Natural Products for the Treatment of Cancer-Related Fatigue

By

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A
Dissertation

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Abstract

Cancer-related fatigue (CRF) is a complex and common issue for many cancer survivors. CRF is a complex multidimensional symptom with poorly understood etiology, wide variation in severity between individuals, and a negative impact on multiple aspects of a cancer survivor's life. CRF can make basic activities of daily living, like showering or grocery shopping, a burdensome chore. A reported 40% or more of cancer survivors use complementary health approaches to manage their symptoms, illustrating a great need to understand why cancer survivors are using these approaches and their efficacy. Current evidence has identified cancer survivors' use of complementary approaches but often do not discuss why the approaches are being used. Natural products are the most reported complementary approach used in the United States. The limited evidence-based options to manage CRF highlight a critical need to determine the acceptability, safety, and efficacy of novel interventions for CRF.

This dissertation is grounded in the Theory of Unpleasant Symptoms. The purpose of this manuscript dissertation is to assess the acceptability, effectiveness, and safety of natural products for the treatment of CRF through two integrative reviews, a retrospective descriptive study, and a prospective descriptive cross-sectional study. Each chapter of this dissertation is designed to answer the overarching question "Why are cancer survivors using natural products, and are they safe, acceptable and effective for the treatment of CRF?"

Results

Our results found that natural products may be a safe and acceptable treatment for CRF; however, there is not enough evidence to support them as a standard of practice to treat CRF. Currently, out of the natural products reviewed, ginseng has the most evidence to support its use as a treatment for CRF. We found that complementary approaches including natural products

may be psychologic and physiologic influencing factors as evidenced by the global assessment of change results, and that those who used complementary approaches reported improved performance, defined as physical activity. Additionally, we confirmed high rates of use and satisfaction with complementary approach usage among cancer survivors. We also found a higher rate of reporting complementary approach usage to care teams in this population of patients who received an integrative health consult. The results of this dissertation support continued research that 1) assesses natural products' safety and efficacy as a treatment for CRF, and 2) identifies interventions to assist both cancer survivors and cancer teams on how to navigate the complex world of complementary approaches in the setting of cancer and cancer treatment.

Conclusion

Due to the increasing success of cancer treatment and aging population, we are seeing the numbers of cancer survivors rise. During and after treatment, CRF is a distressing symptom that can impact many aspects of a cancer survivor's life. Complementary approaches including natural products are a promising and acceptable treatment for CRF. In order to help mitigate this complex symptom, we need to find safe, effective and acceptable treatments. This dissertation helps to support my long-term research goals to 1) find safe and effective treatments for CRF; and 2) develop interventions that help abate the risk or potential risks posed by complementary approaches for cancer survivors.

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CHAPTER I: Introduction to Dissertation

Cancer-related fatigue (CRF) is the most common side effect reported by cancer survivors (Ling, Lui, So, & Chan, 2014). There are over 15 million cancer survivors in the United States and the number is expected to rise to over 20 million by 2026 (American Cancer Society, 2016). The Centers for Disease Control and Prevention (CDC) defines a cancer survivor as someone who has been diagnosed with cancer from time of diagnosis through their lifespan (Centers for Disease Control and Prevention, 2017). CRF is a complex multidimensional symptom with poorly understood etiology, wide variation in severity between individuals, and a negative impact on multiple aspects of a cancer survivor's life (Bower, 2014). CRF can make basic activities of daily living like showering or grocery shopping a burdensome chore. Additionally, CRF can negatively impact relationships and a person's ability to work (Centers for Disease Control and Prevention, 2017). All of this can result in decreased overall quality of life.

The mechanism for CRF is still unclear. Because of the high incidence of fatigue as an acute side effect of treatment and the recognition that CRF can persist following treatment, a large number of studies have examined the characteristics, pattern, measurement, and impact of fatigue. A variety of interventions for preventing and/or managing fatigue have been tested, and there is some research on mechanisms hypothesized to cause CRF. Proposed mechanisms for CRF during treatment include treatment-induced myelosuppression, acute cytokine responses to cytotoxic drugs or immunotherapy, tissue damage, and sleep disruption (Bower, 2014). Proposed mechanisms for post-treatment CRF include muscle mass loss, chronic inflammation, immune dysregulation, and hormone deficiencies (Bower, 2014; Saligan et al., 2015).

The Oncology Nursing Society clinical practice guideline for CRF only recommends exercise/physical activity as a treatment for CRF (Mitchell, 2014). Some limitations in the evidence supporting exercise have been noted. For instance, some of the identified limitations consist of the inclusion of non-fatigued survivors in some studies and barriers to exercise interventions that require an instructor or exercise equipment that may limit who can participate due to access issues like distance, scheduling, and cost (Blaney, 2010; Bower, 2014). Individual variation in exercise adherence may also influence the impact of exercise on CRF (Blaney, 2010; Bower, 2014). The National Comprehensive Cancer Network (NCCN) recommendations for CRF are the first practice guidelines to address any known causes for fatigue in the general population, including emotional distress, sleep disturbances, and anemia. Once these have been ruled out, the NCCN recommends additional interventions including stress reduction strategies, energy conservation skills training, antidepressants, and psychostimulants (Berger, 2016). However, the majority of the evidence used to support these recommendations consists of studies with cross-sectional designs that lacked a comparison group, and utilized small heterogeneous samples (Berger, 2016). Other reviews have concluded that these same interventions have mixed results and that stronger research methods including active controls and larger samples are needed (Bower, 2014).

It is estimated that 40% of cancer survivors report using complementary health approaches to manage their symptoms (Huebner et al., 2014), illustrating a great need to understand why cancer survivors are using these approaches and their efficacy. Current evidence has identified cancer survivors' use of complementary approaches but often do not discuss why the approaches are being used (Adams, 2005; Anderson & Taylor, 2012; Lewith, 2002; Loquai et al., 2017; Samuels, 2015). When patients' reasons were assessed, frequently the symptoms or

approaches were reported in broad categories like physical symptoms (Frenkel, 2010; Heinze, 2015; Samuels, 2015). Complementary health approaches include natural products like herbs and mind and body practices like yoga (National Center for Complementary and Integrative Health, 2016a). Natural products like herbs or supplements are derived from a living organism and are believed to have a pharmacologic effect (National Center for Complementary and Integrative Health, 2016b). Natural products are the most reported complementary approach used in the United States (National Center for Complementary and Integrative Health, 2016a). Herbs are one of the most commonly reported natural products used by cancer survivors (Anderson & Taylor, 2012). The limited evidence-based options to manage CRF highlight a critical need to determine the acceptability, safety, and efficacy of novel interventions for CRF. This dissertation aimed to advance cancer symptom management by evaluating why cancer survivors are using complementary approaches and assessing the efficacy of these approaches, specifically natural products, as a treatment for CRF. These results hope to inform patient-provider strategies for managing CRF.

Theoretical Framework

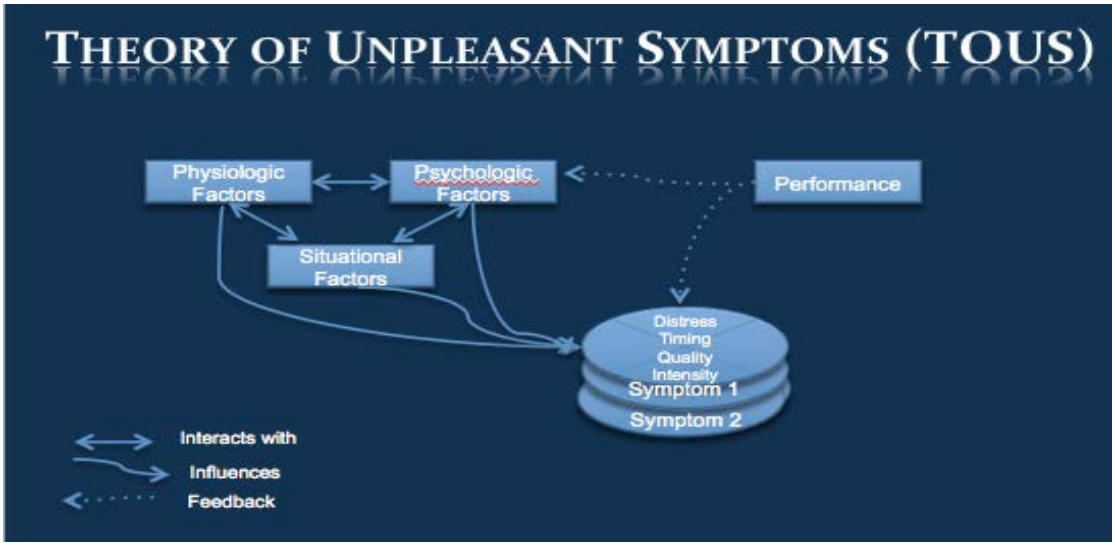

Figure 1: Theory of Unpleasant Symptoms

This dissertation is grounded in the Theory of Unpleasant Symptoms (TOUS) (Figure 1) (Lenz & Pugh, 2014). TOUS has three key concepts: symptom, influencing factors and performance outcomes (Lenz & Pugh, 2014). The theory is a loop, with the influencing factors impacting the symptom(s) and the symptom(s) impacting the performance and, ultimately, the performance impacting the influencing factors (Lenz & Pugh, 2014). Influencing factors in TOUS include physiological factors, psychological factors (mood and cognitive variables), and situational factors (environment, social economic standing, social support, culture) that can impact the symptom experience (Barton et al., 2010; Lenz, Pugh, Milliagan, Gift, & Suppe, 1997; Yennurajalingam et al., 2015). This dissertation aims to evaluate natural products, which are believed to influence both physiologic (i.e., inflammatory response) and psychologic factors (i.e., anxiety, stress) (Barton et al., 2010; Yennurajalingam et al., 2015). These influences by the natural product are expected to improve the symptom experience and result in improved performance. In TOUS, performance is conceptualized as cognitive and functional (Lenz et al., 1997). Cognitive performance is often operationalized as concentration or problem solving (Lenz et al., 1997). Functional performance can be operationalized as activity of daily living, physical activity, social interaction and role performance (Lenz et al., 1997). In this dissertation, we operationalize performance using the functional performance outcome of physical activity (Lenz et al., 1997).

Background

Significance of CRF

Cancer survivors report several symptoms including fatigue, depression, anxiety and pain that can continue years after treatment (Yennurajalingam et al., 2015). With approximately 20 million cancer survivors expected by 2026, there will be a great number of Americans living

with the impact of cancer and cancer treatment (American Cancer Society, 2016). CRF is the most common symptom impacting cancer survivors, with 80-90% of active-treatment and 30% of post-treatment cancer survivors reporting this symptom (Barton et al., 2010; Krishbaum, 2010). The National Comprehensive Cancer Network (NCCN) Guideline: Cancer-Related Fatigue states that "cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (Berger, 2016). CRF can impact physical, social, spiritual and financial aspects of a cancer survivor's life (Centers for Disease Control and Prevention, 2017). CRF negatively impacts cancer survivors' lives more than pain, depression and nausea (Nail, 2002; Ryan et al., 2007; Saligan et al., 2015; Wood, Nail, Gilster, Winters, & Elsea, 2006). CRF is known to impact the ability of cancer survivors to do basic activities of daily living. It can impact their relationships and can result in their inability to work. All of this can decrease their overall quality of life.

Mechanisms of CRF

There are multiple hypotheses for the mechanism of CRF; however, the cause or causes are still unclear (Bower, 2014; Krishbaum, 2010). CRF during treatment is often related to treatment effects including myelosuppression, acute cytokine responses to cytotoxic drugs or immunotherapy (Bower, 2014; Saligan et al., 2015). Mechanisms for post-treatment CRF are hypothesized to include muscle mass loss, chronic inflammation, immune dysregulation, and hormone deficiencies (Bower, 2014).

Treatment for CRF

There is no standard treatment for CRF during or following cancer treatment (Mitchell, 2014). Exercise is currently the only CRF intervention recommended with established efficacy

(Mitchell, 2014); however, exercise presents challenges in terms of access, adherence, and physical safety (Blaney, 2010; Bower, 2014). Limitations related to access include availability of instructors, equipment, and cost (Blaney, 2010). Additionally, studies have evaluated traditional drug interventions, but there is lack of evidence supporting these treatments, including psychostimulants, as interventions for CRF (Barton et al., 2013; Barton et al., 2010; Jiang S.L., 2015; Lo, 2012; Park et al., 2015; Yennurajalingam et al., 2015). Some natural products, like ginseng, have demonstrated efficacy in reducing CRF in multiple settings, including animal models and active treatment clinical trials (Alfano et al., 2012; Barton et al., 2013). Natural products, like ginseng and fish oils, are believed to have anti-inflammatory and stress-modulating effects, which would support one of the most common beliefs for the mechanism of CRF, that it results from the inflammatory process.

Purpose and Specific Aims

The purpose of this manuscript dissertation is to assess the acceptability, effectiveness, and safety of natural products for the treatment of CRF through two integrative reviews, a retrospective descriptive study, and a prospective descriptive cross-sectional study. Each chapter of this dissertation is designed to address the specific aims (Table 1), which help to answer the overarching question "Why are cancer survivors using natural products, and are they safe, acceptable and effective for the treatment of CRF?"

Table 1. Chapters and Aims

Chapter	**Purpose/Specific Aims**
Chapter II: Natural Products as a Treatment for Cancer-Related Fatigue: A Systematic Review **Chapter III:** Ginseng as a Treatment for Fatigue: A Systematic Review	**Aim 1:** Appraise the safety and effectiveness of natural products as a treatment for CRF.

Chapter IV: Reasons for Integrative Health Consults: Differences Between Cancer Survivors, Patients without Cancer and Referring Providers	**Aim 2:** Assess the difference between cancer survivors and patients without cancer who sought an integrative health consult. H1: Cancer survivors will report using more integrative health approaches prior to consult compared to patients without cancer
Chapter V: Cancer Survivors' Reasons for Using Complementary Approaches	**Aim 3:** Identify the complementary approaches used by cancer survivors to treat fatigue and associated symptoms. H1: Cancer survivors who report using complementary approaches to treat fatigue will report higher overall health H2: Cancer survivors who report using complementary approaches to treat fatigue will report higher physical activity **Aim 4:** Identify the resources that cancer survivors' use in their decision to use CAM.

Implications for Nursing Practice

Understanding the evidence and developing recommendation for natural products as a treatment for CRF will support both clinicians and cancer survivors in their CRF treatment decisions. Additionally, knowing cancer survivors' reasons for and satisfaction with complementary approaches will enable clinicians in three key ways. First, understanding the underlying reasons for use can aid clinicians' understanding and support clinicians in screening and/or assessing for these reasons so they can guide cancer survivors to safe and effective treatments. Secondly, cancer care teams need to know what complementary approaches are being used to help cancer survivors navigate any risk of treatment interactions. Finally, understanding

which treatments are being used and if cancer survivors are satisfied with them will help to identify acceptable treatment for CRF. This dissertation aimed to help nurses and other health care providers guide cancer survivors on the safety and efficacy of complementary approaches used to treat CRF.

Summary

This work aimed to inform both patients with cancer-related fatigue and the providers who care for them about complementary approaches for fatigue. Furthermore, the systematic reviews add to the body of evidence to aid in the decision-making process for the use of complementary approaches for the treatment of CRF. Finally, the retrospective and prospective studies add new evidence about why cancer survivors are using complementary approaches, which resources they use and their satisfaction with their complementary approaches. All of these findings help to identify possible CRF treatments and opportunities for future research.

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Chapter II: Natural Products as a Treatment for Cancer-Related Fatigue: A Systematic Review

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This manuscript represents a significant contribution to the dissertation work and lays the foundation for further investigation into cancer-related fatigue. The target journal for this manuscript is the *Journal of Cancer Survivorship,* a peer-reviewed publication focused on the quality of care and quality of life of adult cancer survivors.

Abstract

Purpose: The purpose of this review was to describe and appraise the safety and effectiveness of natural products used to manage cancer-related fatigue (CRF).

Methods: PubMed, CINAHL, Ovid MEDLINE and EMBASE databases were searched.

Results: The search produced 232 non-duplicated articles. After reviewing for inclusion and exclusion criteria, 19 articles were included in this review and categorized by the type of natural product. Study design, safety, and effectiveness are assessed separately for each category of natural product (Herbs and Supplements).

Conclusion: Herbal studies had the strongest evidence to support their use, with three RCTs demonstrating significant improvements in CRF in the intervention group compared to control. Additionally, herbal studies demonstrated a low risk of harm. Ginseng was the most tested natural product with three single-herb studies. At this time, there is not strong enough evidence to recommend any of the natural products as a standard of practice to treat CRF. However, except for L-caritine, there were no serious adverse events reported that were attributed to the intervention.

Implications for Cancer Survivors: Natural products are promising treatment for CRF. Current evidence has demonstrated limited risks from almost all of the natural products except L-carnitine. Ginseng has the most evidence to support its use. However, there needs to be more evidence to demonstrate their efficacy before they should be recommended as a standard of treatment for CRF.

Keywords: cancer-related fatigue; complementary therapies; exercise; natural products; systematic review

Introduction

Sarah, a 45-year-old mother, is 3 years post cancer treatment, yet she struggles daily to muster the energy to keep up with her 5- and 7-year-old children and to do everything that needs to be done each day. Her husband doesn't understand why she can't do everything she did before her cancer diagnosis. She has tried to use the psychostimulants her care team prescribed, but they do not work for her and make her feel edgy. Sarah desperately wants to feel better and is considering alternative therapies; however, her team is unsure which treatments are safe and effective. She does not know what, if anything, she can do to overcome her fatigue. Sarah's story is a common one, detailing the confusion and frustration faced by many cancer survivors.

Understanding safe and effective treatment options for cancer-related fatigue (CRF) is imperative for patients and clinicians. The National Comprehensive Cancer Network Guideline: Cancer-Related Fatigue (Berger, 2015) states that "cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning." CRF is a complex symptom that can impact physical, social, spiritual, and financial aspects of a cancer survivor's life (Centers for Disease Control and Prevention, 2017) at differing points in their cancer journey and with varying severity. Multiple theories about the cause of CRF have been posited to guide research efforts; however, at this time there is no clearly identified cause (Bower, 2014), and the mechanisms proposed in the literature vary greatly. Cited mechanisms range from an inflammatory response to muscle wasting, central nervous system damage, anemia, and changes in endocrine function (Barton et al., 2013; Bower, 2014). This lack of information about the causes of CRF and the multidimensionality of

CRF complicate the process of developing safe and effective interventions.

National advisory groups have highlighted the need to address cancer survivors' supportive care needs. The 2013 Institute of Medicine (IOM) report on cancer care directed attention to the supportive care needs of cancer survivors (Institute of Medicine, 2013), whereas the American College of Surgeons' Commission on Cancer now addresses symptom management in its standards for accreditation of cancer programs (Commission on Cancer, 2013). Effective prevention and treatment of CRF is challenging because: there is limited knowledge of the mechanisms responsible for CRF; most people with cancer experience multiple possible causes of CRF; many of the interventions tested have not been effective; some are not suitable for some people experiencing CRF; others focused on improving adaptation to CRF rather than decreasing the severity of CRF; and most intervention research has been directed at CRF during treatment rather than following treatment. Additionally, there is a lack of evidence to support traditional drug treatments, including psychostimulants (Barton et al., 2013). These factors highlight the need for novel interventions for symptoms, such as CRF.

There is an estimated 15 million cancer survivors in the United States (American Cancer Society, 2016). Many cancer survivors are burdened with symptoms from their disease or treatment. CRF is cited as the most common symptom impacting cancer survivors (Ling, Lui, So, & Chan, 2014) and is estimated to occur in 80% to 90% of patients during active treatment (Krishbaum, 2010) and in 30% of patients after treatment (Barton et al., 2013). Approximately 44% of cancer survivors report using complementary approaches for symptom management (Fouladbakhsh JM, 2013), illustrating a great need to understand the safety and effectiveness of these approaches. Natural products are the most frequently reported complementary approach

used in the United States (National Center for Complementary and Integrative Health, 2016a). Natural products like herbs or supplements are derived from a living organism and believed to have a pharmacologic effect (National Center for Complementary and Integrative Health, 2016b). Some natural products, like ginseng, have demonstrated efficacy in reducing CRF in multiple settings, including animal models and active treatment clinical trials (Barton et al., 2013; Barton et al., 2010; Jiang S.L., 2015; Lo, 2012; Park et al., 2015; Yennurajalingam et al., 2015). Natural products, like ginseng and fish oils, are believed to have anti-inflammatory and cortisol-modulating effects, which would support one of the most common beliefs for the mechanism of CRF, that it results from the inflammatory process (Alfano et al., 2012; Barton et al., 2013). The purpose of this review is to describe the use of natural products as treatments for CRF and appraise the safety and effectiveness of these treatments.

Methods

The National Library of Medicine's (NLM) PubMed, CINAHL (Cumulative Index to Nursing and Allied Health), Ovid MEDLINE and EMBASE databases were searched with no start date limit to May 2017 and limited by English language, clinical trials. The search was conducted using Medical Subject Heading (MeSH) and keyword terms: Coenzyme Q10, Coq10, Echinacea, Fish oil, omega-3, garlic, ginko biloba, ginseng, Panax, ginsenosides, ginsenoside*, glucosamine, green tea, multivitamin, melatonin, turmeric, natural products, herb, supplement, alternative medicine, traditional Chinese medicine, Chinese herb, complementary medicine, fatigue, fatigue syndrome, cancer related fatigue and chronic fatigue (see Figure 1 for detailed search strategy). Inclusion criteria were that the study tested a natural product (i.e., supplements, herbs) taken orally as a treatment for CRF, included adult cancer survivors who suffered from CRF, and measured CRF as a primary outcome using a self-report validated tool.

Studies that did not report cancer survivors' outcomes separately or reported fatigue only as an adverse event were excluded, as the aim of the review was to assess the impact of natural products as a treatment for CRF.

