-.10	-.07	-										
8. Cancer Stage	-.14	.09	-.10	.01	-.01	-.08	.39**	-									
9. Chemotherapy	-.06	-.10	-.07	-.18*	.06	-.05	. 18*	.44**	-								
10. Radiation	.03	.15	-.07	.06	-.13	-.07	-.11	.02	.03	-							
11. Surgery	.20**	-.03	.09	.06	.11	-.07	-.36**	-.31**	-.29**	-.01	-						
12. Years Since Diagnosis	-.02	.28**	-.01	-.06	.02	-.08	-.01	.00	-.02	.11	.09	-					
13. Dep (PHQ-9) baseline	-.04	-.18*	-.07	-.10	-.25**	-.07	.13	-.00	-.03	-.07	-.06	-.06	-				
14. Anx (GAD-7) baseline	.02	-.20**	-.06	-.11	-.11	-.05	.05	.01	.08	-.06	.01	-.00	.81**				
15. Som (PHQ-15) baseline	.01	-.07	-.01	-.14	-.28**	-.02	.16*	.05	-.02	.04	-.00	-.07	.65**	.50**	-		
16. HRQOL baseline	.12	.16*	.07	.08	.15*	.20*	-.18*	-.11	-.05	-.01	.07	.07	-.52**	-.40**	-.56**	-	
17. IH usage (dichotomous)	.02	-.02	-.12	.17*	.11	.06	.01	-.04	-.03	.10	.03	-.02	.18*	.14	.01	-.01	-

Note. *$p < .05$; **$p < .01$; IH usage (1 = Yes; 0 = No) reflects overall use of services (i.e., usage at most recent time point).

Table A-3.
Correlations among demographics and IH variables with outcomes by time point

	Outcome variables																	
	Dep (T1)	Anx (T1)	Som (T1)	QoL (T1)	CRP (T1)	IL6 (T1)	Dep (T2)	Anx (T2)	Som (T2)	QoL (T2)	CRP (T2)	IL6 (T2)	Dep (T3)	Anx (T3)	Som (T3)	QoL (T3)	CRP (T3)	IL6 (T3)
Demographics																		
Gender	-.04	.02	.01	.12	-.23	-.24	.08	.06	.16	-.05	.20	.12	.001	-.03	.03	.04	.30	.20
Age	-.18*	-.20**	-.07	.16*	.05	.14	-.09	-.15	-.10	.01	.26	.28	-.19	-.16	-.19	.08	.08	-.15
Ethnicity	-.07	-.06	-.01	.07	-.08	-.11	-.05	-.03	-.02	.16	-.19	.09	.11	.10	.07	-.01	-.07	<.001
Marital Status	-.10	-.11	-.14	.08	.04	.14	-.05	-.13	-.04	.04	-.20	-.15	-.18	-.23*	-.31**	.14	.21	-.03
Income	-.25**	-.11	-.28**	.15*	.02	.03	-.21*	-.23*	-.25**	.19*	-.10	-.27	-.30**	-.22	-.34**	.29*	.37	.02
Years of Education	-.07	-.05	-.02	.20*	.05	.004	-.01	.04	-.02	.22*	-.48*	-.44*	-.15	-.16	-.04	.22	-.37	-.26
Cancer Type	.13	.05	.16*	-.18*	.10	.09	.12	.10	-.01	-.12	-.24	-.09	.28*	.25*	.36**	-.33**	.16	.30
Cancer Stage	-.004	.01	.05	-.11	.10	.19	.09	-.02	.07	-.07	-.20	-.08	.31**	.24*	.29*	-.34**	.39	.70*
Chemotherapy	-.03	.08	-.02	-.05	.11	.10	-.11	-.15	-.16	.16	.09	.07	.21	.14	.16	-.17	.16	.63*
Radiation	-.07	-.06	.04	-.01	-.01	-.05	-.16	-.07	.04	.02	.33	.29	-.01	-.12	-.08	-.05	.34	-.12
Surgery	-.06	.01	-.004	.07	-.08	-.001	.17	.13	.16	-.03	.23	.24	.01	.03	.05	-.07	.21	.16
Years Since Diagnosis	-.06	-.001	-.07	.07	-.14	-.13	-.004	.06	-.05	.07	-.01	.05	-.09	-.12	-.05	.05	-.08	-.19
IH variables																		
IH usage	.18*	.14	.01	-.01	.03	-.02	.01	-.002	.03	.05	-.18	-.14	-.003	-.03	-.10	.06	.38	.32
Community	-.14	-.12	-.18	.17	.04	.06	-.02	.02	-.02	.12	-.40	-.19	-.05	-.04	.15	.08	<.001	-.08
Composite	.01	.08	.04	-.10	.19	.001	.08	.08	.04	.01	-.54	-.44	.05	-.03	.10	-.07	<.001	-.08
	Dep (T1)	Anx (T1)	Som (T1)	QoL (T1)	CRP (T1)	IL6 (T1)	Dep (T2)	Anx (T2)	Som (T2)	QoL (T2)	CRP (T2)	IL6 (T2)	Dep (T3)	Anx (T3)	Som (T3)	QoL (T3)	CRP (T3)	IL6 (T3)
M (SD)	8.00 (6.4)	6.18 (6.0)	9.06 (5.3)	3.04 (1.1)	0.65 (1.1)	4.5 (5.7)	5.68 (5.4)	4.37 (4.8)	7.49 (4.7)	3.03 (1.1)	0.57 (.79)	3.76 (4.1)	6.64 (6.6)	5.04 (5.3)	7.61 (5.7)	3.14 (1.1)	0.30 (.27)	4.84 (5.0)
n	175	168	174	174	42	46	123	123	121	123	23	29	80	80	80	80	15	16

Note: *$p < .05$; **$p < .01$; IH usage (1 = Yes; 0 = No) reflects overall use of services (i.e., usage at most recent time point);
Community and composite usage (1 = Yes; 0 = No) apply only to a subset of the sample for which this data was available.

Table A-4.
Factors associated with IH usage

	Model 1: Depression (PHQ-9)				
	Est. (SE)	OR (β^e)	CI- lower	CI- upper	*p*
Gender	-0.08 (.62)	.93	0.27	3.12	.90
Age	-0.001 (.02)	1.00	0.97	1.03	.97
Ethnicity	0.85 (.86)	2.34	0.43	12.6	.32
Marital Status	-0.57 (.48)	0.57	0.22	1.44	.23
Income	-0.45 (.47)	0.64	0.26	1.59	.33
Years of Education	0.04 (.05)	1.04	0.94	1.14	.44
Cancer Type	-0.42 (.47)	0.66	0.26	1.65	.37
Chemotherapy	0.14 (.44)	1.15	0.48	2.75	.75
Radiation	-0.79 (.43)	0.45	0.20	1.05	.07
Surgery	-0.51 (.45)	0.60	0.25	1.44	.25
Years Since Diagnosis	-0.01 (.04)	0.99	0.92	1.06	.70
Baseline PHQ-9	0.09 (.03)	1.10	1.03	1.17	.004**
	Model 2: Anxiety (GAD-7)				
	Est. (SE)	OR (β^e)	CI- lower	CI- upper	*p*
Gender	.13 (.64)	1.14	0.32	4.00	.84
Age	-0.001 (.02)	1.00	0.97	1.03	.94
Ethnicity	.90 (.86)	2.45	0.46	13.10	.30
Marital Status	-0.60 (.49)	0.55	0.21	1.42	.22
Income	-0.27 (.46)	0.76	0.31	1.87	.56
Years of Education	.03 (.05)	1.03	0.93	1.13	.57
Cancer Type	-0.44 (.48)	0.64	0.25	1.65	.36
Chemotherapy	.34 (.45)	1.41	0.58	3.42	.45
Radiation	-0.69 (.44)	0.50	0.21	1.18	.11
Surgery	-0.40 (.45)	0.67	0.28	1.63	.38
Years Since Diagnosis	-0.03 (.04)	0.98	0.91	1.05	.51
Baseline GAD-7	.09 (.03)	1.09	1.02	1.16	.01**
	Model 3: Somatic Symptoms (PHQ-15)				
	Est. (SE)	OR (β^e)	CI- lower	CI- upper	*p*
Gender	0.07 (.60)	1.07	.33	3.49	.91
Age	-0.01 (.02)	.99	.96	1.03	.65
Ethnicity	1.09 (.84)	2.98	.58	15.35	.19
Marital Status	-0.49 (.46)	.61	.25	1.51	.29
Income	-0.16 (.45)	.85	.35	2.05	.72
Years of Education	0.03 (.05)	1.03	.94	1.13	.59
Cancer Type	-0.44 (.47)	.65	.26	1.61	.35
Chemotherapy	0.23 (.42)	1.25	.55	2.87	.59
Radiation	-0.58 (.41)	.56	.25	1.24	.15
Surgery	-0.45 (.44)	.64	.27	1.50	.31
Years Since Diagnosis	-0.01 (.03)	.99	.92	1.06	.72
Baseline PHQ-15	0.01 (.04)	1.01	.94	1.13	.83