Results

This strategy resulted in 232 articles after finding one additional article through review of references and removing 104 duplicates. Two assessors (N.M.A. and L.M.N.) independently reviewed each article at each review phase and met to develop consensus on included studies (Figure 2). After reviewing titles and abstracts, 184 articles did not meet inclusion criteria, resulting in 48 articles retrieved for review. Twenty-nine of the articles retrieved were excluded for not including: a natural product (2), adult cancer survivors (3), a validated self-report measure of fatigue (5), fatigue as a primary outcome (4), correct route of administration (e.g., not administered orally) (2), or were review articles or did not report results from an intervention (13). Therefore, 19 articles were included in this review (Table 1) and discussed by two types of natural products (herbs and supplements).

Herbal Studies

Ten studies evaluated herbs in a clinical trial. Five different types of single herbs were studied as a treatment for CRF: cat's claw, ginseng, guarana, noni, and withania. One in ten studies used cat's claw, which is a native of the Amazon found in South America (de Paula et al., 2015). Its bark and plant are believed to have antioxidant, antineoplastic and anti-inflammatory properties due to the pentacyclic oxindole (POA) they contain (de Paula et al., 2015). The POAs are believed to treat the cancer and associated symptoms (de Paula et al., 2015). Two of ten studies tested guarana, which also is a native of the Amazon basin (de Oliveira Campos et al., 2011; del Giglio et al., 2013). The seeds, which contain caffeine, are roasted and used as a

stimulant (de Oliveira Campos et al., 2011; del Giglio et al., 2013). Guarana is believed to have anti-inflammatory effects that decrease CRF (del Giglio et al., 2013). Three of the ten articles research one of the two species of ginseng (Asian and American) as a treatment for CRF (Barton et al., 2013; Barton et al., 2010; Yennurajalingam et al., 2015). They are found in North America and Asia. The root of the ginseng plant contains gensenosides, which are believed to have anti-inflammatory properties that modulate fatigue (Barton et al., 2010). Traditional Chinese Medicine (TCM) considers ginseng to be an adoptogen that brings the body back into balance (Barton et al., 2010). One of the ten studies examined noni, which is an extract from the mulberry plant (Issell, Gotay, Pagano, & Franke, 2009). Traditionally, noni extract has been used by Pacific Islander and Asian populations to treat multiple diseases (Issell et al., 2009). Noni is purported to have anti-inflammatory and anticancer properties which are believed to relieve cancer-related symptoms (Abt, 2008; Issell et al., 2009). One of the ten studies researched withania, which is a plant found in Asia and is often used in ayurvedic medicine (Biswal, Sulaiman, Ismail, Zakaria, & Musa, 2013). The plant or root can be used and has been found to have restorative, antioxidant, anti-inflammatory and antitumor effects (Biswal et al., 2013; Spoerke, 2010). All five single herbs tested as a treatment for CRF are believed to have anti-inflammatory properties.

Two herbal combinations were tested as a treatment for CRF, Bojungikki-Tang and Ren Shen Yangrong Tang (RSYT). One of the ten herbal studies tested Bojungikki-Tang, which is a combination of 10 herbs. This combination in TCM is believed to tonify *qi*, life force, resulting in improved digestion and fatigue (Jeong et al., 2010). One of the ten studies researched RSYT, which is a combination of 12 herbs. Similar to Bojungikki-Tang, TCM uses RSYT to manage the symptoms of *qi* deficiency, like fatigue (Xu, Chen, Li, & Wang, 2015). Similar to the single

herbs, both herbal combinations include herbs that are believed to have anti-inflammatory properties.

Study Design. The herbal studies varied widely in their study designs. Five (5/10) herbal studies were randomized control trials (RCT) (Barton et al., 2013; Barton et al., 2010; de Oliveira Campos et al., 2011; del Giglio et al., 2013; Jeong et al., 2010), with three being double-blind (Barton et al., 2013; Barton et al., 2010; de Oliveira Campos et al., 2011). Two (2/10) herbal studies were RCTs (del Giglio et al., 2013; Jeong et al., 2010). One study used a quasi-experimental design with a control group (Biswal et al., 2013). Three studies (3/10) employed quasi-experimental single arm designs. Delivery methods varied from liquid decoctions to capsules (Table 1) with the majority (6/10) of studies using capsules (Barton et al., 2013; Barton et al., 2010; Biswal et al., 2013; de Oliveira Campos et al., 2011; Issell et al., 2009; Yennurajalingam et al., 2015). Lengths of the studies ranged from 2 weeks to 18 weeks. Most (6/10) studies were either 8-week (Barton et al., 2013; Barton et al., 2010; de Paula et al., 2015) or 6-week (de Oliveira Campos et al., 2011; del Giglio et al., 2013; Xu et al., 2015) trials. Several different fatigue measures were used (Table 1). The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) was used most (4/10) often (de Oliveira Campos et al., 2011; de Paula et al., 2015; del Giglio et al., 2013; Yennurajalingam et al., 2015). Study designs including methods, herb delivery, and assessment measures varied greatly between studies.

Sample. The research samples were homogenous (Table 1). Four (4/10) studies took place in the United States (Barton et al., 2013; Barton et al., 2010; Issell et al., 2009; Yennurajalingam et al., 2015). All reported samples included adults. Most (8/10) studies had a majority of women represented in the samples (Barton et al., 2013; Barton et al., 2010; Biswal et al., 2013; de Oliveira Campos et al., 2011; de Paula et al., 2015; del Giglio et al., 2013; Jeong et

al., 2010; Xu et al., 2015). Two studies only recruited women with breast cancer (Biswal et al., 2013; de Oliveira Campos et al., 2011). One study did not report its sample gender make up (Issell et al., 2009). The majority (6/10) of studies enrolled patients with any cancer (Barton et al., 2013; Barton et al., 2010; del Giglio et al., 2013; Jeong et al., 2010; Xu et al., 2015; Yennurajalingam et al., 2015). Four (4/10) studies enrolled only active treatment patients (Biswal et al., 2013; de Oliveira Campos et al., 2011; del Giglio et al., 2013; Yennurajalingam et al., 2015). Additionally, four (4/10) studies enrolled only post-treatment patients (de Paula et al., 2015; Issell et al., 2009; Jeong et al., 2010; Xu et al., 2015). Only two (2/10) studies enrolled both active and post-treatment patients (Barton et al., 2013; Barton et al., 2010). Samples sizes ranged from 30 to 364 participants. Three (3/10) studies reported 100 or more participants (Barton et al., 2013; Barton et al., 2010; Biswal et al., 2013). Three (3/10) studies were reported as either pilot, preliminary, or dose finding studies (Barton et al., 2010; Issell et al., 2009; Yennurajalingam et al., 2015); however, one of the reported pilot studies had one of the larger numbers of participants (n=282) and was powered at 0.8 with an effect size of 0.41 (Barton et al., 2010). Five (5/10) studies reported powers at 0.8 or greater (Barton et al., 2013; Barton et al., 2010; de Oliveira Campos et al., 2011; del Giglio et al., 2013; Jeong et al., 2010). Studies that reported effect sizes (4/10) ranged from 0.2-0.41, with three (3/10) studies reporting an effect size greater than 0.38 (Barton et al., 2013; Barton et al., 2010; del Giglio et al., 2013). The other studies did not report power or effect size. Attrition ranged from 0-38%, with the reported pilot study seeing the highest rate of attrition (Barton et al., 2010).

Safety. Herbal studies reported no serious (e.g., death, life-threatening or requiring hospitalization) adverse events (AEs) attributed to the intervention. Reported grade ≥3 AEs ranged from 0 to 22%, with four (4/10) studies reporting no AEs (de Oliveira Campos et al.,

2011; Issell et al., 2009; Xu et al., 2015; Yennurajalingam et al., 2015).

Efficacy. Herbal studies show moderate support for efficacy as a treatment for CRF. Two (2/10) studies reported no significant differences between groups in reported AEs (Barton et al., 2013; Barton et al., 2010). Eight (8/10) herbal studies reported significant improvements in reported CRF (Barton et al., 2013; Biswal et al., 2013; de Oliveira Campos et al., 2011; de Paula et al., 2015; del Giglio et al., 2013; Jeong et al., 2010; Xu et al., 2015; Yennurajalingam et al., 2015). Four (4/10) studies demonstrated significant improvement in CRF in the intervention group compared to controls (Barton et al., 2013; Biswal et al., 2013; de Oliveira Campos et al., 2011; Jeong et al., 2010).

Appraisal of Herbal Studies. Three (3/10) herbal studies controlled for multiple types of bias and increased internal validity by employing double-blind randomized control trials (RCT) (Barton et al., 2013; Barton et al., 2010; de Oliveira Campos et al., 2011). Two (2/10) herbal studies controlled for sample bias and strengthened internal validity by conducting RCTs (del Giglio et al., 2013; Jeong et al., 2010). One study used a quasi-experimental design with a control group which decreased threats to internal validity (Biswal et al., 2013). Three studies (3/10) employed quasi-experimental single-arm designs, which posed risks to internal validity and bias. Eight (8/10) herbal studies reported statistically significant improvements in CRF. Only four of the studies that reported significant findings included controls. Two (2/10) of the studies were double-blind RCTs (Barton et al., 2013; de Oliveira Campos et al., 2011), one an open-label RCT (Jeong et al., 2010), and one a non-randomized quasi-experimental study (Biswal et al., 2013). Four (4/10) studies that reported significant findings were single-arm studies (de Paula et al., 2015; del Giglio et al., 2013; Xu et al., 2015; Yennurajalingam et al., 2015). Not having a control group poses the risk that the results may have been caused by something other than the

intervention. Two (2/10) of the studies with significant findings tested herbal combinations, calling into question which part of the intervention resulted in the findings. Significant findings were demonstrated in studies as short as 2 weeks (Jeong et al., 2010). The majority (6/10) of studies included all types of cancer patients (Barton et al., 2013; Barton et al., 2010; del Giglio et al., 2013; Jeong et al., 2010; Xu et al., 2015; Yennurajalingam et al., 2015), which increases the generalizability of these findings; however, since most studies had a majority of women this may limit results to women with cancer.

Supplements

Nine studies tested supplements as interventions for CRF. Four types of single supplements were used to treat CRF including coenzyme Q10 (CoQ10), fish oil, L-carnitine, and probiotic (Table 1). One study out of nine used CoQ10, which is an antioxidant that is believed to create energy within the cell that promotes cell growth and maintenance (Lesser et al., 2013). One study out of nine tested fish oil, which contains Omega 3s, and is believed to modulate the inflammatory process and decrease symptoms like fatigue (Cerchietti, Navigante, & Castro, 2007). Four studies out of nine tested L-carnitine, which is a key amino acid that plays a role in a cell's ability to produce energy. One study out of nine assessed probiotics, which are believed to restore balance in the gastrointestinal (GI) micro-biome, relieving GI symptoms and reducing inflammation. It is theorized that improving GI symptoms in cancer patients will improve quality of life and reduce fatigue (Lee et al., 2014). Each of these single supplements are theorized to leverage or enhance the body's own mechanisms for overcoming fatigue.

Three studies tested three different types of supplement combinations to treat CRF: multivitamins, Inner Power ® and an antioxidant treatment. One study out of nine tested a multivitamin, Centrum Silver ®, which contains a combination of vitamins and minerals. In

western cultures there is a general belief that multivitamins support proper nutrition and will improve health and energy (de Souza Fede et al., 2007). One study out of nine tested Inner Power ®, which is an amino acid jelly containing CoQ10 and L-carnitine. It was initially developed to improve symptoms in advanced cancer, including pain and fatigue (Iwase et al., 2016). One study out of nine tested an antioxidant treatment, which contained a combination of alpha-lipoic acid, carbocysteine lysine salt, vitamin E, vitamin A, and vitamin C. Antioxidants are theorized to be unregulated in patients with cancer. This imbalance is believed to lead to cancer progression and worsening symptoms. It is theorized that treating patients with an antioxidant supplement will help address disease progression and reduce symptoms like fatigue.

Study Design. Supplement studies primarily used RCT design, but varied in length and assessment tools. The majority (5/9) of the supplement studies were double-blind RCTs (Cruciani et al., 2009; Cruciani et al., 2012; de Souza Fede et al., 2007; Lee et al., 2014; Lesser et al., 2013). Three (3/9) of the studies employed a RCT design (Cerchietti et al., 2007; Iwase et al., 2016; Mantovani, 2010). One (1/9) was a single-arm study (Cruciani et al., 2006). Most (6/9) studies used capsules (Cerchietti et al., 2007; de Souza Fede et al., 2007; Lesser et al., 2013) or liquid (Cruciani et al., 2009; Cruciani et al., 2006; Cruciani et al., 2012) to deliver their interventions. Each study used a different time frame and their lengths ranged from 1 week to 24 weeks. A wide variety of fatigue measurements were used, with the Brief Fatigue Inventory used most (3/9) often (Cruciani et al., 2006; Cruciani et al., 2012; Iwase et al., 2016).

Sample. Supplement studies had several similarities within their samples. Most (4/9) studies were conducted in North America (Cruciani et al., 2009; Cruciani et al., 2006; Cruciani et al., 2012; Lesser et al., 2013). The majority (5/9) of studies enrolled both active- and post-treatment cancer patients. Four (4/9) of the studies included only advanced cancer patients. Most

(5/9) had a majority of women (Cruciani et al., 2009; Cruciani et al., 2012; de Souza Fede et al., 2007; Iwase et al., 2016; Lesser et al., 2013), with three enrolling only women (de Souza Fede et al., 2007; Iwase et al., 2016; Lesser et al., 2013). Sample sizes ranged from 24-376, with most (6/9) samples sizes under 100 (Cerchietti et al., 2007; Cruciani et al., 2009; Cruciani et al., 2006; de Souza Fede et al., 2007; Iwase et al., 2016; Lee et al., 2014). Five (5/9) reported powers >0.8 (Cruciani et al., 2009; Cruciani et al., 2012; Iwase et al., 2016; Lee et al., 2014; Lesser et al., 2013) and effects sizes of >0.3 (Cruciani et al., 2012; Iwase et al., 2016; Lee et al., 2014; Lesser et al., 2013). Attrition ranged from 0-41%, with one L-carnitine study exhibiting the greatest attrition (Cruciani et al., 2009).

Safety. Several supplement studies reported non-significant AEs. Grade ≥3 AEs ranged from 0% to 42%. One study testing fish oil reported no AEs (Cerchietti et al., 2007). Additionally, one study reported significant AEs with the use of L-carnitine alone, with 3 deaths (1 attributed to the study) (Cruciani et al., 2012). Most reported AEs were constipation, nausea, and diarrhea.

Efficacy. The majority of studies reported significant finding; however, only one study demonstrated significant improvement in CRF in the intervention group compared to controls. Six (6/9) studies reported significant findings (Cerchietti et al., 2007; Cruciani et al., 2006; de Souza Fede et al., 2007; Iwase et al., 2016; Lee et al., 2014; Mantovani, 2010). One (1/9) reported significant improvements in CRF favoring the intervention group compared to controls (Iwase et al., 2016). One study reported significant improvement in CRF in the placebo group compared to the intervention group (de Souza Fede et al., 2007). One (1/9) study demonstrated significant findings in the single-arm study (Cruciani et al., 2006). Two (2/9) studies demonstrated significant improvement in CRF within the intervention group, but not between

intervention and controls (Cerchietti et al., 2007; Lee et al., 2014). One study found significant improvement in CRF when comparing to other intervention arms (Mantovani, 2010).

Appraisal of Supplement Studies. There are promising findings, but not enough evidence to support the use of supplements as standard of practice to treat CRF. Six (6/9) studies reported significant findings. Two of the studies with significant findings were double-blind RCTs that controlled for multiple types of bias (de Souza Fede et al., 2007; Lee et al., 2014); however, one study found that the placebo group demonstrated significant improvement in CRF compared to the intervention group (multivitamins) (de Souza Fede et al., 2007). And one had significant improvement in CRF within the intervention group, but not between intervention and control groups (Lee et al., 2014). Two were RCTs that controlled for sample bias (Cerchietti et al., 2007; Iwase et al., 2016); however, one only demonstrated significant findings within the intervention group, but not when compared to controls (Cerchietti et al., 2007). One study demonstrated significant findings in one arm of a five-arm study; however, there was no control group (Mantovani, 2010). The last significant study was a single-arm dose-finding study (Cruciani et al., 2006). Since the last two studies lacked control groups it calls into question whether the significant findings were related to the interventions. This leaves one study that found significant improvement in CRF in the intervention (Inner Power ®) group compared to controls (Iwase et al., 2016); however, since this is a combination of supplements it is unclear which part of the combination resulted in the improvement. All but one study reported no significant AEs. Most studies included both active- and post-treatment cancer patients, which increased the generalizability of these findings. However, most studies included only patients with advanced cancer or a single cancer diagnosis. Additionally, many of the studies enrolled a majority of women (Cruciani et al., 2009; Cruciani et al., 2012; de Souza Fede et al., 2007; Iwase

et al., 2016; Lesser et al., 2013). Both of these factors limit the generalizability of these findings.

Discussion

In this review, 19 natural product studies were reviewed. Ten studies tested five different herbs and two herbal combinations. Nine tested four single supplements and three supplement combinations. The herbal studies had stronger evidence to support their use, with three RCTs demonstrating significant improvements in CRF in the intervention group compared to controls (Barton et al., 2013; de Oliveira Campos et al., 2011; Jeong et al., 2010). Additionally, the herbal studies demonstrated a low risk of harm. Ginseng was the most tested natural product with three single-herb studies (Barton et al., 2013; Barton et al., 2010; Yennurajalingam et al., 2015) and one herbal combination (Jeong et al., 2010). Three of these studies demonstrated significant findings favoring ginseng as a treatment for CRF (Barton et al., 2013; Jeong et al., 2010; Yennurajalingam et al., 2015); however, only two were RCTs (Barton et al., 2013; Jeong et al., 2010). At this time, there is not strong enough evidence to recommend any of the natural products as a standard of practice to treat CRF. However, except for L-caritine, there were no serious AEs reported attributed to the intervention. Several of the natural product studies show promising results that should be replicated to determine if the results are reproducible.

Limitations

Including multiple natural products with different types of study designs may confound the results. Limiting this review in this way would have impeded the ability to assess the state of the evidence for natural products as a treatment for CRF.

Clinical Implications

Natural products are promising treatment for CRF. Current evidence has demonstrated limited risks from almost all of the natural products except L-carnitine. At this

time, due to potential risk, L-caritine alone should not be recommended as a treatment for CRF until additional research supports its use. Ginseng has the most evidence to support its use. However, there needs to be more evidence to demonstrate efficacy before natural products should be recommended as a standard of treatment for CRF.

Future Research Recommendations

Future research needs to overcome the gaps identified in the research. First, natural product research should use strong research designs that mitigate multiple types of bias and increase internal validity. Secondly, results need to be replicated to build evidence to aid treatment decisions. Finally, studies need more diverse samples to increase the generalizability of their results.

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For the literature search, the following databases were used: the National Library of Medicine's (NLM) PubMed, CINAHL (Cumulative Index to Nursing and Allied Health), Ovid MEDLINE and EMBASE. All searches were limited to English language and the following types of studies: clinical trials, controlled clinic trials, randomized controlled trials, meta-analyses and systematic reviews.

The search results were as follows: NLM's PubMed yielded 179 citations while CINAHL yielded 29 citations; Ovid MEDLINE produced another 74 citations and EMBASE produced an additional 53 citations for a total of 335 citations. All results were put into an EndNote file where a total of 103 duplicate citations were removed leaving 232 citations.

SUBJECT HEADINGS	KEY/TEXT WORDS
Neoplasm	Neoplasm
Cancer fatigue	Cancer fatigue
Survivor	Fatigue
Alternative medicine	Survivors
Integrative medicine	Integrative medicine
Medicinal plant	Complimentary therap*
Plant extract	Plant extract*
Herb	Herbs

Figure 1: Detailed Search Strategy

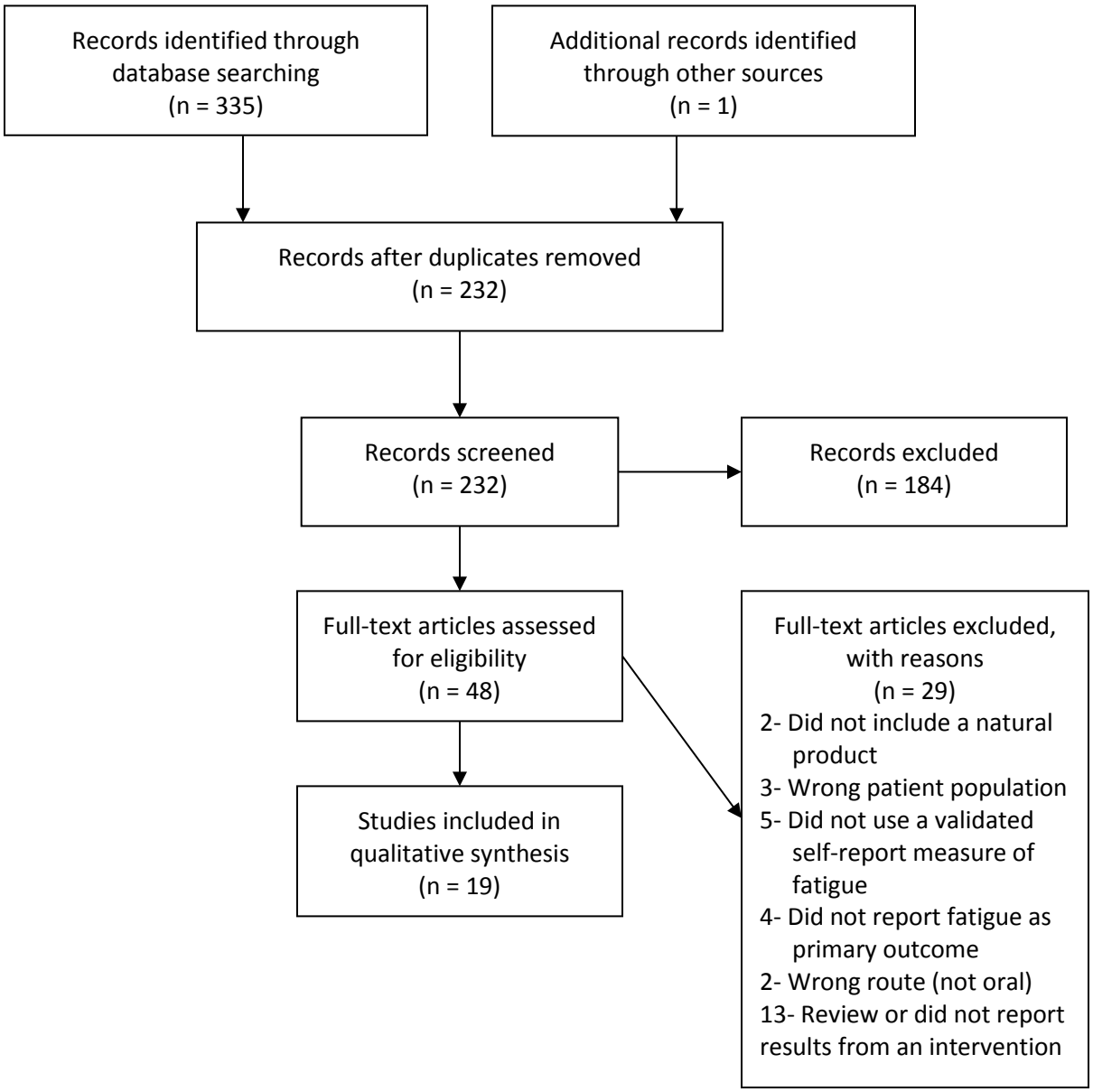

Figure 2: Article Review Flow Diagram

Table 1: Characteristics of Included Studies														
Study	Location	Daily Dose per Arm	Cancer Type	N	Gender	Study Design	Primary Fatigue Assessment	Length	Fatigue Outcome	Power	Effect Size	Alpha	Attrition	Reported AEs**
Single Herb														
Barton, D. L., et al. (2010)	United States	**American Ginseng Capsules** 750 mg 1,000 mg 2,000 mg	All Cancers Active and Post-treatment	282	Women (66%)	Pilot double-blind placebo controlled RCT[2]	Brief Fatigue Inventory	8 weeks	Non-significant findings, highest does of ginseng trended toward positively toward decreasing CRF	0.8	.41	NR	38%	**Placebo**[¥] Grade ≥3 7% **Ginseng** 750 mg Grade ≥3 11% 1,000 mg Grade ≥3 4% 2,000 mg Grade ≥3 7% Most reported AE Anxiety Insomnia Nausea

Table 1: Characteristics of Included Studies														
Study	Location	Daily Dose per Arm	Cancer Type	N	Gender	Study Design	Primary Fatigue Assessment	Length	Fatigue Outcome	Power	Effect Size	Alpha	Attrition	Reported AEs**
Barton, D. L., et al. (2013)	United States	**American Ginseng Capsules** 2,000 mg	All Cancers Active and Post-treatment	364	Women (78%)	Multisite, double-blind placebo controlled RCT[2]	Multidimensional Fatigue Symptom Inventory-Short Form	8 weeks	Significant improvement in fatigue scores in intervention group compared to placebo	0.9	.38	NR	22%	**Placebo**[¥] Grade 3 1% **Ginseng** 2,000 mg Grade 3 1% Most reported AE Anxiety Insomnia Nausea
Biswal, B.M., et al. (2012)	Malaysia	**Withania Capsules** 6 grams	Breast cancer Active Treatment	100	Women (100%)	Quasi-experimental trial, open-label & non-randomized with usual care comparison	Piper fatigue scale, (PFS) Schwartz fatigue scale (SCFS-6)	6 cycles (18 weeks)	PFS statistically improved for intervention group compared to controls. ***SCFS-6 improved for intervention group compared to controls	NR[3]	NR[3]	0.05	6%	Did not report AE grades. Reported symptom scales favored intervention group over controls for Insomnia, appetite, and constipatio n. All others were not significantly different.

Table 1: Characteristics of Included Studies														
Study	Location	Daily Dose per Arm	Cancer Type	N	Gender	Study Design	Primary Fatigue Assessment	Length	Fatigue Outcome	Power	Effect Size	Alpha	Attrition	Reported AEs**
de Oliveira Campos, M. P., et al. (2011)	Brazil	**Guarana capsule** 100mg	Breast cancer Active treatment	75	Women (100%)	Double-blind placebo controlled RCT[2] with cross-over	Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Chalder Fatiguw	21 days then 7-day washout, then 21 days 6 weeks total	Intragroup analysis demonstrated significant improvement in fatigue in the group that received the placebo first then use of guarana. Significantly more patients reported improved fatigue in intervention group at day 21, compared to placebo group.	0.8	NR[3]	0.05	20%	**No Grade ≥3 AEs**
de Paula, L. C., et al. (2015)	Brazil	**Cat's Claw tablet** 300mg	Advance cancer Post-treatment	51	Women (53%)	Single-am open-label	FACIT-F Chalder Fatigue Scale	8 weeks	FACIT-F not significantly different. Chalder Fatigue Scale showed fatigue significantly improved with p at 0.0496.	NR[3]	NR[3]	0.05	NR[3]	**Grade 3** 22%

Table 1: Characteristics of Included Studies														
Study	Location	Daily Dose per Arm	Cancer Type	N	Gender	Study Design	Primary Fatigue Assessment	Length	Fatigue Outcome	Power	Effect Size	Alpha	Attrition	Reported AEs**
del Giglio, A. B., et al. (2013)	Brazil	**Guarana liquid** (PC-18) 75mg	All Cancers Active treatment	40	Women (57.5%)	Single arm open-label then those who improved or stabilized were randomized into intervention or placebo	BFI, FACIT-F Chalder Fatigue Scale	21 day induction and then 3-weeks 6 weeks total	Open label arm saw significant improvement in fatigue from baseline, however, no significant difference seen in second phase RCT	0.8	0.4	0.05	10%	Grade 3--2
Issell, B. F., et al. (2009)	Unites States	**Noni capsules** 7 doses that ranged from 2g -14g	Advance cancer Post-treatment	51	NR[3]	Single-arm dose finding study	QLQ-C30, BFI	4 weeks	Maximum dose tolerated 7 capsules 4-times of days (14g total), showed a trend of improvement of fatigue. Did not report any data or tables	NR[3]	NR[3]	0.05	24%	**No Grade 3 or higher reported**

Table 1: Characteristics of Included Studies

Study	Location	Daily Dose per Arm	Cancer Type	N	Gender	Study Design	Primary Fatigue Assessment	Length	Fatigue Outcome	Power	Effect Size	Alpha	Attrition	Reported AEs**
Yennurajalingam, S., A. Reddy, et al. (2015).	United States	**Panax Ginseng C.A Meyer capsules** 800 mg	All Cancer Active treatment	30	Women (50%)	Preliminary single arm pre/post	Functional Assessment of Chronic Illness Therapy—Fatigue	29 days	significantly improved fatigue scores at day 15 & day 29 from base line	NR[3]	NR[3]	NR[3]	20%	No AEs attributed to the study. Grade >3 6% These were not attributed to the study. Most reported AEs Pain Nausea

Table 1: Characteristics of Included Studies														
Study	Location	Daily Dose per Arm	Cancer Type	N	Gender	Study Design	Primary Fatigue Assessment	Length	Fatigue Outcome	Power	Effect Size	Alpha	Attrition	Reported AEs**
Herbal Combination														
Jeong et al. (2010)	Korea	**Bojungikki-Tang granules** 7.5 g Herbs included: Astragali radix, Atractylodis lanceae rhizome, ginseng radix, angelicae radix, bupleuri radix, zizyphi fructus, aurantii noblis pericarpium, glycrrhizae radix, cimicifugae rhizome, zingiberis rhizome	All Cancers Post-treatment	40	Women (60%)	Placebo controlled RCT[2] with waitlist control	Visual Analogue Scale of Global Fatigue	2 weeks	Intervention group had significantly improved fatigue compared to placebo	0.8	0.2	0.05	10%	No serious AEs reported Reported 10% AEs but did not clarify if intervention or placebo group Most reported AE Flatulence Dyspepsia

Table 1: Characteristics of Included Studies														
Study	Location	Daily Dose per Arm	Cancer Type	N	Gender	Study Design	Primary Fatigue Assessment	Length	Fatigue Outcome	Power	Effect Size	Alpha	Attrition	Reported AEs**
Xu, Y., et al. (2015)	China	Ren Shen Yangrong Tang decoction amounts tailored to the participant twice per day Herbs included: Dangshen, Huanqi, Baizhu, Fuling, Chenpi, Shengdi, Baishao, Danggui, Wuweizi, Yuanshi, Rougui, Gancao	All Cancers Post-treatment	33	Women (58%)	Open-label single arm pre/post	MD Anderson Symptom Inventory-C	6 weeks	Significantly decreased fatigued. Reported that most saw the decreased in fatigue at week 4	NR[3]	NR[3]	0.05	0%	No AEs
Single Supplement														
Cerchietti, L. C .A., et al. (2007)	Argentina	**Fish oil 6g capsules+ Placebo + Food supplementation + 75mg Aspirin** **Fish oil** 6g capsules w/ Celecoxib 600mg; **+ Food supplementation + 75mg Aspirin**	Advance cancer Active and Post-treatment	36	Male (77%)	Pilot with 12 participants in max dose trial; then 24 participants in a placebo controlled RCT	0-10 numeric scale	6 weeks	Fatigue significantly improved in both groups. **no significant difference in fatigue between groups	NR[3]	NR[3]	0.05	0%	No AEs reported

Table 1: Characteristics of Included Studies														
Study	Location	Daily Dose per Arm	Cancer Type	N	Gender	Study Design	Primary Fatigue Assessment	Length	Fatigue Outcome	Power	Effect Size	Alpha	Attrition	Reported AEs**
Cruciani, R. A., et al. (2009)	United States	**L-caritine liquid** 2g	Advance cancer Active and post-treatment	33	Women (55%)	Double-blind placebo controlled RCT, then open-label	FACT-An; Linear VAS for energy level	2 weeks blinded 2 weeks open-label	No significant differences in fatigue scores between	0.8	NR[3]	NR[3]	41%	2 AEs associated with intervention - diarrhea, constipation
Cruciani, R. A., et al. (2006)	United States	**L-caritine liquid** started at 250, and increased 500 until a maximum dose of 3000, taken for 1 week	Advance cancer Active and post-treatment	27	Male (63%)	Open-label single arm maximum dose finding study	Brief Fatigue Inventory	1 week	Fatigue decreased significantly	NR[3]	NR[3]	NR[3]	22%	2 mild nausea
Cruciani, R. A., et al. (2012)	United States	**L-caritine liquid** 2g	Any invasive malignancy Active and post-treatment	376	Women (58%)	Double-blind placebo controlled RCT[2]	Brief Fatigue Inventory	4 weeks	Fatigue improved, but did not show a significant difference between groups	85%	0.5	0.05	15%	**Grade 5** 2 deaths not attributed 1 death possibly attributed to the study drug
Lee, J. Y., et al. (2014)	Korea	**Probiotic tabs** Lacidofil 4 tabs daily	Colorectal cancer Post-treatment	66	Male (53%)	Double-blind placebo controlled RCT	FACT-F	12 weeks	Significant difference pre/post in the intervention group, but no significant difference between groups	0.8	0.3	0.1	10%	No significant AEs on either arm

Table 1: Characteristics of Included Studies														
Study	Location	Daily Dose per Arm	Cancer Type	N	Gender	Study Design	Primary Fatigue Assessment	Length	Fatigue Outcome	Power	Effect Size	Alpha	Attrition	Reported AEs**
Lesser, G. J., et al. (2013)	United States	**Placebo** + 300 IU Vit E **CoQ10 capsules** 300mg CoQ10 + 300-IU vit E	Breast Cancer Active treatment	236	Women (100%)	Double-blind placebo controlled RCT	POMS-F	24 weeks	*12% of participants on CoQ10 levels did not rise and were lower than baseline. No significant differences between groups on fatigue measures	0.9	0.3	0.05	41%	**CoQ10 Grade ≥3** 37 **Placebo Grade ≥3** 26 *no significant differences
Supplement combination														
de Souza Fede, A. B., et al. (2007)	Brazil	**Multivitamin capsule** Centrum Silver	Breast cancer Active treatment	40	Women (100%)	Double-blind placebo controlled RCT[2] with cross-over	Chalder Fatigue Scale	3 phases, unclear as to length	Placebo demonstrated significant improvement in fatigue scores compared to multivitamin	NR[3]	NR[3]	NR[3]	12%	NR[3]
Iwase, S., et al. (2016)	Japan	**Acid jelly** 2500 mg, CoQ10 30mg, , l-carnitine 50mg)	Breast cancer Active treatment	59	Women (100%)	RCT open label with usual care comparison	BFI	3 weeks	Worst fatigue in 24 hr significantly improved in intervention group compared to control	0.8	0.5	0.05	3%	**NP Combination Grade ≥3** 42.9% **Usual Care Grade ≥3** 58%

Table 1: Characteristics of Included Studies														
Study	Location	Daily Dose per Arm	Cancer Type	N	Gender	Study Design	Primary Fatigue Assessment	Length	Fatigue Outcome	Power	Effect Size	Alpha	Attrition	Reported AEs**
Mantovani, G., et al. (2010)	Italy	**1- 500mg medroxyprogestrone** 2- EPA 3- L-carnitine 4g 4- thailidomide 200mg 5- combination of the above	Advance Cancer Active and post-treatment	332	Male (54%)	5-Arm Randomized comparative effectiveness trial	MFSI-SF	16 weeks	Fatigue improved significantly in Arm 5.	NR[3]	0.2	0.05	3%	**Total Grade ≥3** 5

1 Cancer-Related Fatigue
2 Randomized Control Trial
3 Not Reported
4 Multiple Sclerosis
5 These are raw numbers, due to inability to calculated a rate
* Only recruited women
¥ No significant differences in reported AEs between intervention and placebo groups
**Grade 3 or higher

Chapter III: Ginseng as a Treatment for Fatigue: A Systematic Review

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This manuscript represents a significant contribution to the dissertation work and lays the foundation for further investigation of the acceptability, efficacy and safety of a natural product, ginseng, as a treatment for cancer-related fatigue. The manuscript was accepted for publication March 5, 2018 in *Journal of Complementary and Integrative Medicine,* a peer-reviewed publication focused on publishing evidence about the safety and efficacy of integrative medicine practice including herbal and traditional medicines. Reprinted with permission from JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE, published by Mary Ann Liebert, Inc., New Rochelle, NY (Appendix C).

Abstract

Background: Millions of people with chronic illness suffer from fatigue. Fatigue is a complex, multidimensional symptom with poorly understood causes, wide variations in severity among individuals, and negative effects on multiple domains of daily life. Many patients with fatigue report the use of herbal remedies. Ginseng is one of the most widely used because it is believed to improve energy, physical and emotional health, and well-being.

Objective: To systematically review the published evidence to evaluate the safety and effectiveness of the 2 types of Panax ginseng (Asian [*Panax ginseng*] and American [*Panax quinquefolius*]) as treatments for fatigue.

Data Sources: PubMed, CINAHL, Ovid MEDLINE, and EMBASE databases were searched using Medical Subject Heading and keyword terms, including ginseng, Panax, ginsenosides, ginsenoside* (wild card), fatigue, fatigue syndrome, cancer-related fatigue, and chronic fatigue.

Study Eligibility, Participants, and Intervention: Studies were included if participants had fatigue, had used 1 of the 2 Panax ginsengs as an intervention, and had scores from a self-report fatigue measure.

Study Appraisal and Synthesis Methods: Two reviewers independently assessed each article at each review phase and met to develop consensus on included studies. Risk of bias was assessed using version 5.3 of the Cochrane Collaboration Review Manager (RevMan), and results were synthesized in a narrative summary.

Results: The search strategy resulted in 149 articles, with 1 additional article located through review of references. After titles, abstracts, and full text were reviewed, 139 articles did not meet inclusion criteria. For the 10 studies reviewed, there was a low risk of adverse events associated with the use of ginseng and modest evidence for its efficacy.

Conclusions: Ginseng is a promising treatment for fatigue. Both American and Asian ginseng may be viable treatments for fatigue in people with chronic illness. Because of ginseng's widespread use, a critical need exists for continued research that is methodologically stronger

and that includes more diverse samples before ginseng is adopted as a standard treatment option for fatigue.

Keywords: complementary and integrative health; herbal; *Panax;* symptom management

Abbreviations

AE, adverse event

CRF, cancer-related fatigue

MeSH, Medical Subject Heading

NLM, National Library of Medicine

Introduction

Millions of people in the United States experience fatigue as a symptom of chronic illness or as an adverse event (AE) of the treatment of chronic illness, or both (Centers for Disease Control and Prevention, 2013; Jiang et al., 2017). Fatigue is a complex, multidimensional symptom with poorly understood causes, wide variations in severity among individuals, and negative effects on multiple domains of daily life (Bower, 2014). Negative effects include decreased work productivity, physical activity, social interaction, and recreational activity, as well as feelings of loss and sadness (Centers for Disease Control and Prevention, 2015).

Over 32% of the population of the United States uses complementary and alternative medicine (National Center for Complementary and Integrative Health, 2017), with ginseng being on the top-10 list of the most-used natural products (National Center for Complementary and Integrative Health, 2016). People who experience fatigue often report the use of herbal remedies (Cutshall et al., 2015), and one of the most commonly used is ginseng. Traditional Chinese medicine and herbal medicine philosophies consider ginseng to be an adaptogen that helps restore balance to the body. Ginseng is believed to improve energy, physical and emotional health, and well-being (Barton et al., 2013; Coleman, Hebert, & Reddy, 2003; Panossian, Wikman, Kaur, & Asea, 2009). In the *Panax* genus (Asian [*Panax ginseng*] and American [*Panax quinquefolius*]), the root is the part of the plant with medicinal properties. Asian and American ginseng both contain ginsenosides, which are the active compounds believed to act on the central nervous system (Braz, Morais, Paula, Diniz, & Almeida, 2013) and to have antioxidant (H. G. Kim et al., 2013) and anti-inflammatory properties (Barton et al., 2013), as well as cortisol-modulating effects (Barton et al., 2013). These are some of the reasons why researchers have considered *Panax ginseng* to be a potential treatment for fatigue in multiple populations with chronic illness, including cancer survivors, patients with fibromyalgia, and patients with multiple sclerosis. The accepted and studied dosages of Panax ginseng range from 500 mg to 2,000 mg (Barton et al., 2013). Knowing whether ginseng is a safe and effective treatment for fatigue in people with physical illness is important for clinicians and patients.

We located 1 published meta-analysis of the efficacy of ginseng supplements by using our search strategy and limiting it to reviews that assessed ginseng as a treatment for fatigue (Bach, Kim, Myung, & Cho, 2016). The meta-analysis included 12 randomized controlled trials designed to determine whether ginseng reduced fatigue and improved physical performance. However, the analysis was limited by its broad scope. The studies reviewed included subjects who were not experiencing fatigue or who did not have physical illness, included outcomes based on self-report and physical performance, and combined all results into a single outcome for the analysis. Therefore, we aimed to expand on this work by evaluating the safety and effectiveness of the 2 types of Panax ginseng (*P ginseng* and *P quinquefolius*) as treatments for fatigue, focusing only on studies that included fatigued participants with a chronic illness and employed a self-report measure for fatigue, in order to assess the state of knowledge about the safety and effectiveness of Asian and American ginseng in managing fatigue in people with chronic illness (National Comprehensive Cancer Network, 2017; Oncology Nursing Society, 2017).

Methods

The National Library of Medicine's (NLM) PubMed, CINAHL (Cumulative Index to Nursing and Allied Health), Ovid MEDLINE, and EMBASE databases were searched with no start date limit to April 2016 and limited to English language, clinical trials. The search was conducted using MeSH and keyword terms, including ginseng, Panax, ginsenosides, ginsenoside* (wild card), fatigue, fatigue syndrome, cancer-related fatigue, and chronic fatigue (Box 1 includes the detailed search strategy). Studies were included if participants had fatigue, 1 of the 2 Panax ginsengs were used as an intervention, either as a single agent or in combination with other natural products, and scores from self-report measures of fatigue outcomes were reported. Studies that did not use a self-reported fatigue measure or that included only participants without fatigue (healthy subjects), or both, were excluded because the aim of this review was to assess the impact of ginseng as a treatment for those experiencing fatigue associated with chronic illness. Additionally, self-report measures of fatigue aligned with the

accepted definition that fatigue is a subjective, multidimensional symptom (Hann et al., 1998; Mota & Pimenta, 2006). Studies that reported results of non-Panax ginsengs (e.g., Siberian ginseng) were excluded because they have different compositions of active ingredients and do not contain ginsenosides (U.S. Fish and Wildlife, 2017).

Results

The search strategy found 149 articles after 52 duplicates were removed, and 1 additional article was located through review of references (Figure 1). Two assessors (N.M.A. and L.M.N.) independently reviewed each article at each review phase and met to develop consensus on included studies. After reviewing titles and abstracts, 134 articles did not meet inclusion criteria, resulting in 15 articles retrieved for review. Five of the articles retrieved were excluded for not including a Panax ginseng (2), not reporting fatigue as an outcome (1), or including only subjects without fatigue (2). Therefore, 10 articles were included in this review (Barton et al., 2013; Barton et al., 2010; Braz et al., 2013; Etemadifar et al., 2013; Jeong et al., 2010; E. Kim et al., 2011; H. G. Kim et al., 2013; Le Gal, Cathebras, & Strüby, 1996; Wang et al., 2013; Yennurajalingam et al., 2015) (Table 1). These studies are too heterogeneous to conduct a meaningful meta-analysis (doses, populations, and length of treatment vary widely). This review is not limited to randomized controlled trials or single-agent studies in order to assess the current state of evidence for ginseng as a treatment for fatigue. Risk of bias was assessed using version 5.3 of the Cochrane Collaboration Review Manager (RevMan), and results were synthesized in a narrative summary categorized by the type of ginseng tested: 4, American ginseng (*P quinquefolius*)(Barton et al., 2013; Barton et al., 2010; E. Kim et al., 2011; Wang et al., 2013) and 6, Asian ginseng (*P ginseng*) (Braz et al., 2013; Etemadifar et al., 2013; Jeong et al., 2010; H. G. Kim et al., 2013; Le Gal et al., 1996; Yennurajalingam et al., 2015).