Table A-4 Continued

	Model 4: Health-Related Quality of Life (HRQOL)				
	Est. (SE)	OR (β^e)	CI- lower	CI- upper	*p*
Gender	0.15 (.61)	1.16	0.35	3.82	.81
Age	-0.01 (.02)	0.99	0.96	1.03	.61
Ethnicity	1.09 (.84)	2.95	0.57	15.27	.20
Marital Status	-0.42 (.46)	0.65	0.26	1.62	.36
Income	-0.12 (.44)	0.89	0.38	2.11	.79
Years of Education	0.03 (.05)	1.03	0.93	1.13	.61
Cancer Type	-0.38 (.46)	0.68	0.28	1.70	.41
Chemotherapy	0.19 (.42)	1.21	0.53	2.78	.65
Radiation	-0.64 (.41)	0.53	0.24	1.18	.12
Surgery	-0.42 (.44)	0.66	0.28	1.55	.34
Years Since Diagnosis	-0.02 (.04)	0.98	0.91	1.05	.54
Baseline HRQOL	0.02 (.18)	1.02	0.72	1.44	.92

Note. *$p < .05$; **$p < .01$;
IH usage (1 = Yes; 0 = No) reflects overall use (i.e., usage at most recent time point);
Due to a high degree of correlation between cancer variables (i.e., cancer type, cancer stage, and treatment type), cancer stage was removed from the model to increase power.

Table A-5.
Outcomes data for IH usage at 3-month follow-up

	Model 1a: Depression (PHQ-9); $R^2 = .38$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-1.40 (.81)	-0.13	-3.01	0.21	.09
Baseline PHQ-9	0.53 (.06)	0.63	0.41	0.66	.000**
	Model 1b: Depression (PHQ-9); $R^2 = .37$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.003 (.003)	-0.07	-0.01	0.003	.34
Baseline PHQ-9	0.52 (.06)	0.62	0.40	0.64	.000**
	Dep (T1)	Dep (T2)	n		
M (SD)	7.66 (6.4)	5.73 (5.4)	122		
	Model 2a: Anxiety (GAD-7); $R^2 = .37$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-0.48 (.74)	-0.05	-1.94	0.98	.52
Baseline GAD-7	0.50 (.06)	0.62	0.39	0.62	.000**
	Model 2b: Anxiety (GAD-7); $R^2 = .37$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.002 (.003)	-0.06	-0.01	0.003	.41
Baseline GAD-7	0.51 (.06)	0.63	0.39	0.63	.000**
	Anx (T1)	Anx (T2)	n		
M (SD)	5.84 (5.9)	4.47 (4.8)	118		
	Model 3a: Somatic Symptoms (PHQ-15); $R^2 = .49$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-0.17 (0.64)	-0.02	-1.44	1.11	.80
Baseline PHQ-15	0.64 (0.06)	0.70	0.52	0.76	.000**
	Model 3b: Somatic Symptoms (PHQ-15); $R^2 = .48$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	0.000 (.002)	0.01	-0.01	.005	.93
Baseline PHQ-15	0.64 (.06)	0.70	0.52	0.76	.000**
	Som (T1)	Som (T2)	n		
M (SD)	8.65 (5.2)	7.57 (4.7)	119		
	Model 4a: Health-Related Quality of Life (HRQOL); $R^2 = .48$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	0.32 (.15)	0.14	0.03	0.62	.03*
Baseline HRQOL	0.70 (.07)	0.70	0.57	0.83	<.001**