American Ginseng (P *quinquefolius*)

American ginseng is native to Canada and the United States. Four trials evaluated the impact of American ginseng on fatigue (Barton et al., 2013; Barton et al., 2010; E. Kim et al., 2011; Wang et al., 2013). One study evaluated the impact of American ginseng within a natural

product combination (Immune No. 2) on symptoms, which included fatigue (Wang et al., 2013). Each study used a different fatigue measure, including the Brief Fatigue Inventory, Multidimensional Fatigue Symptom Inventory–Short Form, Fatigue Severity Scale, and the Scores of Symptoms and Signs (Barton et al., 2013; Barton et al., 2010; E. Kim et al., 2011; Wang et al., 2013).

Design. All 4 American ginseng trials used bias controls, including double-blinding and a placebo (Barton et al., 2013; Barton et al., 2010; E. Kim et al., 2011; Wang et al., 2013). Three trials ranged from 8 weeks to 6 months (Barton et al., 2013; Barton et al., 2010; Wang et al., 2013). One study was a crossover trial that ran 6 weeks followed by a 2-week washout, and then the crossover for an additional 6 weeks (E. Kim et al., 2011). Two of the studies had primary aims of evaluating the safety of ginseng and included multiple dosages of ginseng in the trials (Barton et al., 2010; E. Kim et al., 2011). Two of the studies included 2,000 mg per day as their highest dose of American ginseng (Barton et al., 2013; Barton et al., 2010), and 1 study had a maximum dose of 400 mg per day of American ginseng (E. Kim et al., 2011). The study testing the Immune No. 2 combination did not include information about the ginseng dose used (Wang et al., 2013).

Sample. Three of the 4 studies were conducted in the United States (Barton et al., 2013; Barton et al., 2010; E. Kim et al., 2011), and 1 was conducted in China (Wang et al., 2013). The sample consisted of cancer survivors in 2 studies, patients with multiple sclerosis in 1 study, and patients with HIV in the combination study. All participants were adults (Barton et al., 2013; Barton et al., 2010; E. Kim et al., 2011; Wang et al., 2013). Three studies included only those who reported fatigue for 1 month or more (Barton et al., 2013; Barton et al., 2010; E. Kim et al., 2011). Sample sizes ranged from 56 to 364. One study with 282 participants was described as a pilot study; however, it was powered at 80%, with an effect size of 0.41 (Barton et al., 2010). The smallest sample (n=56) was from a study that employed a crossover design and was powered at 80%, with an effect size of 0.8 (E. Kim et al., 2011). Three studies included mostly white women (Barton et al., 2013; Barton et al., 2010; E. Kim et al., 2011). One study had

mostly male participants (62%) (Wang et al., 2013). Attrition ranged from 12% to 39%, with the largest attrition rate occurring in the cancer survivors' pilot study (Barton et al., 2010).

Safety and Efficacy. All dosages of American ginseng were tolerated well, with no serious adverse events (AEs) reported. Three of the 4 studies showed no differences in AE rates between the ginseng and placebo groups (Barton et al., 2013; Barton et al., 2010; Wang et al., 2013), 2 of which used 2,000 mg of ginseng as the highest dose (Barton et al., 2013; Barton et al., 2010). None reported serious AEs (i.e., life-threatening events, death, or inpatient hospitalization). AEs reported included nausea, insomnia, headache, rash, and flu-like symptoms (Barton et al., 2013; Barton et al., 2010; E. Kim et al., 2011). All 4 studies showed improvements in fatigue over time; however, only the 8-week 2,000-mg trial and the 6-month American ginseng combination (Immune No. 2) demonstrated significant improvements in the primary fatigue outcome in the intervention group compared with that in the control group (Barton et al., 2013; Wang et al., 2013). However, the 400-mg trial did show a statistically significant improvement in the real-time digital fatigue scale for those who received ginseng compared with controls, but the study's authors did not believe this result was clinically meaningful (E. Kim et al., 2011).

Appraisal of the Reviewed American Ginseng Research. Overall, the study designs were strong because they controlled for multiple types of bias (Figures 2 and 3). Three trials were powered at 80% or greater (Barton et al., 2013; Barton et al., 2010; E. Kim et al., 2011). Three of the 4 studies demonstrated significant improvements in fatigue in the intervention group compared with the control group (Barton et al., 2013; E. Kim et al., 2011; Wang et al., 2013). One study's authors did not believe their results to be clinically meaningful, but this was difficult to assess because they reported only a combined baseline (intervention and control groups together) fatigue score (E. Kim et al., 2011). The valid and reliable digital fatigue scale that tracked self-reported fatigue in real time by using a watch-like device (E. Kim et al., 2011) has the potential to inform our understanding of fatigue patterns because it provides more data than the traditional self-report approach, which requires participants to think back over days, weeks,

or months. In 1 study, it was not clear if the fatigue evaluation was valid or reliable, which could undermine the results (Wang et al., 2013). One study completed a per-protocol analysis because 2 participants were removed for not taking their ginseng (Wang et al., 2013), which could have led to a bias in missing data. Furthermore, 1 study found significant results testing a combined treatment (Immune No. 2) that included American ginseng (Wang et al., 2013). Testing a combination of ingredients produces results that cannot be attributed to any of the individual components. None of the study reports revealed any significant safety concerns.

Asian Ginseng (P ginseng)

Asian ginseng is found in China, Korea, and Russia and is believed to be 1 of the most-researched species of ginseng (Kiefer & Pantuso, 2003). Six studies evaluated Asian ginseng as a treatment for fatigue. Four trials tested Asian ginseng (*P ginseng* C.A. Meyer) (Braz et al., 2013; H. G. Kim et al., 2013; Yennurajalingam et al., 2015) or *P ginseng* (Korean ginseng) (Etemadifar et al., 2013). Two studies tested Asian ginseng as part of a combination of natural products (Bojungikki-tang and Pharmaton) (Jeong et al., 2010; Le Gal et al., 1996). Multiple fatigue assessments were utilized, including a Visual Analogue Scale (Braz et al., 2013; Jeong et al., 2010; H. G. Kim et al., 2013), the Modified Fatigue Impact Scale (Etemadifar et al., 2013), a Numeric Self-Rating Scale (H. G. Kim et al., 2013), the Functional Assessment of Chronic Illness Therapy–Fatigue (Yennurajalingam et al., 2015), and 1 investigator-developed, self-report tool (Le Gal et al., 1996).

Design. Four of the 6 studies were double-blind, placebo-controlled trials (Braz et al., 2013; Etemadifar et al., 2013; Jeong et al., 2010; H. G. Kim et al., 2013; Le Gal et al., 1996). One study was a randomized controlled trial with a waitlist control (Jeong et al., 2010). One study was a single-arm, prospective, open-label trial (Yennurajalingam et al., 2015). Overall, risk of bias was found to be unclear to high (Figures 4 and 5). Study durations ranged from 4 weeks to 3 months (Braz et al., 2013; Etemadifar et al., 2013; Jeong et al., 2010; H. G. Kim et al., 2013; Le Gal et al., 1996; Yennurajalingam et al., 2015). Daily doses ranged from 80 mg to 2,000 mg of *P ginseng* (Braz et al., 2013; Etemadifar et al., 2013; Jeong et al., 2010; H. G. Kim et al.,

2013; Le Gal et al., 1996; Yennurajalingam et al., 2015), with the longest trial using a 250-mg dose twice daily, for a total daily dose of 500 mg, for 3 months (Etemadifar et al., 2013). Five of the 6 studies were designed to evaluate the efficacy of ginseng as a treatment for fatigue (Braz et al., 2013; Etemadifar et al., 2013; Jeong et al., 2010; H. G. Kim et al., 2013; Le Gal et al., 1996), and 1 was designed to evaluate the safety and tolerability of ginseng as a treatment for fatigue (Yennurajalingam et al., 2015).

Sample. The 6 studies were conducted in different countries (Braz et al., 2013; Etemadifar et al., 2013; Jeong et al., 2010; H. G. Kim et al., 2013; Le Gal et al., 1996; Yennurajalingam et al., 2015). Study participants had the following diagnoses: cancer (Jeong et al., 2010; Yennurajalingam et al., 2015), fibromyalgia (Braz et al., 2013), chronic fatigue (H. G. Kim et al., 2013), multiple sclerosis (Etemadifar et al., 2013), and functional fatigue (Le Gal et al., 1996). All studies included only adults. Four of 6 studies required participants to report fatigue as an inclusion criteria (Jeong et al., 2010; H. G. Kim et al., 2013; Le Gal et al., 1996; Yennurajalingam et al., 2015). Sample sizes ranged from 30 to 232. The trial with the smallest sample (n=30) was reported as a preliminary study (Yennurajalingam et al., 2015). One study that was reported as a pilot study (n=40) was powered at 80%, with an effect size of 0.2 (Jeong et al., 2010). None of the other studies reported the power of the study to detect change. Two of the 6 studies included only women (Braz et al., 2013; Etemadifar et al., 2013). Three additional studies included mostly women: 60%, 76%, and 65%, respectively (Jeong et al., 2010; H. G. Kim et al., 2013; Le Gal et al., 1996). The study conducted in the United States was the only one to report race; most participants were white (84%) (Yennurajalingam et al., 2015). The lowest attrition rate was 0% (Etemadifar et al., 2013), with attrition rates in the other 5 studies reported as a minimum of 2% and a maximum of 27% (Braz et al., 2013; Jeong et al., 2010; H. G. Kim et al., 2013; Le Gal et al., 1996; Yennurajalingam et al., 2015).

Safety and Efficacy. No study reported serious AEs in the intervention group (Braz et al., 2013; Etemadifar et al., 2013; Jeong et al., 2010; H. G. Kim et al., 2013; Le Gal et al., 1996; Yennurajalingam et al., 2015). One study that tested ginseng in a natural product combination

(Pharmaton) reported a single, serious AE in the control group; a participant had to be admitted to the hospital for edema of the uvula that resolved after corticosteroid therapy (Le Gal et al., 1996). The single-arm study reported a 6% rate for serious AEs; however, none were attributed to ginseng (Yennurajalingam et al., 2015). One study did not report any AEs, but the investigators noted that 9 participants (3 from each arm) dropped out because of AEs (Braz et al., 2013). Only 3 of the 6 studies reported AEs in detail, with rates that ranged from 10% to 53% (Jeong et al., 2010; Le Gal et al., 1996; Yennurajalingam et al., 2015). In the study that reported the largest AE rate (53%), none of the AEs were attributed to the intervention (Yennurajalingam et al., 2015). The most-reported AEs included nausea/vomiting, sleep disorders, abdominal pain, and bowel disorders (Etemadifar et al., 2013; Jeong et al., 2010; H. G. Kim et al., 2013; Le Gal et al., 1996; Yennurajalingam et al., 2015). Fatigue decreased in all 6 studies, with 5 studies reporting significant differences in fatigue measures in the invention group (Etemadifar et al., 2013; Jeong et al., 2010; H. G. Kim et al., 2013; Le Gal et al., 1996; Yennurajalingam et al., 2015).

Appraisal of Reviewed Asian Ginseng Research. Most (4 of 6) of the studies were double-blind, placebo-controlled trials; however, they did not report how they mitigated bias (Figures 4 and 5) (Braz et al., 2013; Etemadifar et al., 2013; H. G. Kim et al., 2013; Le Gal et al., 1996). Four of the 6 studies showed that the intervention group had significantly improved fatigue outcomes compared with the placebo group (Etemadifar et al., 2013; Jeong et al., 2010; H. G. Kim et al., 2013; Le Gal et al., 1996; Yennurajalingam et al., 2015); the single-arm prospective, open-label trial showed significantly improved fatigue scores at 15 and 29 days compared with fatigue at baseline (Yennurajalingam et al., 2015). The single-arm trial also had the highest risk of bias (Yennurajalingam et al., 2015). Because this study did not have a control group, it is possible that the improvement over time resulted from something other than the ginseng treatment (Yennurajalingam et al., 2015). Three studies excluded participants from the analysis if they did not adhere to the study protocol, thus a per-protocol analysis was done rather than an intent-to-treat analysis (Etemadifar et al., 2013; Le Gal et al., 1996; Yennurajalingam et

al., 2015). A per-protocol analysis may result in bias related to missing data (Higgins, Green, & Cochrane, 2011). However, 1 study reported no attrition, but it is not clear if the attrition count was defined as including participants who were excluded for not following the study protocol (Etemadifar et al., 2013). One study used an investigator-developed fatigue measure but did not report validity or reliability of the measure (Le Gal et al., 1996). If the fatigue measure was not valid and reliable, this would challenge the validity of the results (Le Gal et al., 1996). Furthermore, 2 studies tested Asian ginseng in a combination with other natural products, making it difficult to ascertain the relative contribution of the ingredients to the study outcomes (Jeong et al., 2010; Le Gal et al., 1996). None of the studies reported significant safety concerns for the intervention group.

Cancer-Related Fatigue

A subanalysis was conducted for the studies of cancer-related fatigue (CRF) because they made up the largest illness group in this review. Four of the 10 studies evaluated ginseng's impact on CRF (Barton et al., 2013; Barton et al., 2010; Jeong et al., 2010; Yennurajalingam et al., 2015). Two studies included both active treatment and post-treatment cancer survivors (Barton et al., 2013; Barton et al., 2010). One study included only results at 2 months after treatment (Jeong et al., 2010), and the other included only active-treatment cancer survivors (Yennurajalingam et al., 2015).

Ginseng doses ranged from 800 mg to 2,000 mg. Ginseng doses in 3 of the 4 studies were greater than 1,000 mg, and intervention periods ranged from 2 weeks to 8 weeks (Barton et al., 2013; Barton et al., 2010; Jeong et al., 2010). Three of the 4 CRF studies reported significant results (Barton et al., 2013; Jeong et al., 2010; Yennurajalingam et al., 2015). Two showed that ginseng (1, *P quinquefolius*; 1, *P ginseng*) improved fatigue significantly in the study groups versus the controls (Barton et al., 2013; Jeong et al., 2010), while the other study showed that *P ginseng* significantly improved participants' fatigue scores from those at baseline (Yennurajalingam et al., 2015).

Although the studies were promising for their effectiveness in decreasing CRF, the results should be approached cautiously. Two of the 4 studies had sample sizes of fewer than 50 participants (Jeong et al., 2010; Yennurajalingam et al., 2015). Three had mostly women participants (Barton et al., 2013; Barton et al., 2010; Jeong et al., 2010). Both the sample size and sample composition may have impacted the generalizability of the results. To date, none of the positive results of the CRF ginseng studies have been replicated.

Discussion

This review aimed to evaluate the safety and effectiveness of the 2 types of Panax ginseng (Asian [*P ginseng*] and American [*P quinquefolius*]) as a treatment for fatigue through examining study designs, samples, safety, and efficacy. Key strengths of the studies included the study designs and the safety and efficacy results. Most of the studies (8/10) were double-blind, randomized controlled trials (Barton et al., 2013; Barton et al., 2010; Braz et al., 2013; Etemadifar et al., 2013; E. Kim et al., 2011; H. G. Kim et al., 2013; Le Gal et al., 1996; Wang et al., 2013), which allows for control of multiple types of bias; however, mitigating detection and attrition bias would increase the overall strength of the evidence (Figures 6 and 7). Four (4/10) studies reported being powered at 80% or greater, which can add to the strength of the studies to detect the effects of the treatment (Barton et al., 2013; Barton et al., 2010; Jeong et al., 2010; E. Kim et al., 2011). None of the studies reported significant AEs attributed to ginseng. One study did report a serious AE attributed to the placebo (Le Gal et al., 1996). Reported rates of grade ≥3 AEs ranged from 1% to 11% (Barton et al., 2013; Barton et al., 2010; Jeong et al., 2010; Le Gal et al., 1996; Yennurajalingam et al., 2015). Three of 10 studies showed no significant differences in AEs between the ginseng and placebo groups (Barton et al., 2013; Barton et al., 2010; Wang et al., 2013). The most common, nonserious AEs reported were nausea/vomiting, sleep disorders, abdominal pain, and bowel disorders. Most (7/10) studies showed significant improvements in fatigue scores in the intervention group compared with the control group (Barton et al., 2013; Etemadifar et al., 2013; Jeong et al., 2010; E. Kim et al., 2011; H. G. Kim et al., 2013; Le Gal et al., 1996; Wang et al., 2013). Additionally, 1 single-arm study showed significant improvement

in fatigue scores from baseline at 15 and 29 days (Yennurajalingam et al., 2015); however, this study did not have a control group. Therefore, there could be plausible explanations other than treatment with ginseng for the improvement in fatigue over time (Yennurajalingam et al., 2015). Furthermore, 1 study's authors interpreted their findings as not being clinically meaningful; however, because the authors reported a combined (placebo and intervention) baseline for fatigue, it was difficult to assess the rationale for their conclusion (E. Kim et al., 2011). Five of the 6 studies reporting significant differences in fatigue between the ginseng and placebo groups may have been biased from missing data, because they completed per-protocol analyses and/or did not seem to adhere to intention-to-treat analysis (Etemadifar et al., 2013; H. G. Kim et al., 2013; Le Gal et al., 1996; Wang et al., 2013; Yennurajalingam et al., 2015). This type of analysis limits the ability to overcome biases related to attrition or missing data, or both, which could favor the intervention group (Higgins et al., 2011). Two studies did not show significant improvements in fatigue: 1 was a dose-finding pilot study (Barton et al., 2010), and the other was a 3-arm randomized controlled trial with 52 participants that tested the second-lowest dose of ginseng (100 mg) (Braz et al., 2013).

Most of the studies (6/10) were conducted in Western countries (Barton et al., 2013; Barton et al., 2010; Braz et al., 2013; E. Kim et al., 2011; Le Gal et al., 1996; Yennurajalingam et al., 2015). Sample sizes ranged from 30 to 364 (Barton et al., 2013; Barton et al., 2010; Braz et al., 2013; Etemadifar et al., 2013; Jeong et al., 2010; E. Kim et al., 2011; H. G. Kim et al., 2013; Le Gal et al., 1996; Wang et al., 2013; Yennurajalingam et al., 2015). Three (3/10) studies were either pilot or preliminary studies (Barton et al., 2010; Jeong et al., 2010; Yennurajalingam et al., 2015). Cancer was the most common (4/10) condition studied (Barton et al., 2013; Barton et al., 2010; Jeong et al., 2010; Yennurajalingam et al., 2015). Eight (8/10) of the studies included mostly women participants (Barton et al., 2013; Barton et al., 2010; Braz et al., 2013; Etemadifar et al., 2013; Jeong et al., 2010; E. Kim et al., 2011; H. G. Kim et al., 2013; Le Gal et al., 1996)—possibly because women may be more likely to seek alternative treatments, such as ginseng, or because the conditions studied primarily impacted women (e.g., fibromyalgia and multiple

sclerosis). Two studies' inclusion criteria specified that participants had to be women (Braz et al., 2013; Etemadifar et al., 2013; Krasselt & Baerwald, 2017; Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000). Because of the preponderance of women participants, the study results cannot necessarily be generalized to men.

No consistent dosage for ginseng was used. Study interventions varied from 80 mg to 2,000 mg daily (Barton et al., 2013; Barton et al., 2010; Braz et al., 2013; Etemadifar et al., 2013; Jeong et al., 2010; E. Kim et al., 2011; H. G. Kim et al., 2013; Le Gal et al., 1996; Wang et al., 2013; Yennurajalingam et al., 2015). Three of the 10 studies used 2,000 mg as the maximum dose (Barton et al., 2013; Barton et al., 2010; H. G. Kim et al., 2013). All but 2 (6/8) studies that demonstrated significant improvements in fatigue in the intervention group tested ginseng doses of 400 mg or more (Barton et al., 2013; Etemadifar et al., 2013; Jeong et al., 2010; E. Kim et al., 2011; H. G. Kim et al., 2013; Yennurajalingam et al., 2015). Study durations for treatment ranged from 2 weeks to 6 months (Barton et al., 2013; Barton et al., 2010; Braz et al., 2013; Etemadifar et al., 2013; Jeong et al., 2010; E. Kim et al., 2011; H. G. Kim et al., 2013; Le Gal et al., 1996; Wang et al., 2013; Yennurajalingam et al., 2015). Most (7/8) studies that showed significant improvements in fatigue were trials that lasted 4 weeks or more (Barton et al., 2013; Etemadifar et al., 2013; E. Kim et al., 2011; H. G. Kim et al., 2013; Le Gal et al., 1996; Wang et al., 2013; Yennurajalingam et al., 2015).

Limitations

One limitation of this review is limiting the studies to English language only, which could have led to a language bias. However, in a meta-analysis, Morrison et al. (Morrison et al., 2012) showed that although limiting to English only in reviews is perceived to lead to a language bias, a language limitation in search strategy did not result in systematic bias. Additionally, not limiting this review to single agent use of ginseng may have confounded the results regarding efficacy of ginseng as a treatment for fatigue. However, limiting the studies to single-agent use of ginseng would have ignored the traditional uses of ginseng (often multi-agent combinations)

and would have narrowed the assessment of the state of evidence on the effectiveness of ginseng for fatigue in people with chronic illness.

Conclusion and Clinical Implications

Overall, there was modest support for ginseng as a treatment for fatigue. Both American and Asian ginseng may be viable treatments for fatigue in people with chronic illness because of the low risk associated with its use, coupled with modest evidence for its efficacy. However, it is critical that future research build on the evidence provided by the studies reviewed about ginseng dose and duration of treatment, be methodologically strong, and include more diverse samples before ginseng, which is already in widespread use, is adopted as a standard treatment option for fatigue.

Future Research Recommendations

Future research should focus on developing safe and effective interventions for fatigue. We found 3 obvious gaps in the literature regarding American and Asian ginseng as treatments for fatigue in people with chronic illness that should be considered for additional research. First, future research reports should include a clear presentation of the statistical methods used and specify how missing data were handled to address attrition bias. Second, larger and more diverse samples are needed to increase the generalizability and statistical power of the studies. Third, future studies should be designed for a regimen of 400 mg or more of ginseng for at least 4 weeks. Finally, the results of current studies with significant findings should be replicated by future studies to assure that the findings can be reproduced.

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Box 1. Search Strategy

For the literature search, the following databases were used: the National Library of Medicine's PubMed, CINAHL (Cumulative Index to Nursing and Allied Health), Ovid MEDLINE, and EMBASE. All searches were limited to English language and the following types of studies: clinical trials, controlled clinical trials, randomized controlled trials, meta-analyses, and systematic reviews. The search results were as follows: PubMed, 22 citations; CINAHL, 27 citations; Ovid MEDLINE, an additional 24 citations; and EMBASE, an additional 127 citations—total, 200 citations. All results were put into an EndNote file and 52 duplicate citations were removed, leaving 148 citations.

Subject headings used: panax ginsenosides; fatigue; fatigue syndrome, chronic; neoplasms.

Key/text words used: ginseng, ginsenosides, fatigue, chronic fatigue, cancer-related fatigue, cancer.

Table 1. Characteristics of Included Studies

Study	Location	Type of Ginseng	Daily Dose per Arm	Diagnosis	N	Gender	Study Design	Primary Fatigue Assessment	Length	Results	Power	Effect Size	Attrition, %	Reported AEs[a]
(Barton et al., 2010)	United States	American	Ginseng: 750 mg 1,000 mg 2,000 mg	CRF	282	Women (66%)	Pilot double-blind placebo controlled RCT	Brief Fatigue Inventory	8 weeks	Non-significant findings but data showed decreasing CRF with the use of ginseng at 2 higher doses.	0.8	.41	38	Placebo[b] Grade ≥3, 7% Ginseng: 750 mg Grade ≥3, 11% 1,000 mg Grade ≥3, 4% 2,000 mg Grade ≥3, 7% Most reported AE: Anxiety Insomnia Nausea

Study	Location	Type of Ginseng	Daily Dose per Arm	Diagnosis	N	Gender	Study Design	Primary Fatigue Assessment	Length	Results	Power	Effect Size	Attrition, %	Reported AEs[a]
(Barton et al., 2013)	United States	American	Ginseng: 2,000 mg	CRF	364	Women (78%)	Multisite, double-blind placebo controlled RCT	Multidimensional Fatigue Symptom Inventory-Short Form	8 weeks	Significant improvement in fatigue scores in intervention group compared with placebo.	0.9	.38	22%	Placebo[b]: Grade 3, 1% Ginseng 2,000 mg Grade 3, 1% Most reported AE: Anxiety Insomnia Nausea

Study	Location	Type of Ginseng	Daily Dose per Arm	Diagnosis	N	Gender	Study Design	Primary Fatigue Assessment	Length	Results	Power	Effect Size	Attrition, %	Reported AEs[a]
(Braz et al., 2013)	Brazil	*Panax ginseng* C.A. Meyer	Amitriptyline: 25 mg Ginseng: 100 mg	Fibromyalgia	52	Women[c] (100%)	Double-blind RCT Comparative (amitriptyline, placebo, *P ginseng*)	Fatigue Visual Analogue Scale	12 weeks	Fatigue decreased for all 3 groups, with no significant differences between groups.	NR	NR	27%	AEs not reported. Each group had 3 participants drop out because of adverse effects.

Study	Location	Type of Ginseng	Daily Dose per Arm	Diagnosis	N	Gender	Study Design	Primary Fatigue Assessment	Length	Results	Power	Effect Size	Attrition, %	Reported AEs[a]
Etemadifar et al (2013)	Iran	Korean	Ginseng: 500 mg	MS	52	Women[c] (100%)	Double-blind placebo controlled RCT	Modified Fatigue Impact Scale	3 months	Total fatigue was significantly different in favor of ginseng. Physical dimension on the fatigue scale was significantly different for the ginseng group.	NR	NR	0%	Reported no serious AEs. Did not report AEs in detail. Only reported 1 patient who had constipation, which resolved.

Study	Location	Type of Ginseng	Daily Dose per Arm	Diagnosis	N	Gender	Study Design	Primary Fatigue Assessment	Length	Results	Power	Effect Size	Attrition, %	Reported AEs[a]
Jeong et al (2010)	Korea	Combination, including *P ginseng*	Bojungikki-Tang Ginseng dose: 1,252.5 mg	CRF	40	Women (60%)	Placebo controlled RCT with waitlist	Visual Analogue Scale of Global Fatigue	2 weeks	Intervention group had significantly improved fatigue compared with placebo.	0.8	0.2	10%	No serious AEs reported. Reported 10% AEs but did not clarify if intervention or placebo group. Most reported AEs: Flatulence Dyspepsia

Study	Location	Type of Ginseng	Daily Dose per Arm	Diagnosis	N	Gender	Study Design	Primary Fatigue Assessment	Length	Results	Power	Effect Size	Attrition, %	Reported AEs[a]
Kim et al (2011)	United States	American	Ginseng: 400 mg	MS	53	Women (94%)	Double-blind placebo controlled crossover	Fatigue Severity Scale	6 weeks	Both groups improved. No significant difference between groups. Mixed modeling showed significantly improved RDFS; however, authors do not believe this was clinically	0.8	0.8	11%	Placebo, 26[d] Ginseng, 29[d] No serious AEs reported. Most reported AEs: Nausea Insomnia Headache Rash Flulike syndrome

Study	Location	Type of Ginseng	Daily Dose per Arm	Diagnosis	N	Gender	Study Design	Primary Fatigue Assessment	Length	Results	Power	Effect Size	Attrition, %	Reported AEs[a]
Kim et al (2013)	Korea	*P ginseng* C.A. Meyer	Ginseng: 1,000 mg 2,000 mg	Idiopathic chronic fatigue	90	Women (76%)	Double-blind placebo controlled RCT	Fatigue Numeric Rating Scale (NRS) and Visual Analogue Scale (VAS)	4 weeks	NRS questions decreased for all 3 groups, with no significance between groups.[c] VAS scores declined for all groups, with *P ginseng* (2 g) arm scores significantly lower	0.9	0.53	2%	AEs not reported.

Study	Location	Type of Ginseng	Daily Dose per Arm	Diagnosis	N	Gender	Study Design	Primary Fatigue Assessment	Length	Results	Power	Effect Size	Attrition, %	Reported AEs[a]
(Le Gal et al., 1996)	France	Combination with *P ginseng* C.A. Meyer	Pharmaton Ginseng dose: 80 mg	Functional fatigue	232	Women (65%)	Multicenter, double-blind placebo controlled RCT	Investigator developed self-report tool	6 weeks	Intervention group had significantly improved fatigue over placebo.	NR	NR	5.6%	Placebo, 9% Pharmaton,17% AE grades not reported. 1 serious AE reported in placebo group. Most reported AEs: Nausea/vomiting Sleep disorders Abdominal pain

Study	Location	Type of Ginseng	Daily Dose per Arm	Diagnosis	N	Gender	Study Design	Primary Fatigue Assessment	Length	Results	Power	Effect Size	Attrition, %	Reported AEs[a]
(Wang et al., 2013)	China	Combination containing American Ginseng	Immune No.2 Ginseng dose NR	HIV after highly active anti-retroviral therapy (HAART)	264	Men (62%)	Double-blind placebo controlled RCT	Fatigue item in Scores of Symptoms and Signs	6 months	Intervention group had significantly improved fatigue than placebo.	NR	NR	12%	AEs not listed.[b]

Study	Location	Type of Ginseng	Daily Dose per Arm	Diagnosis	N	Gender	Study Design	Primary Fatigue Assessment	Length	Results	Power	Effect Size	Attrition, %	Reported AEs[a]
(Yennurajalingam et al., 2015)	United States	*P ginseng* C.A. Meyer	Ginseng: 800 mg	CRF	30	Women (50%)	Single arm pre/post	Functional Assessment of Chronic Illness Therapy Fatigue	29 days	Significantly improved fatigue scores at day 15 and day 29 from baseline.	NR	NR	20%	No AEs attributed to the study. Grade >3, 6% These were not attributed to the study. Most reported AEs: Pain Nausea

Abbreviations: AE, adverse event; CRF, cancer-related fatigue; MS, multiple sclerosis; NR, not reported; RCT, randomized controlled trial.

[a] Grade 3 or higher.
[b] No significant differences in reported AEs between intervention and placebo groups.
[c] Only recruited women.
[d] Raw numbers because of inability to calculate a rate.

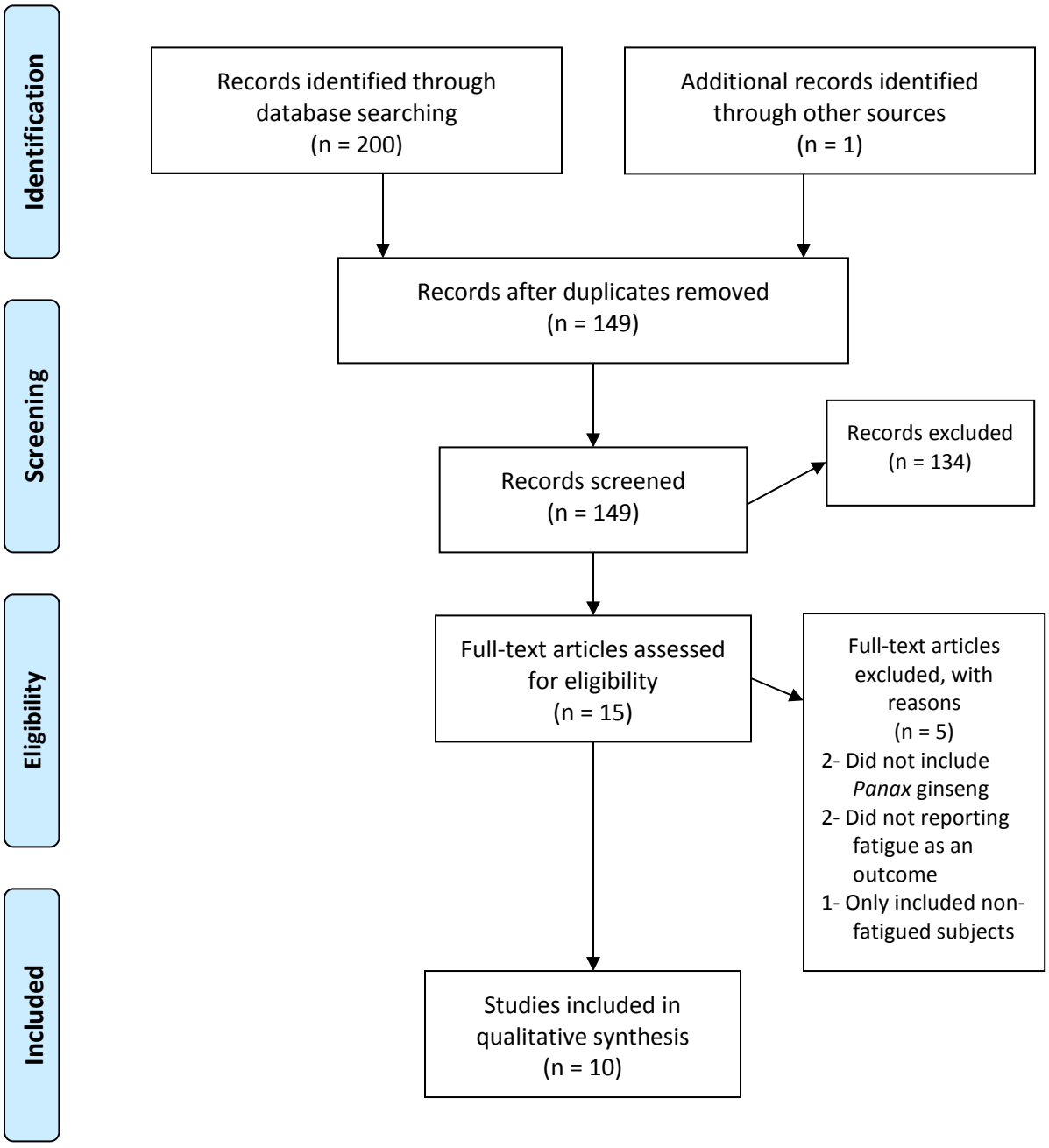

Figure 1. PRISMA Flow Diagram.

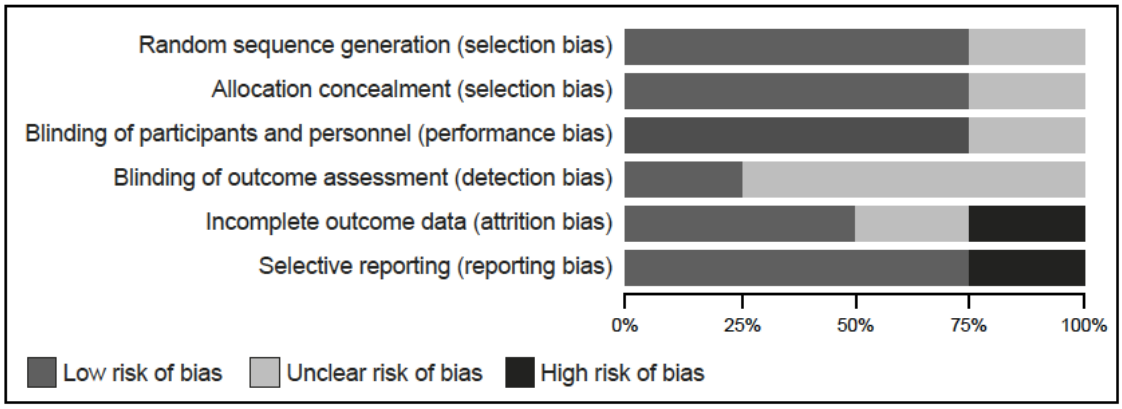

Figure 2. Overall Risk of Bias: American Ginseng. The authors' judgments about each risk-of-bias item are shown as percentages across all included studies of American ginseng.

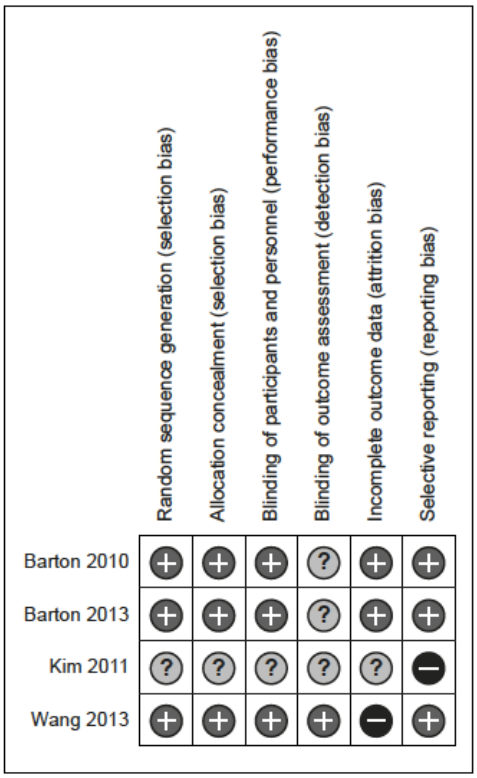

Figure 3. Risk of Bias: American Ginseng. The authors' judgments about each risk-of-bias item are shown for each included study of American ginseng. The + indicates low risk of bias; −, high risk of bias; ?, unclear risk of bias.

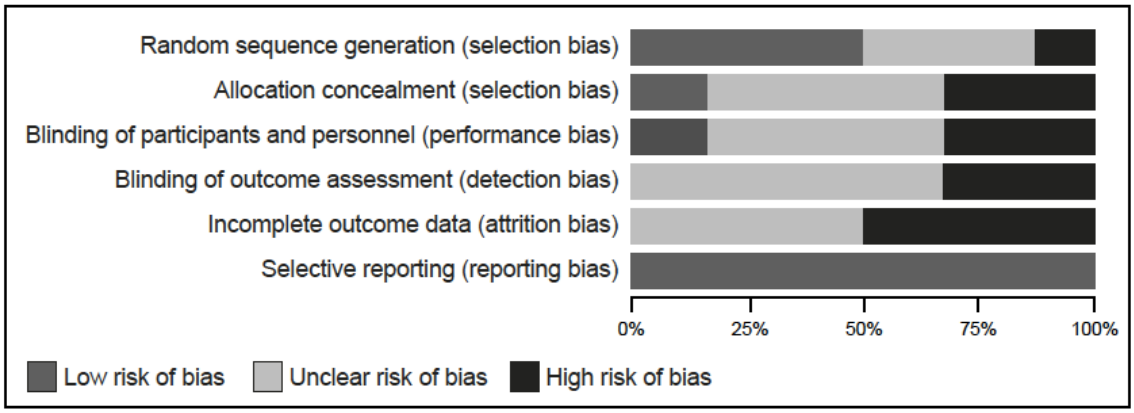

Figure 4. Overall Risk of Bias: Asian Ginseng. The authors' judgments about each risk-of-bias item are shown as percentages across all included studies of Asian ginseng.

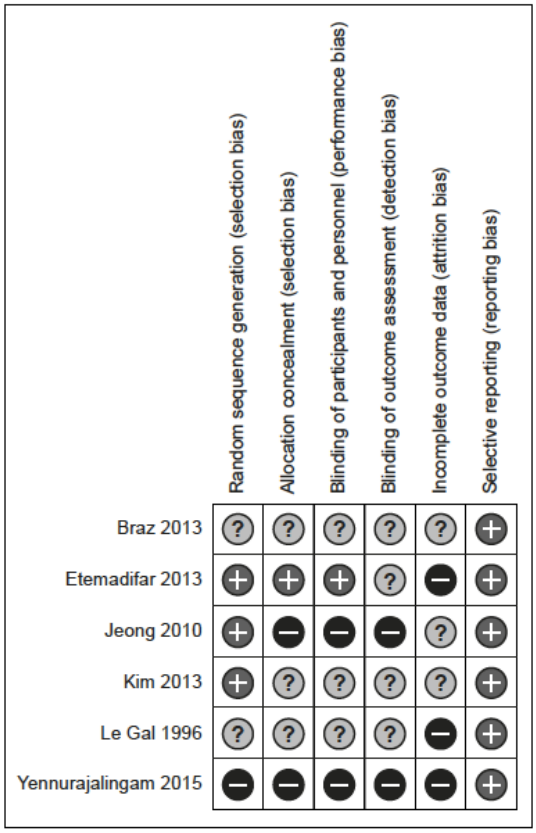

Figure 5. Risk of Bias: Asian Ginseng. The authors' judgments about each risk-of-bias item for each included study of Asian ginseng. The + indicates low risk of bias; −, high risk of bias; ?, unclear risk of bias.

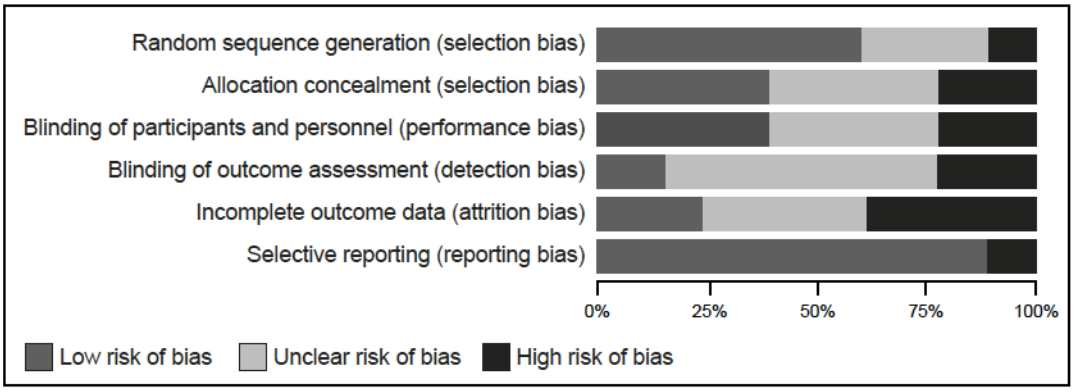

Figure 6. Risk of Bias: The authors' judgments about each risk-of-bias by percentage across all included studies.

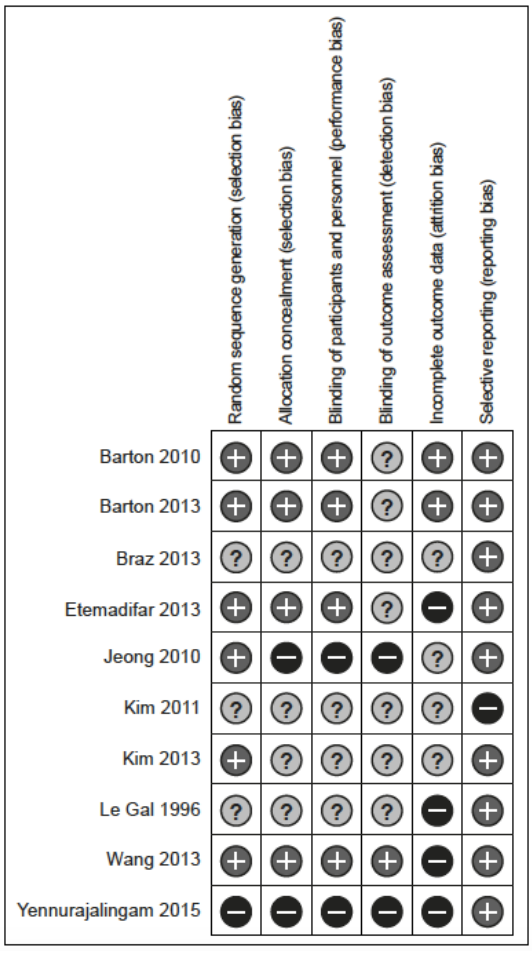

Figure 7. Risk of Bias. The authors' judgments about each risk-of-bias item for each included study. The + indicates low risk of bias; −, high risk of bias; ?, unclear risk of bias.