Table A-5 Continued

	Model 4b: Health-Related Quality of Life (HRQOL); $R^2 = .47$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	0.001 (.001)	0.07	-0.001	0.002	.30
Baseline HRQOL	0.69 (.07)	0.69	0.56	0.82	<.001**
	QoL (T1)	QoL (T2)	n		
M (SD)	3.10 (1.1)	3.02 (1.1)	122		
	Model 5a: C-Reactive Protein (CRP); $R^2 = .35$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-0.32 (.32)	-0.19	-0.99	0.34	.32
Baseline CRP	0.83 (.25)	0.61	0.30	1.36	.004**
	Model 5b: C-Reactive Protein (CRP); $R^2 = .33$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.001 (.001)	-0.13	-0.004	0.002	.50
Baseline CRP	0.83 (.26)	0.61	0.29	1.37	.01**
	CRP (T1)	CRP (T2)	n		
M (SD)	0.53 (0.6)	0.62 (0.8)	20		
	Model 6a: Interleukin-6 (IL-6); $R^2 = .55$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-1.25 (1.1)	-0.15	-3.60	1.09	.28
Baseline IL-6	0.68 (.12)	0.75	0.43	0.94	.000**
	Model 6b: Interleukin-6 (IL-6); $R^2 = .56$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.01 (.01)	-0.18	-0.02	0.003	.20
Baseline IL-6	0.68 (.12)	0.74	0.43	0.93	.000**
	IL-6 (T1)	IL-6 (T2)	n		
M (SD)	4.14 (4.6)	4.07 (4.2)	26		

Note. *$p < .05$; **$p < .01$

Table A-6.
Outcomes data for IH usage at 3-month follow-up, controlling for community usage (subset only)

	Model 1a: Depression (PHQ-9); $R^2 = .32$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-0.87 (1.0)	-0.08	-2.90	1.15	.39
Baseline PHQ-9	0.54 (.09)	0.61	0.36	0.71	.00**
Community usage	0.88 (1.1)	0.08	-1.22	2.97	.41
	Model 1b: Depression (PHQ-9); $R^2 = .31$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.002 (.004)	-0.05	-0.01	0.01	.62
Baseline PHQ-9	0.53 (.09)	0.59	0.35	0.70	.00**
Community usage	0.74 (1.0)	0.07	-1.33	2.82	.48
	Dep (T1)	Dep (T2)	n		
M (SD)	7.10 (5.9)	5.56 (5.2)	77		
	Model 2a: Anxiety (GAD-7); $R^2 = .32$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-0.56 (.84)	-0.07	-2.24	1.12	.51
Baseline GAD-7	0.51 (.08)	0.60	0.34	0.68	.00**
Community usage	1.60 (.91)	0.18	-0.22	3.42	.09
	Model 2b: Anxiety (GAD-7); $R^2 = .32$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.002 (.003)	-0.08	-0.01	0.004	.43
Baseline GAD-7	0.51 (.08)	0.60	0.34	0.67	.00**
Community usage	1.54 (.90)	0.17	-0.25	3.33	.09
	Anx (T1)	Anx (T2)	n		
M (SD)	5.12 (5.1)	4.00 (4.3)	74		
	Model 3a: Somatic Symptoms (PHQ-15); $R^2 = .53$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-0.31 (0.75)	-0.03	-1.80	1.19	.69
Baseline PHQ-15	0.69 (0.07)	0.75	0.54	0.83	.00**
Community usage	1.02 (0.79)	0.11	-0.56	2.60	.20
	Model 3b: Somatic Symptoms (PHQ-15); $R^2 = .53$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.002 (.003)	-0.05	-0.01	.004	.52
Baseline PHQ-15	0.68 (.07)	0.75	0.53	0.83	.00**
Community usage	0.99 (.78)	0.10	-0.57	2.54	.21
	Som (T1)	Som (T2)	n		
M (SD)	8.49 (5.1)	7.60 (4.6)	75		