Chapter IV: Reasons for Integrative Health Consults: Differences Between Cancer Survivors, Patients without Cancer and Referring Providers

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This manuscript represents a significant contribution to the dissertation work as it aims to describe the demographic and complementary and alternative practice differences between cancer survivors and patients without cancer, and assess cancer survivors' and referring providers' reasons for integrative health consults. The target journal for this manuscript is *The Journal of Alternative and Complementary Medicine*, a peer-reviewed publication of scientific work aimed at health care professionals, practitioners, and scientists with the goal of integrating complementary and alternative practices into mainstream practice.

Abstract

Objectives: The objectives of this study were to 1) compare the difference between demographics, reported symptoms and QOL measures in patients with and without cancer who sought an integrative health (IH) consult and 2) to compare the reasons for integrative health consult between cancer survivors and referring providers.

Methods: Descriptive cross-sectional study that employed both a secondary analysis of an integrative health database supplemented by clinical and demographic data from a retrospective medical record review of 839 adults over the age of 18 seeking IH consultation at an academic medical center in the southwestern United States.

Results: Number of complementary approaches reported prior to consult were not significantly different between cancer survivors and patients without cancer. Most reported complementary approaches used by cancer survivors were multivitamins (23.6%), exercise (20.3%), and turmeric (15.6%). Patients without cancer reported significantly higher pain ($\bar{x}$=4.68) levels at referral compared to cancer survivors ($\bar{x}$=3.81, t (781) = -3.56, p = <0.001). Cancer survivors reported significantly higher energy levels ($\bar{x}$=4.89 vs. $\bar{x}$=4.07, *t* (804) = 4.13, p = <0.001), sleep levels ($\bar{x}$=2.51 vs. $\bar{x}$=2.25, *t* (825) = 3.04, p= <0.01), overall health ($\bar{x}$=2.82 vs. $\bar{x}$=2.55, *t* (809) = 4.45, p = <0.001), spiritual wellbeing ($\bar{x}$=3.67 vs. $\bar{x}$=3.38, *t* (810) = 3.19, p = <0.01), and significantly better relationships ($\bar{x}$=3.86 vs. $\bar{x}$=3.60, *t* (813) = 3.06, p = <0.01) compared to patients without cancer. Other patient-reported measures like stress, anxiety, and physical activity did not differ significantly between groups. Cancer survivors reported fatigue (51.9%) and cancer (76.4%) as the top reasons for IH consult. Integrative Medicine and Health Physicians recommended significantly more complementary approaches for patients without cancer compared to cancer survivors ($\bar{x}$=6.11 vs. $\bar{x}$=5.63, *t* (837) = -2.04, p=<0.05). There was little

agreement between cancer survivors' reasons for an IH consult compared with physician referral reasons.

Conclusion: The limited agreement on reason for consultation alludes to an opportunity for cancer survivors and referring providers to gain further understanding of how IMH physicians can support cancer survivors.

Manuscript Key words: Integrative Health, Complementary and Alternative Medicine, Symptoms, Physician Referrals, Cancer

Introduction

It is estimated that between 30-50% of cancer survivors are using complementary approaches to treat symptoms and promote health (Adams, 2007; Horneber et al., 2012). Complementary approaches include natural products like herbs and supplements and mind and body practices like yoga (National Center for Complementary and Integrative Health, 2016). Many estimates of the prevalence of complementary approach use by cancer patients are believed to be lower than actual use. Factors contributing to underreporting include patients' reluctance to share their usage with their healthcare team and narrow definitions of complementary approaches used in many prevalence studies (Berretta, 2017; Zavery, Appleton, Sandiford, Wong, & Hughes, 2013). The most frequently reported types of complementary approaches used by cancer survivors are herbal preparations and natural products like vitamins and minerals (Loquai et al., 2017; Zavery et al., 2013). Cancer survivors are defined as patients diagnosed with cancer from the time of diagnosis until their end of life (Centers for Disease Control and Prevention, 2017). As many as 59% of cancer survivors who reported complementary approach use were found to be at risk of their complementary approach adversely interacting with their conventional treatments (Firkins et al., 2018). Additionally, in the United States the natural product industry is unregulated. This places cancer survivors with compromised immune systems at risk for infection from products that may be of poor quality and pose a threat of contamination with bacteria or fungi (Tascilar, de Jong, Verweij, & Mathijssen, 2006). Furthermore, research has shown that cancer survivors' main source of information about complementary approaches are family and friends. Family and friends may be using unreliable or anecdotal evidence to support their recommendations. Additionally, they may be unaware of potential interactions between their recommendation and their cancer survivors'

current medical treatments. Furthermore, survivors are not reporting their complementary approach use to their healthcare team (Zavery et al., 2013). There is a critical risk posed by the cancer care teams' lack of involvement and/or knowledge of the cancer survivors' use of complementary approaches.

The integrative medicine and health (IMH) physician is one key avenue to help patients and cancer care providers navigate the complex world of complementary approaches. Integrative Medicine and Health (IMH) physician consultations include an in-depth review of the patient's health story, including their diet, movement practices, stress, spirituality, and preferences for integrative medicine modalities that culminate in specific multidisciplinary integrative health recommendations. Current evidence on why cancer survivors seek integrative health consults is limited. Integrative health (IH) is defined as incorporating complementary or non-Western healthcare approaches with traditional Western or mainstream approaches (National Center for Complementary and Integrative Health, 2016). Often studies of IH consults do not assess why patients sought consultation and/or why they were referred for consultation (E. Ben-Arye, Kruger, D., Samuels, N., Keinan-Boker, L., Shalom, T., Schiff, E., 2014; E. Ben-Arye, Schiff, E., Raz, O. G., Samuels, N., Lavie, O., 2014). Research has identified a mismatch between the health care providers' reasons for placing an IH consult compared to the reasons cancer survivors gave for the IH consult (Samuels, 2015). Additionally, research has identified that having cancer, being a woman, prior use of integrative health, higher rates of symptoms, younger age, increased physical activity, receipt of adjuvant chemotherapy and/or multiple cancer treatment modalities predict complementary approach use (Anderson & Taylor, 2012; Loquai et al., 2017; Strizich et al., 2015). However, there is limited knowledge about which patients seek an integrative health consult. Comparing cancer survivors to patients without cancer can help identify additional

needs and possible opportunities that can enable us to overcome these critical issues. The purpose of this study was to 1) compare the difference between demographics, reported symptoms and QOL measures in patients with and without cancer who sought an integrative health (IH) consult, and 2) to compare the reasons for integrative health consult between cancer survivors and referring providers. It is critical IH and cancer care providers understand why patients seek IH consults, so we can identify ways to support their use of this valuable resource.

Materials and Methods

Study Design

This descriptive cross-sectional study employed both a secondary analysis of information in the Baseline Integrative Medicine Intake Form database supplemented by clinical and demographic data from a retrospective medical record review. Participants were adults at least 18 years old who sought integrative health consultation from an established IH service at an academic medical center in the southwestern United States. Content validity of the Baseline Integrative Medicine Intake Form was established through internal peer review. To ensure fidelity in data collection, clear variable guidelines and abstraction tools were employed by chart reviewers. The local Institutional Review Board reviewed and approved this study.

Sample

The convenience sample consisted of all 839 adult Integrative Health patients who sought initial integrative health consultations and completed the Baseline Integrative Medicine Intake Form between 2013-2017. Participants were eligible for inclusion if they were ≥18 and had completed the Baseline Integrative Medicine Intake Form. The study excluded patients who were deceased or reported that they did not intend to have an IH consult.

Measures

The Baseline Integrative Medicine Intake Form captured patients' reported demographics, reason for consultation and referral source. Numeric box rating scales from 0-10 anchored with 0 ("as bad as it can be") and 10 ("as good as it can be") were used for stress level, pain level, energy level and anxiety level symptom assessment, which has been shown to be a reliable measure of symptoms (Paice, 1997). Quality of diet, relationships, spiritual wellbeing, sleep and overall health were captured on a Likert scale (1 = Excellent, 5 = Poor). Average physical activity level was also captured on a Likert scale (1= Sedentary, 4 = Highly Active).

Participant demographics were collected from the electronic health record (EHR), including gender; marital status; type of cancer diagnosis; time from cancer treatment; length of time since diagnosis of cancer, fibromyalgia, or heart disease until the integrative health consult; any previous and/or current use of IH interventions such as herbs, massage, acupuncture, and/or yoga reported at IH consult; and medications at time of IH consult.

Data Analysis

Descriptive statistics were used to summarize patient responses and to identify differences between the two groups (cancer versus other). Differences between the two groups were determined by using Pearson chi-square and Student t, as appropriate. P values <0.05 were considered significant. All of the Baseline Integrative Medicine Intake Form scales, except energy level, were reverse scored for analysis purposes. Variables with expected cell counts less than 5 were excluded from analysis (Siegel & Castellan, 1988). Statistical analysis was performed using IBM SPSS Statistics version 23 (IBM Corporation).

Results

The sample included 839 patients who sought an integrative health consult at an academic medical center in the Southwest between July 2013 and October 2017. Demographic and clinical characteristics of the total sample and the subgroups of participants with and without cancer are presented in Table 1. The average age was 51 (SD 15.4), 66.9% married, 50.9% lived within 24 miles of the institution, majority (80.1%) were female, 25.2% diagnosed with cancer, 75.6% had prior experience with integrative health, and 76.4% were referred by their physician (see Table 1).

The sample included 212 patients who had a diagnosis of cancer at the time of their consult. Breast (35.5%), gastrointestinal (10.9%) and hematologic (16.6%) cancers were the top three cancer diagnoses (Table 1). As a group, those with a history of cancer were older at the time of IH consult than the group that did not have a history of cancer (57.6 years and 49.2 years, $t(837) = 7.08$, $p = <0.001$) respectively. The majority (56.4%) were post-treatment cancer survivors with a mean of 1.47 years from completion of treatment. At the time of consult, 10.4% of cancer survivors were on hormone treatment. Cancer survivors were primarily treated with surgery (72.2%), chemotherapy (57%) and radiation (46.2%).

Integrative Health Usage

Prior IH health use for the entire sample was 75.6%. Cancer survivors reported their prior IH use as 78.8%, which was not significantly different from the patients without cancer (74.5%). The number of IH modalities reported prior to consult was not significantly different between groups with an average of 1.56 reported for the entire sample (Table 2). Multivitamins (22.1%), exercise (17.3%), and vitamin D (12.5%) were the top three reported previously used IH approaches (Table 2). The most reported IH approaches used by cancer survivors were

multivitamins (23.6%), exercise (20.3%), and turmeric (15.6%). Significantly more cancer survivors reported higher prior use of turmeric (15.6%) compared to patients without cancer (6.2%, p = <0.001). Significantly more cancer survivors reported prior use of mindfulness (9.4%) compared to patients without cancer (4.3, p=<0.01). Otherwise, use of complementary approaches did not significantly differ between groups.

Integrative Health Recommendations

Integrative medicine and health (IMH) physicians recommended significantly more IH approaches for patients without cancer ($\bar{x}$= 6.11) compared to cancer survivors ($\bar{x}$=5.63, *t* (837) = -2.042, p=<0.05) (Table 2). The majority of patients received recommendations of exercise (64.7%), breathing exercises (57.7%), and mindfulness (57.2%). Compared to cancer survivors, IMH physicians recommended significantly more that patients without cancer use cognitive behavioral therapy*, COQ10, magnesium, mindfulness, and nutmeg. Significantly more cancer survivors were recommended to use massage, turmeric, and yoga compared to patients without cancer.

Patient Reported Measures

Patient reported measures did differ between groups (Table 3). Patients without cancer reported significantly higher pain ($\bar{x}$=4.68) levels compared to cancer survivors ($\bar{x}$=3.81, $\underline{t}$ (781) = -3.56, p = <0.001). Cancer survivors reported significantly higher levels of energy ($\bar{x}$=4.89 vs. $\bar{x}$=4.07, $\underline{t}$ (804) = 4.13, p = <0.001), sleep ($\bar{x}$=2.51 vs. $\bar{x}$=2.25, $\underline{t}$ (825) = 3.04, p = <0.01), overall health ($\bar{x}$=2.82 vs. $\bar{x}$=2.55, $\underline{t}$ (809) = 4.45, p = <0.001), spiritual wellbeing ($\bar{x}$=3.67 vs. $\bar{x}$=3.38, $\underline{t}$ (810) = 3.19, p = <0.01), and significantly better relationships ($\bar{x}$=3.86 vs. $\bar{x}$=3.60, *t* (813) = 3.06, p = <0.01) compared to patients without cancer (Table 3). Other patient-reported measures like stress, anxiety and physical activity did not differ.

Reasons for Consult

Cancer survivors' reasons for consults were primarily symptom related. A majority of patients reported their IH consult reasons as fatigue (59.4%) and pain (51.5%). Fatigue (51.9%), stress (38.2%), and cancer (76.4%) were the top three consult reasons reported by cancer survivors. Patients were able to identify more than one reason for their consult. Patients without cancer, when compared to cancer survivors, significantly more frequently reported that their reason for consult was pain (58.4% vs. 31.1%, p = <0.001), fatigue (61.9% vs 51.9%, p=0.010), gastrointestinal issues (17.2% vs 6.1%, p = <0.001) and anxiety (43.7% vs. 34%, p=0.0013). Cancer survivors reported consult reason of cancer (76.4% vs 1.1%, p = <0.001) significantly more than patients without cancer.

The top three reasons for physician referral for IH consult were cancer (14%), fatigue (15.6%), and pain (11.7%). Referring providers' consult reason of cancer was significantly higher for cancer survivors than those without cancer (55.3% vs. 1.4%, p = <0.001). Physician consult reasons of fatigue (15.6% vs. 4%, p = <0.001), pain (14.1% vs. 4.0%, p = <0.01), gastrointestinal (GI) (13.6% vs. 4%, p = <0.01), and sleep (7.1% vs. 0%, p = <0.001) were significantly higher for patients without cancer compared to cancer survivors.

There was little agreement between cancer survivors' reasons for an IH consult compared with physician referral reasons (Table 4). Reasons of migraines had the highest agreement with a moderate Cohen's *K* of 0.493 (p = <0.001). Neurological and GI reasons both had significant fair agreement between cancer survivors and physicians with Cohen's *K* of 0.231 (p= <0.01) and 0.342 (p = <0.001), respectively. Furthermore, 35.3% of patients with a provider referral and cancer reported sleep as a reason for consult, but there were no provider consults for sleep for these patients (Cohen's *K*=0). All other agreements were <0.167 or had a slight non-significant

agreement. Additionally, 50.7% of cancer survivors who had a physician referral reported fatigue as a reason for consult and only 3.3% had fatigue as a physician consult reason (Cohen's *K*= 0.444, p=0.143). However, this was not statistically significant.

Discussion

Our results demonstrated a high use of IH approaches in our total sample with 75.6% reporting prior IH use. Additionally, cancer patients' reported prior IH usage at 78.8% was higher than other reports of cancer patients' IH use (Adams, 2007; Horneber et al., 2012; Kim et al., 2018). We found that IH use was not significantly higher in cancer survivors compared to patients without cancer, which differs from research that found cancer was a significant predictor for CAM use (Anderson & Taylor, 2012). We may have seen higher IH use than national datasets due to the potential bias towards IH use by those who would choose or agree to an integrative health consult. There is also the potential that participants were referred to for an IH consult due to their IH usage; however, this was not documented in referral orders.

In our study, we found that participants without cancer reported higher levels of pain. Additionally, cancer survivors reported significantly higher levels of energy, sleep, overall health, spiritual wellbeing, and significantly better relationships compared to patients without cancer. This differs from previous research that found cancer survivors were more likely to report symptoms of anxiety like feeling sad or nervous than non-cancer patients (Anderson & Taylor, 2012). These differences may be due to differences in the sample of cancer survivors. Our cancer survivors may not be representative of a national sample since more than 78% of our cancer survivors were women and more than 56% of the cancer survivors were post-treatment with an average of 1.47 years from cancer treatment. This distance from cancer treatment may improve symptoms like anxiety and/or there may have been a response shift or normalization of

the symptoms that would explain these findings. Also our sample was taken from cancer survivors who were seeking IH treatment and may be more focused on doing things to improve their health than a national sample. In addition, these differences could reflect the high use of IH approaches and their impact on cancer survivors' patient-reported measures.

Similar to previous research, we found that the most frequently used IH approaches by cancer survivors were nutritional and herbal therapies like multivitamins, turmeric and vitamin D (Loquai et al., 2017; Zavery et al., 2013). IMH physicians recommended significantly more IH approaches for patients without cancer compared to cancer survivors. This may be a result of the differing patient needs, as evidenced by the differences in patient-reported measures between patients without cancer and cancer survivors.

Similar to previous studies, we found that there was very little agreement between cancer survivors' reason for consult and physician referral reasons (Samuels, 2015) for an IH consult. This may represent a difference in communication styles between cancer survivors, who are focused on symptoms, and physicians, who are often focused on medical diagnosis, as apposed to a true mismatch. Additionally, this lack of agreement could be due to a limited understanding of the role of IMH physician can play during a patient's cancer journey. This role can include navigating both the cancer team and cancer survivor through the complex world of IH by identifying appropriate supportive treatments during and after cancer treatment, guiding to trusted products, resources and services, and assessing for potential interactions with medical treatments.

Limitations

Limitations of the secondary analysis include the inability to determine causation as well as the limitations of only being able to use what was captured either in the dataset and/or

electronic health record. However, this study did employ the use of a prospectively collected intake form. Additionally, we are unable to assess patients' perceptions of satisfaction or efficacy with their IH usage.

Conclusion

Due to the high reported use of IH approaches and limited agreement on reason for consultation, this seems to highlight an opportunity to clarify how IMH physicians can support cancer survivors and cancer teams during the cancer journey. Future research should address our limitations and use prospective designs to assess the cancer survivors' satisfaction with IH consults and perceptions of IH approaches' efficacy and relationship to overall health.

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Table 1: Demographics

	Cancer Survivors 212	Patients without Cancer 627	Total 839	Sig
	Mean (SD)	Mean (SD)	Mean (SD)	
Age	57.7 (12.8)	49.3 (15.6)	51.4 (15.4)	<0.001[1]
Distance from Clinical Site	247.9 (586.1)	319.4 (682.6)	301.4 (660)	0.174[1]
	N (%)	N (%)	N (%)	
Gender—Female	167 (78.8)	505 (80.5)	672 (80.1)	0.577[3]
Marital Status				0.052[3]
Divorced	13 (6.1)	28 (4.5)	41 (4.9)	
Married	158 (74.5)	403 (64.2)	561 (66.9)	
Single	33 (15.5)	166 (26.5)	199 (23.7)	
Other	8 (3.7)	30 (4.7)	38 (4.5)	
Referral Source				<0.05[3]
Self-referral	22 (10.3)	62 (9.8)	84 (10.0)	
Physician	150 (70.6)	491 (78.3)	641 (76.4)	
Other	34 (16)	69 (11)	103 (12.3)	
Cancer Type*	N (%)			
Brain	12 (5.7%)			
Breast	79 (37.4%)			
GI	23 (10.9%)			
GU	16 (7.5%)			
GYN	16 (7.6%)			
Head and Neck	14 (6.6%)			
Heme	36 (17.0%)			
Skin	12 (5.6%)			
Other	7 (3.3%)			
Cancer Treatment				
Chemotherapy only	26 (12.3%)			
Chemotherapy,	13 (6.2%)			

Radiation				
Chemotherapy, Surgery	39 (18.5%)			
Chemotherapy, Surgery, Radiation	43 (20.4%)			
Radiation only	8 (3.8%)			
Surgery only	37 (17.5%)			
Surgery, Radiation	34 (16.1%)			
Other	11 (1.4%)			

1 T-test, 2 Fisher's Exact, 3 Chi-Square * Patients may have more than 1 type of cancer

Table 2: Prior Integrative Health (IH) Use

	Cancer Survivors 212	Patients without Cancer 627	Total 839	Sig
	Mean (SD)	Mean (SD)	Mean (SD)	
Prior Number of Complementary Approaches Used	1.74 (1.8)	1.5 (1.7)		0.081[1]
Number of IH Physician Recommendations	5.63 (2.5)	6.11 (3.1)	5.99 (2.9)	<0.05[1]
	N (%)	N (%)	N (%)	
Prior IH Use	167 (78.8)	467 (74.5)	634 (75.6)	0.121[2]
Reported Use (yes/no)				
Acupuncture	7 (3.3)	19 (3)	26 (3.1)	0.488[2]
Breathing Exercises	15 (7.1)	40 (6.4)	55 (6.6)	0.415[2]
Calcium	13 (6.1)	28 (4.5)	41 (4.9)	0.212[2]
Coenzyme Q10	14 (6.6)	41 (6.5)	55 (6.6)	0.542[2]
Exercise	43 (20.3)	102 (16.3)	145 (17.3)	0.110[2]