Table A-6 Continued

	Model 4a: Health-Related Quality of Life (HRQOL); $R^2 = .42$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	0.43 (.19)	0.20	0.05	0.82	.03*
Baseline HRQOL	0.65 (.09)	0.66	0.47	0.82	<.001**
Community usage	-0.03 (.21)	-0.01	-0.44	0.38	.89
	Model 4b: Health-Related Quality of Life (HRQOL); $R^2 = .38$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	0.00 (.001)	0.04	-0.001	0.002	.70
Baseline HRQOL	0.62 (.09)	0.64	0.44	0.80	<.001**
Community usage	0.05 (.21)	0.02	-0.36	0.47	.81
	QoL (T1)	QoL (T2)	n		
M (SD)	3.16 (1.1)	3.05 (1.1)	76		
	Model 5a: C-Reactive Protein (CRP); $R^2 = .38$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-0.19 (.71)	-0.09	-2.02	1.63	.80
Baseline CRP	1.07 (.60)	0.56	-0.46	2.61	.13
Community usage	-1.02 (.68)	-0.43	-2.76	0.72	.19
	Model 5b: C-Reactive Protein (CRP); $R^2 = .38$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.001 (.002)	-0.08	-0.01	0.01	.81
Baseline CRP	1.09 (.57)	0.57	-0.38	2.56	.12
Community usage	-1.05 (.67)	-0.44	-2.78	0.68	.18
	CRP (T1)	CRP (T2)	n		
M (SD)	0.57 (0.6)	0.76 (1.2)	9		
	Model 6a: Interleukin-6 (IL-6); $R^2 = .63$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-1.48 (1.7)	-0.16	-5.27	2.31	.40
Baseline IL-6	0.88 (.20)	0.78	0.43	1.33	.001**
Community usage	-1.68 (1.6)	-0.17	-5.32	1.95	.33
	Model 6b: Interleukin-6 (IL-6); $R^2 = .63$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.01 (.01)	-0.14	-0.02	0.01	.43
Baseline IL-6	0.90 (.20)	0.79	0.46	1.34	.001**
Community usage	-1.83 (1.6)	-0.19	-5.50	1.83	.29
	IL-6 (T1)	IL-6 (T2)	n		
M (SD)	3.92 (4.4)	3.87 (5.0)	14		

Note. *$p < .05$; **$p < .01$

Table A-7.

Outcomes data for Composite usage (IH usage + Community usage) at 3-month follow-up (subset only)

	Model 1: Depression (PHQ-9); $R^2 = .32$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
Composite usage (0=No; 1=Yes)	0.19 (1.0)	0.02	-1.80	2.19	.85
Baseline PHQ-9	0.51 (.08)	0.58	0.34	0.68	.000**
	Dep (T1)	Dep (T2)	n		
M (SD)	7.10 (5.9)	5.56 (5.2)	77		
	Model 2: Anxiety (GAD-7); $R^2 = .31$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
Composite usage (0=No; 1=Yes)	1.04 (.84)	0.12	-0.64	2.71	.22
Baseline GAD-7	0.48 (.08)	0.57	0.31	0.64	<.001**
	Anx (T1)	Anx (T2)	n		
M (SD)	5.12 (5.1)	4.00 (4.3)	74		
	Model 3: Somatic Symptoms (PHQ-15); $R^2 = .53$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
Composite usage (0=No; 1=Yes)	0.16 (0.76)	0.02	-1.35	1.67	.83
Baseline PHQ-15	0.67 (0.07)	0.73	0.52	0.81	.000**
	Som (T1)	Som (T2)	n		
M (SD)	8.49 (5.1)	7.60 (4.6)	75		
	Model 4: Health-Related Quality of Life (HRQOL); $R^2 = .40$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
Composite usage (0=No; 1=Yes)	0.17 (.20)	0.08	-0.23	0.56	.41
Baseline HRQOL	0.63 (.09)	0.64	0.45	0.81	<.001**
	QoL (T1)	QoL (T2)	n		
M (SD)	3.16 (1.1)	3.05 (1.1)	76		
	Model 5: C-Reactive Protein (CRP); $R^2 = .65$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
Composite usage (0=No; 1=Yes)	-1.60 (.60)	-0.59	-3.07	-0.13	.04*
Baseline CRP	0.90 (.42)	0.47	-0.14	1.94	.08
	CRP (T1)	CRP (T2)	n		
M (SD)	0.57 (0.6)	0.76 (1.2)	9		
	Model 6: Interleukin-6 (IL-6); $R^2 = .74$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
Composite usage (0=No; 1=Yes)	-3.61 (1.5)	-0.34	-6.93	-0.28	.04*
Baseline IL-6	0.88 (.16)	0.78	0.53	1.24	.000**
	IL-6 (T1)	IL-6 (T2)	n		
M (SD)	3.92 (4.4)	3.87 (5.0)	14		