Fish Oil	29 (13.7)	73 (11.6)	102 (12.2)	0.215[2]
Magnesium	21 (9.9)	82 (13.2)	103 (12.3)	0.136[2]
Massage	11 (5.2)	26 (4.1)	37 (4.4)	0.320[2]
Melatonin	10 (4.7)	36 (5.7)	46 (5.5)	0.356[2]
Mindfulness	20 (9.4)	27 (4.3)	47 (5.6)	<0.05[2]
Multivitamin	50 (23.6)	135 (21.5)	185 (22.1)	0.297[2]
Prayer	18 (8.5)	34 (5.4)	52 (6.2)	0.078[2]
Probiotic	21 (9.9)	46 (7.3)	67 (8.0)	0.148[2]
Turmeric	33 (15.6)	39 (6.2)	72 (8.6)	<0.001[2]
Vitamin B12	14 (6.6)	37 (5.9)	51 (6.1)	0.410[2]
Vitamin D	29 (13.7)	76 (12.1)	105 (12.5)	0.314[2]
Yoga	18 (8.5)	55 (8.8)	73 (8.7)	0.514[2]

1 T-test, 2 Fisher's Exact

Table 3: Patient Reported Measures

	Cancer Survivors 212	Patients without Cancer 627	Total 839	*T (df)*	Sig[1]
	Mean (SD)	Mean (SD)	Mean (SD)		
Anxiety	4.68 (2.7)	4.80 (2.6)	4.77 (2.6)	-0.55 (796)	0.585
Energy Level	4.89 (2.5)	4.07 (2.4)	4.28 (2.5)	4.13 (804)	<0.001
Pain	3.81 (3.2)	4.68 (2.9)	4.46 (2.9)	-3.56 (781)	<0.001
Stress	4.70 (2.5)	5.04 (2.4)	4.96 (2.4)	-1.77 (802)	0.078
Diet	3.19 (0.97)	3.12 (1.0)	3.14 (1.0)	0.862(818)	0.389
Relationships	3.86 (1.0)	3.60 (1.0)	3.67 (1.0)	3.06 (813)	<0.01
Spiritual Wellbeing	3.67 (1.1)	3.38 (1.0)	3.45 (1.1)	3.19 (810)	<0.01
Sleep	2.51 (1.1)	2.25 (1.1)	2.31 (1.0)	3.04 (825)	<0.01
Overall Health	2.82 (1.1)	2.45 (0.98)	2.55 (1.0)	4.45 (809)	<0.001
Physical Activity	2.60 (0.83)	2.48 (.88)	2.51 (0.87)	1.69 (804)	0.090
Relaxation Technique Use	2.16 (1.4)	2.29 (1.3)	2.26 (1.4)	-1.15 (810)	0.250

1 T-test

Table 3: Cancer Survivor and Physician Consult Reason Agreement

	Kappa	Sig
Anxiety	0.023	0.187
Cancer	0.098	0.186
Diet	-0.012	0.767
Depression	-0.018	0.814
Fatigue	0.044	0.141
Gastrointestinal	0.342	<0.001
Genitourinary	-0.018	0.813
Menopause or hormones	0.177	<0.05
Migraines or Headache	0.493	<0.001
Numbness and tingling	0.231	<0.01
Pain	0.080	0.070
Stress	0.017	0.251
Weight	-0.022	0.719

Chapter V: Cancer Survivors' Reasons for Using Complementary Interventions

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This manuscript represents a significant contribution to the dissertation work as it aims to fill the gap in understanding why cancer patients are using complementary approaches and if they are satisfied. The target journal for this manuscript is *Supportive Care in Cancer,* a peer-reviewed publication by the Multinational Association of Supportive Care in Cancer (MASCC), which focuses on supportive therapy during the continuum of cancer care.

Abstract

Purpose: The purpose of this study was to assess the reasons why cancer survivors are using specific complementary approaches, their satisfaction with the approaches, and to determine if cancer survivors' satisfaction with complementary approaches differs by the resources used to inform them about the complementary approaches.

Methods: This study is descriptive cross-sectional study that employed survey methodologies. A convenience sample of 56 adult Integrative Health (IH) patients who were cancer survivors at the time of consult were recruited from an academic medical center in the southwestern United States. Participants completed the Integrative Health Symptom and Complementary Interventions Inventory, a study-team-developed questionnaire, which included numeric rating scales (NRS) for symptoms including fatigue, pain, and numbness and tingling, complementary approaches used to treat symptoms and global assessments of change questions assessing quality of life, effect, and emotional state since starting the complementary approach.

Results: Majority of participants used complementary approaches (78.6%). Multivitamins (64.3%) were the most reported IH approach used before IH consult. The majority (67.9%) were satisfied with their complementary approaches. Fatigue was reported by 73% of participants. Breathing exercises (34.1%), meditation (29.3%) and multivitamins (28.5%) were the most reported approaches used for fatigue. Participants who used a complementary approach to treat fatigue reported significantly more physical activity (t (38) = 2.15 p=.038). Pain was reported by 46% of the participants.

Massage (42.3%), acupuncture (26.9%), and breathing exercises (26.9%) were the most frequently reported approaches used for pain. Numbness and tingling were reported by 44.6% of participants. Massage was reported by 24% of participants to treat numbness and tingling.

Memory problems were reported by 55.3% of participants. Those who reported satisfaction with their complementary approach used to treat memory problems used meditation significantly more than those who were not satisfied. Sleep problems were reported by 69.6% of participants. Most reported complementary approaches for sleep were breathing exercises (38.5%), melatonin (30.8%), and meditation (25.6%). Hot flashes were reported by 39.2% of participants. All nine participants were satisfied. Acupuncture (33.3%) was the most reported complementary approach used for hot flashes. Hot flashes were reported as not being treated by 50% of those with hot flashes. Breathing exercises were reported as one of the most common complementary approaches for fatigue (34.1%), pain (26.9%), and sleep (38.5%). Meditation was reported as one of the most common complementary approaches for fatigue (29.3%), memory problems (22.6%) and sleep (25.6%). Massage was the most common complementary approach used for pain (42.3%), as well as numbness and tingling (24%).

The most common sources of information about complementary approaches used were Integrative Health Provider (e.g., acupuncturist, massage therapist), friends and family, and Integrative Medicine Physician. Significantly more satisfied participants sought information from their Integrative Health Provider (55.3% vs. 16.7%, $p = <.01$). The majority of participants shared that they were using complementary approaches with their primary care provider (81.5%). Significantly more participants who were satisfied with their complementary approach shared their usage with their specialty provider (84.2% vs. 58.8%, $p= .041$).

Manuscript Key words: Integrative Health, Complementary and Alternative Medicine, Symptoms, Supplements, Herbs

Introduction

Complementary approaches are used by an estimated 40% of cancer survivors (Adams, 2007; Horneber et al., 2012; Kang et al., 2012). Complementary approaches include supplements, herbs, and mind and body practices like yoga (National Center for Complementary and Integrative Health, 2016). Cancer survivors are defined as a person diagnosed with cancer from the time of diagnosis to the end of their life (Centers for Disease Control and Prevention, 2017). Natural products are the most frequently reported complementary approach used by cancer survivors (John et al., 2016). Natural products, like herbs, have also been associated with the greatest risk for interacting with cancer treatments (Firkins et al., 2018; McLay, Stewart, George, Rore, & Heys, 2012). The potential risks posed by complementary approaches is heightened by the fact that cancer survivors are seeking information about complementary approaches from potentially unreliable sources like the internet (Weeks, 2014). Additionally, they are not likely to report their complementary approach use to their cancer care providers (Frenkel, 2014; National Center for Complementary and Integrative Health, 2014). This leads to a dynamic where cancer survivors can unwittingly be taking complementary interventions, like St. John's wort, that can interfere with their cancer treatments (Berretta, 2017).

Cancer care teams need to know if their patients are using complementary approaches. Often studies assessing cancer survivors' complementary approach usage report their reasons for use and satisfaction in broad categories like physical symptoms or complementary approaches (Heinze, 2015; Huebner et al., 2014; Kim et al., 2018; Samuels, 2015). These broad categories limit the ability to apply the results to clinical situations. The current evidence highlights a gap in knowledge of the reasons and satisfaction with cancer survivors' chosen complementary approaches. It is critical to understand why and which complementary approaches cancer

survivors are using, so cancer care teams can address cancer treatment compatibility concerns and work with trusted resources like Integrative Health providers to provide appropriate education and resources to meet cancer survivors' needs. The purpose of this study is to 1) assess the reasons cancer survivors are using specific complementary approaches and their satisfaction with the approach, 2) evaluate if there are differences in satisfaction related to complementary approach used, and 3) determine if cancer survivors' satisfaction with complementary approaches differs by the resources used to inform complementary approaches.

Methods

This prospective descriptive cross-sectional study employed survey methodologies including phone, paper and electronic delivery of the assessment. The research was conducted in an academic medical center in the southwestern United States. The study was reviewed and approved by the local Institutional Review Board. Informed consent was obtained from all participants included in the study.

Sample

A convenience sample of 203 Integrative Health patients who were cancer survivors that sought initial consultations between 2013-2017 were approached for inclusion. Participants were eligible if they were ≥18 and diagnosed with cancer prior to the time of their integrative health consult.

Measure

Integrative Health Symptom and Complementary Interventions Inventory is a study-team-developed questionnaire, which has undergone content validity. The questionnaire asks if the participant has a symptom, if so how they would rate their symptom severity, and how long they have had the symptom. The questionnaire used a numeric rating scale (NRS) for symptom

severity and included items on fatigue, pain, and numbness and tingling. Additionally, the questionnaire rated complementary approaches used to treat symptoms and global assessments of change questions assessing quality of life, effect, and emotional state since starting the complementary approach. The questionnaire leverages numeric rating scales (NRS) for symptom assessment, which has been shown to be a reliable measure of symptoms (Paice, 1997), and the clinically relevant global assessment of change (Hurst & Bolton, 2004; Kamper, 2009). NRS scales range 1-10, with 10 being the worst. The global assessment of change questions ask about quality of life, treatment effect, and emotional state since starting the treatment. The scale ranges from -3 (very much worse) to +3 (very much better) (Hurst & Bolton, 2004; Kamper, 2009). Level of physical activity was rated on scale from 1- Sedentary (no physical activity) to 4 - Highly active (over 60 minutes a week that raises your heart rate).

Analysis Plan

Descriptive statistics were used to summarize participant responses and to identify differences between those who were satisfied versus unsatisfied with their complementary approaches. Differences were determined using Chi-square for categorical variables and two-sample t-test for continuous variables. P values <.05 were considered significant. Statistical analysis was performed using IBM SPSS Statistics version 23 (IBM Corporation).

Results

There was a 28% response rate with 56 participants of the 203 contacted consented and signed HIPAA forms. Average age of the sample was 57.8 (See Table 1). The majority of participants was married (85.7%), had used complementary approaches (78.6%) and was female (78.6%). Multivitamins (64.3%) were the most reported complementary approach used before IH consult. The most common cancer diagnoses were breast (30.3%) and hematological (23.2%)

cancers. The mean number of cancer treatment modalities received was 1.84. The majority of participants received chemotherapy (71.4%) and surgery (66.1%). Participants reported moderate, 45-60 minutes of physical activity that raised their heart rate per week ($\bar{x}$=3.11), and good to very good ($\bar{x}$ =2.78) overall health. The majority (67.9%) of the sample was satisfied with the complementary approaches they used. There were no significant differences in demographic characteristics between those who were satisfied with their complementary use and those who were not.

Reasons for Complementary Approaches

Fatigue. Fatigue was reported by 73.2% of participants. Mean reported fatigue severity was 5.11. Reported fatigue levels did not differ between groups (satisfied versus unsatisfied) (Table 2). The most common range of time with fatigue was 1-4 years (46%); however, 27% reported having fatigue for 5 years or more. A small portion (12.2%) reported not treating their fatigue. The most common complementary approaches used for fatigue were breathing exercises (34.1%), meditation (29.3%) and multivitamins (28.5%). Complementary approaches used for fatigue did not significantly differ between satisfied or unsatisfied participants. The global assessment of change questions responses for quality of life (t (29)= 2.71, p=.011), treatment effect (t (29) = 4.69 p=<.001), and emotional state (t (29) = 3.89, p=<.001) were significantly higher for those who reported being satisfied with their complementary approach (Table 3). Participants who used a complementary approach to treat fatigue reported significantly more physical activity (t (38) = 2.15 p=.038) (Table 4). Overall health did not significantly differ between participants who used a complementary approach to treat fatigue compared to those who did not.

Pain. Pain was reported by 46.4% of the participants. Mean reported pain was 4.83, with no difference in pain score between satisfied or unsatisfied participants (Table 2). The most common range of time with pain was 1-4 years (38.5%); however, 35% reported having pain for 5 years or more. More than 7% reported not treating their pain. The most common complementary approaches used for pain were massage (42.3%), acupuncture (26.9%), and breathing exercises (26.9%). Complementary approaches used for pain did not significantly differ between participants who were satisfied or unsatisfied. The global assessment of change questions did not differ between satisfied or unsatisfied participants (Table 3). Participants who used a complementary approach to treat pain did not report significantly more physical activity or better overall health (Table 5).

Numbness and tingling. Numbness and tingling were reported by 44.6% of participants. The mean reported numbness and tingling was 3.96, with no significant difference between groups (satisfied vs. unsatisfied) (Table 2). The majority (64%) of participants reported having numbness and tingling for 1-4 years. Thirty-six percent of participants reported not treating their numbness and tingling. Massage (24%) was the most reported complementary approach, and all who reported its use also reported being satisfied. Complementary approaches used for numbness and tingling did not significantly differ between the satisfied and unsatisfied. Responses to the global assessment of change questions did not significantly differ between groups (satisfied vs. unsatisfied) (Table 3). Participants who used a complementary approach to treat numbness and tingling did not report significantly more physical activity or better overall health (Table 5).

Memory Problems. The majority (55.3%) of participants reported memory problems. Memory problems severity mean was 4.85, with no significant difference between groups

(satisfied vs. unsatisfied) (Table 5). Most (58.1%) reported having memory problems for 1-4 years. Over 35% of participants reported not treating their memory problems. Meditation was used by 22.6% of those reporting memory problems. Those who reported satisfaction with their complementary approach used to treat memory problems used meditation significantly more than the unsatisfied (58.3% vs. 0%, p=.038). Those that reported using meditation reported 100% satisfaction with its use (Table 5). All other use of complementary approaches did not significantly differ. The global assessment of change questions related to quality of life (t (15) = 2.81, p= .013), treatment effect (t (15) = 5.28, p=<.001), and emotional state (t (15) = 4.36, p=<.001) were significantly higher for those who reported being satisfied with their complementary approach (Table 3). Participants who used a complementary approach to treat their memory problems did not report significantly more physical activity or better overall health (Table 4).

Sleep Problems. Sleep problems were reported by 69.6% of participants. Mean sleep scores were 5.94 and did not significantly differ between groups (satisfied vs. unsatisfied) (Table 2). Over 42% reported sleep problems for 1-4 years; however, 39% reported having sleep problems for 5 years or more. A small portion (7.7%) reported not treating their sleep problem. The most common complementary approaches for sleep were breathing exercises (38.5), melatonin (30.8%), and meditation (25.6%). There were no significant differences in complementary approaches between the satisfied and unsatisfied groups. The means for the global assessment of change questions regarding quality of life (t (27) = 6.56, p=<.001), treatment effects (t (27) = 5.92, p=<.001), emotional state (t (27) = 5.18, p=<.001) were significantly higher for those who reported satisfaction versus those who reported being unsatisfied with their complementary approach (Table 3). Participants who used a

complementary approach to treat their sleep problems did not report significantly more physical activity or better overall health.

Hot Flashes. Hot flashes were reported by 39.2% of participants. Mean Hot Flash score was 4.71 (Table 2). All nine participants that reported hot flashes were satisfied with their complementary approaches. The majority (64%) of participants reported having hot flashes for 1-4 years; however, 44% reported having hot flashes for 5 years or more. Acupuncture (33.3%) was the most reported complementary approaches used for hot flashes. Fifty percent of those reporting hot flashes also reported that they were not treating them. Participants who used a complementary approach to treat their hot flashes did not report significantly more physical activity or better overall health (Table 4).

Overall Complementary Approach Usage. Mind-body approaches were used to treat multiple symptoms. Breathing exercises was reported as one of most common complementary approaches for fatigue (34.1%), pain (26.9%), and sleep (38.5%). Meditation was reported as one of the most common complementary approaches for fatigue (29.3%), memory problems (22.6%) and sleep (25.6%). Massage was the most common complementary approach used for pain (42.3%), as well as numbness and tingling (24%).

Resources Used to Inform Complementary Approaches

The most common sources of information about complementary approaches used were Integrative Health Provider (e.g., acupuncturist, massage therapist) (42.9%), Friends and Family (41.1%), and Integrative Medicine Physician (39.3%) (Table 5). Significantly more satisfied participants sought information from their Integrative Health Provider (55.3% vs. 16.7%, p=<.01). The most commonly reported resources that influenced participants' decision to use complementary approaches were Integrative Medicine Physician (42.9%), Friends and Family

(32.1%), and Integrative Health Provider (e.g., acupuncturist, massage therapist) (30.4%) (Table 5). The majority of participants shared that they were using complementary approaches with their primary care provider (81.5%) (Table 5). Significantly more participants who were satisfied with their complementary approach shared their usage with their specialty provider (84.2% vs. 58.8%, p=.041).

Discussion

The majority of cancer survivors are satisfied with their complementary approaches. Our study found that complementary approach use was reported at 78.6%, which is similar to other studies that reported complementary approach usage as high as 94% (Kang, McArdle, & Suh, 2014). Similar to other studies, natural products were the most reported complementary approach; specifically, we found that multivitamins were the most reported complementary approach in our sample (Kim et al., 2018). In line with other studies, we found that the majority of the sample was satisfied with their complementary approach (Kim et al., 2018). Additionally, we found that those who were satisfied with their fatigue, memory and sleep complementary approaches also had significantly higher scores on the global assessment of change questions (QOL, treatment effect and emotional state) compared to those who were not satisfied. This may be why they were satisfied with their approach. Additionally, this could allude to a perception of symptom improvement; however, symptom improvement over time was not evaluated in this study.

Meditation is being used as a treatment for memory problems. In our study 35% of participants did not treat their memory problems, which is lower than previous work that found 54% of their sample did not treat memory-related issues (Heinze, 2015). Additionally, meditation used for memory problems was the only approach used significantly more by those

who reported being satisfied with their approach. All of the participants with memory problems that reported using meditation also reported being satisfied. This is similar to other research that found participants were satisfied with meditation; however, they did not specify why meditation was being used (Huebner et al., 2014; Kang et al., 2014). Breathing exercises, meditation and massage were reported as the most common complementary approaches used for multiple symptoms, including pain and fatigue. These results are supported by recent research that found moderate rates of mind-body practice among cancer survivors (Kim et al., 2018). These results highlight mind-body practices as a promising treatment for cancer-related symptoms.

Many participants did not treat their reported problems. We found that 36% of participants with numbness and tingling did not treat their symptoms; however, previous research found that only 19% of their participants did not treat their numbness and tingling (Heinze, 2015). Additionally, 50% of the cancer survivors with hot flashes reported not treating them. There are multiple reasons why participants are not treating their symptoms including their symptom is at a manageable level and they feel it no longer needs to be treated. Or not treating their symptoms could be a result of using treatments that have not been effective, the treatment may have been more burdensome that the original problem, there may not be a treatment available, or they might not have been aware of available treatments.

Fatigue is a significant issue for cancer survivors. The majority (73%) of participants reported fatigue, which is not surprising as it is the most common symptom reported in cancer survivors with estimates of 80-90% reporting it during treatment and up to 30% reporting fatigue post-treatment (Barton et al., 2010; Krishbaum, 2010). Surprisingly, the most reported complementary approaches used for fatigue were breathing exercises (34.1%), meditation (29.3%) and multivitamins (28.5%). At this time, physical activity is the only evidence-based

complementary approach recommended for fatigue; however, ginseng, massage, and mindfulness-based stress reduction have been identified as likely to be effective (Mitchell, 2014). In addition, one study found that multivitamins did not significantly decrease fatigue (de Souza Fede et al., 2007). These results highlight the critical need to guide cancer survivors to trusted resources for complementary approach decision-making.

Our participants listed their most common sources of information about complementary approaches as Integrative Health Provider (e.g., acupuncturist, massage therapist) (42.9%), Friends and Family (41.1%), and Integrative Medicine Physician (39.3%). This differs from the literature that found the survivor, their family and friends, and media were the most common sources for information (Kim et al., 2018). Our sample may differ because they had all sought integrative health consultation. This difference may highlight a potential way to increase use of trusted resources for complementary approaches. Additionally, participants were significantly more satisfied if they sought information from their Integrative Health Provider (55.3% vs. 16.7%, p=<.01). This may be one of the benefits of using a trusted resource that can guide cancer survivors to safe and effect treatments for their specific issue.

Satisfied cancer survivors report their complementary approach use to their health care team. Unlike previous research, the majority (81.5%) of our participants shared that they were using complementary approaches with their primary care provider (Huebner et al., 2014; Kim et al., 2018). Additionally, those satisfied with their complementary approach reported their use to their specialty provider significantly more than those who were unsatisfied (84.2% vs. 58.8%, p=.041). These results differ from previous research, which found that even though the majority of participants were satisfied with their complementary approach, only 22.5% reported their use to their care team (Kim et al., 2018). These results identify a potential strategy of linking cancer

survivors to trusted resources to guide their complementary approach use and to potentially increase their reporting to their cancer care team.

Limitations related to the study's cross-sectional design are that it is unable to assess for statistical changes in reported symptoms or usage over time, or to determine causality. We were unable to assess dose or adherence. Additionally, this study had a small sample size, which may limit its ability to be generalized or power to detect differences. However, this study starts to fill the gap in knowledge of complementary approach reasons for their use and satisfaction.