Note. *$p < .05$; **$p < .01$

Table A-8.
One-way ANOVA of Outcome Mean Change Scores (T2-T1) by IH Service

	Service Type								
	Massage therapy		Psychotherapy		Acupuncture		*F*	*p*	η^2
Outcomes	*n*	M (SE)	*n*	M (SE)	*n*	M (SE)			
Depression (T2-T1)	20	-1.65 (.73)	14	-7.71 (2.0)	10	-1.50 (.78)	4.93	.005**	.265
Anxiety (T2-T1)	18	-0.78 (.93)	14	-6.07 (1.5)	10	0.60 (.85)	5.86	.002**	.311
Somatic Symptoms (T2-T1)	20	-0.65 (.87)	14	-3.14 (1.1)	10	-0.40 (1.3)	1.67	.188	.109
HRQOL (T2-T1)	20	0.05 (.17)	14	0.21 (.33)	10	0.30 (.30)	.175	.913	.013

Note. *$p < .05$; **$p < .01$

Table A-9.
Independent T-test of Outcome Mean Change Scores (T2-T1) by IH usage

	IH usage						
	Yes		No		*t*	*p*	η^2
Outcomes	*n*	M (SE)	*n*	M (SE)			
Depression (T2-T1)	45	-3.58 (.83)	77	-0.97 (.56)	2.70	.008**	.057
Anxiety (T2-T1)	43	-2.12 (.78)	75	-0.93 (.53)	1.29	.201	.014
Somatic Symptoms (T2-T1)	45	-1.29 (.62)	74	-0.95 (.42)	0.47	.638	.002
HRQOL (T2-T1)	45	0.16 (.14)	77	-0.23 (.09)	-2.39	.018*	.046

Note. *$p < .05$; **$p < .01$

Table A-10.

Independent T-test of Outcome Mean Change Scores (T2-T1) by Self-Reported Community usage.

	Community usage						
	Yes		No		*t*	*p*	η^2
Outcomes	*n*	M (SE)	*n*	M (SE)			
Depression (T2-T1)	27	-0.52 (.78)	50	-2.10 (.79)	-1.30	.197	.022
Anxiety (T2-T1)	24	0.58 (.87)	50	-1.94 (.61)	-2.37	.021*	.072
Somatic Symptoms (T2-T1)	26	0.77 (.62)	49	-1.41 (.53)	-1.73	.087	.039
HRQOL (T2-T1)	26	-0.15 (.19)	50	-0.80 (.13)	0.33	.746	.001

Note. *$p < .05$; **$p < .01$

Table A-11.

Outcomes data for IH usage at 12-month follow-up

	Model 1a: Depression (PHQ-9); R^2 = .51				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-1.73 (1.2)	-0.12	-4.12	0.66	.15
Baseline PHQ-9	0.73 (.08)	0.73	0.57	0.88	<.001**
	Model 1b: Depression (PHQ-9); R^2 = .51				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.003 (.002)	-0.10	-0.01	0.001	.19
Baseline PHQ-9	0.72 (.08)	0.72	0.56	0.87	<.001**
	Dep (T1)	Dep (T2)	n		
M (SD)	7.84 (6.6)	6.72 (6.6)	79		
	Model 2a: Anxiety (GAD-7); R^2 = .36				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-1.80 (1.2)	-0.14	-4.14	0.55	.13
Baseline GAD-7	0.53 (.08)	0.62	0.37	0.69	<.001**
	Model 2b: Anxiety (GAD-7); R^2 = .37				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.004 (.002)	-0.16	-0.01	0.001	.09
Baseline GAD-7	0.52 (.08)	0.62	0.37	0.68	<.001**
	Anx (T1)	Anx (T2)	n		
M (SD)	6.80 (6.3)	5.01 (5.4)	76		
	Model 3a: Somatic Symptoms (PHQ-15); R^2 = .47				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-1.09 (1.1)	-0.08	-3.25	1.07	.32
Baseline PHQ-15	0.73 (0.09)	0.69	0.55	0.91	<.001**
	Model 3b: Somatic Symptoms (PHQ-15); R^2 = .47				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.001 (.002)	-0.04	-0.01	.003	.66
Baseline PHQ-15	0.73 (.09)	0.69	0.55	0.91	<.001**
	Som (T1)	Som (T2)	n		
M (SD)	9.05 (5.4)	7.71 (5.7)	78		
	Model 4a: Health-Related Quality of Life (HRQOL); R^2 = .42				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	0.02 (.22)	0.01	-0.41	0.45	.93
Baseline HRQOL	0.68 (.09)	0.66	0.50	0.85	<.001**

Table A-11 Continued

	Model 4b: Health-Related Quality of Life (HRQOL); $R^2 = .43$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	.000 (.000)	0.07	.000	.001	.44
Baseline HRQOL	0.67 (.09)	0.65	0.49	0.84	<.001**
	QoL (T1)	QoL (T2)	n		
M (SD)	3.12 (1.1)	3.11 (1.1)	79		
	Model 5a: C-Reactive Protein (CRP); $R^2 = .17$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	0.09 (.15)	0.17	-0.24	0.43	.56
Baseline CRP	0.19 (.12)	0.45	0.07	0.45	.14
	Model 5b: C-Reactive Protein (CRP); $R^2 = .24$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.001 (.001)	-0.35	-0.002	0.001	.26
Baseline CRP	0.30 (.12)	0.72	0.03	0.57	.03*
	CRP (T1)	CRP (T2)	n		
M (SD)	0.63 (0.6)	0.31 (0.3)	14		
	Model 6a: Interleukin-6 (IL-6); $R^2 = .54$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-1.59 (2.5)	-0.15	-6.99	3.81	.53
Baseline IL-6	0.78 (.23)	0.81	0.28	1.27	.01**
	Model 6b: Interleukin-6 (IL-6); $R^2 = .68$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.02 (.01)	-0.58	-0.04	-0.007	.01**
Baseline IL-6	1.04 (.19)	1.08	0.64	1.45	.000**
	IL-6 (T1)	IL-6 (T2)	n		
M (SD)	4.63 (5.3)	5.07 (5.1)	15		

Note. *$p < .05$; **$p < .01$

Table A-12.

Outcomes data for IH usage at 12-month follow-up, controlling for community usage (subset only)

	Model 1a: Depression (PHQ-9)); R^2 = .48				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-1.31 (1.8)	-0.10	-4.95	2.32	.47
Baseline PHQ-9	0.84 (.14)	0.74	0.55	1.13	<.001**
Community usage	0.69 (1.7)	0.05	-2.67	4.05	.68
	Model 1b: Depression (PHQ-9); R^2 = .47				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	.000 (.004)	0.01	-0.01	0.01	.93
Baseline PHQ-9	0.82 (.14)	0.72	0.53	1.10	<.001**
Community usage	0.22 (1.7)	0.02	-3.30	3.75	.90
	Dep (T1)	Dep (T2)	n		
M (SD)	6.14 (5.5)	5.44 (6.2)	36		
	Model 2a: Anxiety (GAD-7); R^2 = .20				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-2.13 (1.5)	-0.24	-5.08	0.83	.15
Baseline GAD-7	0.43 (.13)	0.51	0.16	0.71	.003**
Community usage	1.40 (1.4)	0.17	-1.45	4.24	.33
	Model 2b: Anxiety (GAD-7); R^2 = .16				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.003 (.004)	-0.12	-0.01	0.005	.47
Baseline GAD-7	0.41 (.14)	0.48	0.13	0.68	.01**
Community usage	1.14 (1.47)	0.14	-1.86	4.14	.44
	Anx (T1)	Anx (T2)	n		
M (SD)	5.22 (4.8)	3.58 (4.1)	36		
	Model 3a: Somatic Symptoms (PHQ-15); R^2 = .48				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-2.13 (1.6)	-0.17	-5.36	1.10	.19
Baseline PHQ-15	0.78 (.14)	0.69	0.49	1.06	.000**
Community usage	2.04 (1.5)	0.18	-0.97	5.04	.18
	Model 3b: Somatic Symptoms (PHQ-15); R^2 = .46				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	-0.003 (.004)	-0.09	-0.01	.01	.51
Baseline PHQ-15	0.77 (.14)	0.68	0.49	1.06	<.001**
Community usage	1.87 (1.6)	0.16	-1.35	5.09	.25
	Som (T1)	Som (T2)	n		
M (SD)	8.33 (5.0)	6.78 (5.6)	36		

Table A-12 Continued

	Model 4a: Health-Related Quality of Life (HRQOL); $R^2 = .41$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH usage (0=No; 1=Yes)	-0.06 (.34)	-0.25	-0.75	0.62	.86
Baseline HRQOL	0.71 (.14)	0.68	0.43	0.98	<.001**
Community usage	0.10 (.31)	0.04	-0.54	0.74	.75
	Model 4b: Health-Related Quality of Life (HRQOL); $R^2 = .42$				
	Est. (SE)	β	CI- lower	CI- upper	*p*
IH dosage (minutes)	.000 (.001)	0.08	-0.001	0.002	.61
Baseline HRQOL	0.69 (.14)	0.66	0.41	0.97	<.001**
Community usage	0.01 (.33)	0.01	-0.65	0.68	.97
	QoL (T1)	QoL (T2)	n		
M (SD)	3.22 (1.1)	3.19 (1.1)	36		

Note. *$p < .05$; **$p < .01$

Table A-13.

***Outcomes data for Composite usage (IH usage + Community usage) at 12-month follow-up* (subset only)**

	Model 1: Depression (PHQ-9); R^2 = .49				
	Est. (SE)	β	CI- lower	CI- upper	*p*
Composite usage (0=No; 1=Yes)	-0.18 (1.5)	-0.02	-3.21	2.85	.91
Baseline PHQ-9	0.82 (.14)	0.72	0.54	1.10	<.001**
	Dep (T1)	Dep (T2)	n		
M (SD)	6.14 (5.5)	5.44 (6.2)	36		
	Model 2: Anxiety (GAD-7); R^2 = .17				
	Est. (SE)	β	CI- lower	CI- upper	*p*
Composite usage (0=No; 1=Yes)	-0.09 (1.26)	-0.01	-2.65	2.46	.94
Baseline GAD-7	0.39 (.13)	0.46	0.12	0.66	.01**
	Anx (T1)	Anx (T2)	n		
M (SD)	5.22 (4.8)	3.58 (4.1)	36		
	Model 3: Somatic Symptoms (PHQ-15); R^2 = .45				
	Est. (SE)	β	CI- lower	CI- upper	*p*
Composite usage (0=No; 1=Yes)	0.14 (1.40)	0.001	-2.84	2.87	.99
Baseline PHQ-15	0.78 (0.14)	0.69	0.49	1.07	<.001**
	Som (T1)	Som (T2)	n		
M (SD)	8.33 (5.0)	6.78 (5.6)	36		
	Model 4: Health-Related Quality of Life (HRQOL); R^2 = .43				
	Est. (SE)	β	CI- lower	CI- upper	*p*
Composite usage (0=No; 1=Yes)	-0.16 (.28)	-0.07	-0.73	0.41	.57
Baseline HRQOL	0.71 (.13)	0.68	0.44	0.98	<.001**
	QoL (T1)	QoL (T2)	n		
M (SD)	3.22 (1.1)	3.19 (1.1)	36		

Note. *$p < .05$; **$p < .01$

VITA

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