Conclusion

Cancer survivors are using complementary approaches to manage their symptoms. The majority of survivors are satisfied with their complementary approaches ability to address their symptom. In addition, many that are satisfied with their approach have a perception of that they are improving their symptom, QOL and emotional state. It is imperative that cancer care teams know which complementary approaches cancer survivors are using to help prevent possible interactions with treatments. It is clear that cancer survivors need trusted resources to help inform their complementary approach decision-making. One option that may increase communication with cancer care teams and guide cancer survivors to evidence-based complementary approaches is leveraging trusted resources like Integrative Medicine Physicians or Providers. Based on these results future research should assess the types of information cancer survivors received about complementary approaches and how that information impacts cancer survivors' complementary approach decision-making. An additional research opportunity is to assess the confidence of treatment teams in their ability to navigate the complexity of complementary approaches and their potential interaction with medical treatments. Finally, intervention-based studies looking at who, how and what information is given about

complementary approaches and assessing how differences in content and delivery impact patient outcomes are needed to understand how best to support cancer survivors and their care teams as they navigate complementary approaches.

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Table 1: Demographics

	Used a Complementary Approach[4]			
	Satisfied 38	Unsatisfied 6	Total Sample 56	Sig
	Mean (SD)	Mean (SD)	Mean (SD)	
Age	55.5 (12.1)	62.6 (10.8)	57.8 (12.1)	.282[1]
Monthly Spending on Complementary Approaches	$265.48 ($390.40)	$155.00 ($94.21)	231.36 (336.91)	.538[1]
Overall Health	2.81 (0.9)	3.17 (0.9)	2.78 (0.93)	.397[1]
Physical Activity	3.21 (0.9)	2.83 (1.2)	3.11 (0.99)	.391[1]
Number of Cancer Treatment Modalities	1.79 (0.7)	1.50 (0.5)	1.84 (.71)	.343[1]
	N (%)	N (%)	N (%)	
Gender—Female	30 (78.9)	5 (83.3)	44 (78.6)	.644[3]
Complementary Approach Usage	38 (100)	6 (100)	44 (78.6)	
Marital Status				.168[2]
Married	33 (86.8)	5 (83.3)	48 (85.7)	
Other	5 (13.2)	1 (16.7)	561 (66.9)	
Cancer Type*			N (%)	
Breast			17 (30.3)	
GI			7 (12.5)	
Head and Neck			6 (10.7)	
Heme			13 (23.2)	
Other			14 (25)	
Cancer Treatment Type*				.850[2]
Chemotherapy	26 (68.4)	4 (66.7)	40 (71.4)	
Radiation	15 (39.5)	1 (16.6)	24 (42.9)	
Surgery	24 (63.2)	5 (83.3)	37 (66.1)	
Post-Treatment			27 (48)	
Active-Treatment			29 (52)	
Reported symptoms	n (%)	n (%)	n (%)	
Fatigue	20 (49)	12 (29)	41 (73)	

Pain	18 (69)	3 (12)	26 (47)	
Numbness and Tingling	8 (32)	3 (12)	25 (45)	
Memory Problems	12 (39)	6 (19)	31 (55)	
Sleep Problems	18 (46)	11 (28)	39 (70)	
Hot Flashes	9 (36)	0	25 (45)	

1 T-test, 2 Chi-Square, 3 Fisher's Exact, 4 Participants who used a complementary approach and marked their satisfaction * Patients may have more than 1 type of cancer or treatment

Table 2: Patient Reported Measures

	Used a Complementary Approach[2]				
	Satisfied	Unsatisfied	Total		
	Mean (SD)	Mean (SD)	Mean (SD)	*t* (df)	Sig[1]
Fatigue Scale	4.72 (1.8)	5.92 (1.4)	5.11 (1.9)	-1.91 (28)	.066
Pain Scale	4.76 (2.0)	4.0 (0)	4.83 (2.1)	.36 (16)	.721
Numbness & Tingling Scale	4.63 (2.3)	5.00 (2.7)	3.96 (2.1)	-0.24 (9)	.819
Memory Scale	4.36 (1.9)	6.40 (2.2)	4.85 (2.3)	-1.89 (14)	.079
Sleep Scale	5.88 (2.5)	7.00 (1.9)	5.94 (2.3)	-1.22 (24)	.235
Guidance Therapy (e.g., counseling)Hot Flash Scale	5.67 (2.9)		4.71 (2.5)		

1 T-test, 2 Participants who used a complementary approach and marked their satisfaction

Table 3: Global Assessment of Change

	Satisfied	Unsatisfied	Total		
	Mean (SD)	Mean (SD)	Mean (SD)	*t* (df)	Sig[1]
Fatigue					
QOL	6.16 (1.0)	5.08 (1.1)	5.64 (1.2)	2.71 (29)	.011
Treatment Effect	5.79 (0.63)	4.58 (0.79)	5.24 (0.93)	4.69 (29)	<.001
Emotional State	6.11 (1)	4.58 (1.1)	5.45 (1.3)	3.89 (29)	<.01
Pain					
QOL	5.94 (0.73)	6.33 (1.2)	6 (0.78)	-0.79 (19)	.435
Treatment	5.56 (0.86)	4.67 (0.58)	5.43 (0.87)	1.72 (19)	.102

Effect					
Emotional State	5.61 (1.1)	6.33 (1.2)	5.71 (1.1)	-1.05 (19)	.305
Numbness & Tingling					
QOL	5.63 (0.9)	4.33 (0.6)	5.27 (1.0)	2.24 (9)	.052
Treatment Effect	5.75 (0.9)	4.67 (0.6)	5.45 (0.9)	1.93 (9)	.085
Emotional State	5.88 (0.8)	4.67 (1.2)	5.55 (1.0)	1.95 (9)	.083
Memory					
QOL	6.27 (0.65)	5.17 (0.983)	5.88 (0.93)	2.81 (15)	.013
Treatment Effect	6.09 (0.70)	4.17 (0.75)	5.41 (1.2)	5.28 (15)	<.001
Emotional State	6.27 (0.91)	4.33 (0.816)	5.59 (1.3)	4.36 (15)	<.01
Sleep					
QOL	6.11 (0.6)	4.55 (0.7)	5.43 (1.1)	6.56 (27)	<.001
Treatment Effect	5.94 (0.7)	4.45 (0.5)	5.33 (0.9)	5.92 (27)	<.001
Emotional State	6.06 (0.8)	4.55 (0.7)	5.48 (1.1)	5.18 (27)	<.001
Hot Flashes					
QOL	5.89 (1.2)		6.00 (1.3)		
Treatment Effect	5.89 (1.3)		6.00 (1.3)		
Emotional State	5.56 (2.9)		5.70 (1.3)		

1 T-Test

Table 4: Complementary Use and Physical Activity and Overall Health

		Complementary Approaches			
		Used	Not Used	*t* df)	Sig[1]
Overall Health	M (SD)	2.86 (0.9)	2.45 (0.8)	1.31 (52)	.197
Physical Activity	M (SD)	3.16 (0.9)	2.91 (1.0)	0.743 (53)	.461
Fatigue					
Fatigue Scale	M (SD)	5.25 (1.7)	4.33 (2.9)	1.07 (36)	.291
Overall Health	M (SD)	2.97 (0.9)	3.14 (1.1)	-0.46 (37)	.644
Physical Activity	M (SD)	3.21 (0.9)	2.29 (1.4)	2.15 (38)	.038
Pain					
Pain Scale	M (SD)	4.72 (1.9)	5.20 (2.6)	-0.45 (21)	.660
Overall Health	M (SD)	3.10 (0.9)	3.4 (0.9)	-0.67 (23)	0.516
Physical Activity	M (SD)	3.0 (0.2)	2.6 (1.1)	0.78 (24)	0.440
Numbness & Tingling					
Numbness & Tingling Scale	M (SD)	4.73 (2.2)	3.25 (1.8)	1.77 (21)	.092
Overall Health	M (SD)	2.91 (1.2)	3.08 (0.9)	-.39 (22)	.698
Physical Activity	M (SD)	3.36 (1.0)	2.77 (1.1)	1.37 (22)	.186
Memory					
Memory Scale	M (SD)	5.0 (2.2)	4.64 (2.6)	0.39 (25)	.695
Overall Health	M (SD)	2.67 (0.9)	3.31 (0.8)	-1.9 (29)	.056
Physical Activity	M (SD)	3.28 (0.7)	3.08 (1.0)	0.63 (29)	.536
Hot Flashes					
Hot flash Scale	M (SD)	5.60 (2.8)	3.91 (2.1)	0.27 (20)	.793
Overall Health	M (SD)	2.70 (1.2)	2.58 (0.9)	1.59 (19)	.130
Physical Activity	M (SD)	3.00 (1.1)	3.25 (1.2)	-0.51 (20)	.616
Sleep					
Sleep Scale	M (SD)	6.26 (2.3)	4.50 (1.9)	1.76 (31)	.089
Overall Health	M (SD)	2.83 (0.8)	3.22 (1.2)	-1.10 (36)	.278
Physical Activity	M (SD)	3.10 (0.9)	3.00 (1.3)	0.25 (37)	.803

1 T- Test

Table 5: Complementary Approach Information

	Used a Complementary Approach[2]			
	Satisfied 38	Unsatisfied 18	Total Sample 56	Sig[1]
Obtained Information for Complementary Approach Use				
	N (%)	N (%)	N (%)	
Physician	8 (21.1)	6 (33.3)	14 (25)	.251
Integrative Medicine Physician	16 (42.1)	6 (33.3)	22 (39.3)	.573
Naturopathic Physician	11 (28.9)	3 (16.7)	14 (25)	.510
Hematologist/Oncologist	11 (28.9)	3 (16.7)	14 (25)	.510
Online	12 (31.6)	4 (22.2)	16 (28.6)	.542
Integrative Health Provider*	21 (55.3)	3 (16.7)	24 (42.9)	<.01
Friends and Family	19 (50)	4 (22.2)	23 (41.1)	.080
Influenced the Decision to Use Complementary Approach				
Integrative Medicine Physician	16 (42.1)	8 (44.4)	24 (42.9)	.87
Integrative Health Provider*	14 (36.8)	3 (16.7)	17 (30.4)	.213
Friends and Family	15 (39.5)	3 (16.7)	18 (32.1)	.128
Participants Shared Complementary Approach Use With				
Primary Care Physician	32 (84.2)	12 (75)	44 (81.5)	.331
Specialty Providers	32 (84.2)	10 (58.8)	42 (76.4)	.041
Hematologist/Oncologist	21 (55.3)	9 (50)	30 (53.6)	.466

1 Fisher's Exact, * (e.g., acupuncturist, massage therapist), 2 Participants who used a complementary approach and marked their satisfaction

Chapter VI: Discussion and Summary

Over 90% of patients report more than one symptom related to cancer (Deshields, Potter, Olsen, & Liu, 2014). Symptom burden is negatively correlated with cancer survivors' quality of life (Deshields et al., 2014). Cancer-related fatigue (CRF) is one of the most reported symptoms and negatively impacts a large number of cancer survivors (Bower, 2014). The mechanism(s) for CRF are unknown (Bower, 2014; Saligan et al., 2015). Similar to numbness and tingling, there are not many treatment options for this important and burdensome symptom (Bower, 2014; Majithia, 2016; Saligan et al., 2015). Clinical guidelines for CRF currently only recommend exercise/physical activity as a treatment for CRF, which has shown to have some barriers for cancer survivors, including access issues like scheduling and cost (Blaney, 2010; Mitchell, 2014). Cancer survivors are using complementary approaches to manage their symptoms; however, current research reports often do not clarify which specific symptom is being treated and/or which specific approach is being used (Adams, 2005; Anderson & Taylor, 2012; Lee, N.D.; Lewith, 2002; Loquai et al., 2017; Samuels, 2015). When patients' reasons were assessed, frequently the symptoms or approaches were reported in broad categories like "physical symptoms" (Frenkel, 2010; Heinze, 2015; Samuels, 2015). Natural products, like herbs, are one of the most commonly reported complementary approaches used by cancer survivors (Anderson & Taylor, 2012). Due to the limited evidence-based treatment options for CRF, this dissertation aimed to advance cancer symptom management by evaluating why cancer survivors are using complementary approaches and assess the effects of these approaches, specifically looking at natural products as a treatment for CRF. This dissertation aimed to answer the overarching question "What are safe, acceptable and effective natural products for the treatment of CRF?"

This dissertation is grounded in the Theory of Unpleasant Symptoms (TOUS) (Lenz & Pugh, 2014). We posit that there are multiple factors that influence CRF (Lenz & Pugh, 2014), and that these factors influence cancer survivors' performance (Lenz & Pugh, 2014). This dissertation focused on natural products, because they are believed to influence both physiologic (i.e., inflammatory response) and psychologic factors (i.e., anxiety, stress), resulting in improved performance, which is operationalized as physical activity (Barton et al., 2010; Lenz, Pugh, Milliagan, Gift, & Suppe, 1997; Yennurajalingam et al., 2015).

To achieve Aim 1, which was to appraise the safety and effectiveness of natural products as a treatment for CRF, two systematic review manuscripts were undertaken: "Natural Products as a Treatment for Cancer-Related Fatigue: A Systematic Review" (Chapter II) and "Ginseng as a Treatment for Fatigue: A Systematic Review" (Chapter III). Aim 2 of this dissertation assessed the difference between cancer survivors and patients without cancer who sought an integrative health consult. This aim was met through an empirical manuscript titled "Reasons for Integrative Health Consults: Differences Between Cancer Survivors, Patients without Cancer and Referring Providers" (Chapter IV). The empirical manuscript "Cancer Survivors' Reasons for Using Complementary Approaches" (Chapter V) achieved Aim 3, which identified the complementary approaches used to treat fatigue, and Aim 4, which identified the resources that cancer survivors utilize in their decision to use complementary approaches.

Principle Findings, Aim 1: Safety and Effectiveness of Natural Products as a Treatment for CRF

An extensive review of the natural product literature identified that the natural products categorized as herbs had the strongest evidence to support their use as a treatment for CRF (Barton et al., 2013; Barton et al., 2010; de Oliveira Campos et al., 2011; Jeong et al., 2010;

Yennurajalingam et al., 2015). We also identified ginseng as the most tested natural product as a treatment for CRF with three single-herb studies (Barton et al., 2013; Barton et al., 2010; Yennurajalingam et al., 2015) and one herbal combination (Jeong et al., 2010). These results led to an assessment of ginseng as a treatment for fatigue. One of the key strengths of the American and Asian ginseng evidence was that the majority of the studies had strong study designs including double-blinding and placebo controls (Barton et al., 2013; Barton et al., 2010; Braz, Morais, Paula, Diniz, & Almeida, 2013; Etemadifar et al., 2013; E. Kim et al., 2011; H. G. Kim et al., 2013; Le Gal, Cathebras, & Strüby, 1996; Wang et al., 2013). None of the studies reported significant adverse events (AEs) attributed to ginseng. Finally, the majority of the ginseng evidence demonstrated significant improvements in fatigue scores in the intervention group compared with the control group (Barton et al., 2013; Etemadifar et al., 2013; Jeong et al., 2010; E. Kim et al., 2011; H. G. Kim et al., 2013; Le Gal et al., 1996; Wang et al., 2013).

Discussion of Natural Products as a Treatment for CRF

We found that there is not strong enough evidence to recommend any of the natural products as a standard of practice to treat CRF. At this time, due to potential risk, L-caritine alone should not be recommended as a treatment for CRF until additional research supports its use (Cruciani et al., 2012). The ginseng evidence demonstrated modest support for ginseng as a treatment for fatigue. Because of the low risk and modest evidence for its effectiveness, ginseng (American and Asian ginseng) is a promising treatment for fatigue. There are several natural products that are promising treatments for CRF. A significant contribution of this work (Chapters II and III) is the ability to state that natural products may be safe and effective, but further research is needed before they can be recommended as a standard of practice to treat CRF. Currently, ginseng has the most evidence to support its use.

Principle Findings, Aim 2: Difference Between Cancer Survivors and Patients Without Cancer

Understanding the difference between cancer survivors and patients without cancer who sought an integrative health (IH) consult will aid cancer care providers' in understanding which complementary approaches are being used and why patients seek IH consults. There were four main findings from this study. First, complementary approaches reported prior to the IH consult were not significantly different between cancer survivors and patients without cancer. Second, patients without cancer reported significantly higher pain ($\bar{x}$=4.68) levels at referral compared to cancer survivors ($\bar{x}$=3.81, $\underline{t}$ (781) = -3.56, p = <.001). Third, cancer survivors reported significantly higher energy levels ($\bar{x}$=4.89 vs. $\bar{x}$=4.07, $\underline{t}$ (804) = 4.13, p = <.001), sleep levels ($\bar{x}$=2.51 vs. $\bar{x}$=2.25, $\underline{t}$ (825) = 3.04, p= <.01), overall health ($\bar{x}$=2.82 vs. $\bar{x}$=2.55, $\underline{t}$ (809) = 4.45, p = <.001), spiritual wellbeing ($\bar{x}$=3.67 vs. $\bar{x}$=3.38, $\underline{t}$ (810) = 3.19, p = <.01), and significantly better relationships ($\bar{x}$=3.86 vs. $\bar{x}$=3.60, t (813) = 3.06, p = <.01) compared to patients without cancer. Fourth, there was little agreement between cancer survivors' reasons for an Integrative Health consult compared with physician referral reasons.

Discussion of Difference Between Cancer Survivors and Patients Without Cancer

To help inform cancer care teams' understanding of use of complementary approaches, we evaluated the difference between cancer survivors and patients without cancer who sought an integrative health (IH) consult (Aim 2, Chapter IV). First, we found that complementary approaches reported prior to consult were not significantly different between cancer survivors and patients without cancer. Overall, there was a high (75.6%) use of complementary approaches in our sample, which did not significantly differ between cancer survivors and patients without cancer. These results on complementary approach use were higher than other reports of cancer

survivors' use of complementary approaches (Huebner et al., 2014). We may have seen higher complementary approach use than national datasets due to the potential bias towards complementary approach usage by those who would choose or agree to an integrative health consult.

In our study, we found that participants without cancer reported higher levels of pain compared to cancer survivors. Additionally, cancer survivors reported significantly higher levels of energy, sleep, overall health, spiritual wellbeing, and significantly better relationships, which differs from previous research that found cancer survivors were more likely to report symptoms of anxiety, like feeling sad or nervous, than non-cancer patients (Anderson & Taylor, 2012). This is a significant finding as often it is assumed that cancer survivors have a higher perception of symptom burden. Additionally, these results could be reflective of the proportion of patients with other chronic diseases represented in this sample. This finding may be a result of multiple factors including the potential that there was a response shift or normalization of the symptoms that would explain these findings. Or this could be a reflection of the cancer survivors' high use of complementary approaches.

Principle Findings, Aim 3: Identify the Complementary Approaches Used by Cancer Survivors to Treat Fatigue and Associated Symptoms

It is critical to understand cancer survivors' use and satisfaction with complementary approaches used to treat CRF, to help identify acceptable treatments and mitigate potential cancer treatment compatibility concerns. There are six key findings from this study: 1) the majority of cancer survivors (67.9%) were satisfied with their complementary approaches; 2) breathing exercises was reported as one of the top three complementary approaches for fatigue (34.1%), pain (26.9%), and sleep (38.5); 3) meditation was reported as one of the top three

complementary approaches for fatigue (29.3%), memory problems (22.6%) and sleep (25.6%); 4) massage was in the top three complementary approaches used for pain (42.3%), and numbness and tingling (24%); 5) participants who used a complementary approach to treat fatigue reported significantly more physical activity (t (38) = 2.15 p=<0.05); and 6) overall health did not significantly differ between participants who used a complementary approach to treat fatigue compared to those who did not.

Discussion of Complementary Approaches used by Cancer Survivors to Treat CRF

Understanding which approaches cancer survivors are using and if they are satisfied with these approaches, can help guide us to identify acceptable treatments and address potential risk related to their use. Similar to previous research, we found that the cancer survivors are satisfied with their complementary approach (K. Kim et al., 2018). Breathing exercises, meditation and massage were the complementary approaches most often reported as one of the top three approaches used. This differs somewhat for recent research that found natural products were the most reported (Berretta, 2017; K. Kim et al., 2018). Our results may differ because we were assessing use at the symptom level, and breathing exercises, meditation and massage were reported being used to treat multiple symptoms. These results highlight the satisfaction with these complementary interventions. Overall, we can say that the cancer survivors in our study are using and are satisfied with their complementary approaches.

Unsurprisingly, the majority (73%) of cancer survivors reported fatigue, which is in line with previous research (Barton et al., 2010; Krishbaum, 2010). The most reported complementary approaches used for CRF were breathing exercises (34.1%), meditation (29.3%) and multivitamins (28.5%). Currently, physical activity is the only evidence-based complementary approach recommended for CRF; however, ginseng, massage, and mindfulness

based stress reduction are listed as likely to be effective (Mitchell, 2014). The use of multivitamins for fatigue is concerning since research has found that multivitamins do not significantly decrease fatigue (de Souza Fede et al., 2007). These results highlight the critical need to guide cancer survivors to trusted resources for complementary approach decision-making.

In line with TOUS, participants who used complementary approaches, believed to influence physiologic and psychologic factors, to treat fatigue reported significantly more physical activity, a measure of performance. Additionally, we found that those who were satisfied with their complementary approaches for fatigue, memory and sleep also had significantly higher scores on the global assessment of change questions (QOL, treatment effect and emotional state) compared to those who were not satisfied. This may allude to a perception of symptom improvement and improved psychologic factors (emotional state) related to their complementary approach; however, our study design did not assess change in symptoms over time.

Principal Findings, Aim 4: Identify Resources that Cancer Survivors use to Decide on their Complementary Approaches

It is critical to understand where cancer survivors obtain their information about complementary approaches used to treat CRF to help identify strategies to address cancer treatment compatibility concerns. There were four important findings from this study: 1) the top three sources of information about complementary approaches used were Integrative Health Provider (e.g., acupuncturist, massage therapist), Friends and Family, and Integrative Medicine Physician; 2) significantly more satisfied participants sought information from their Integrative Health Provider compared to those who were not satisfied (55.3% vs. 16.7%, p=0.009); 3) the

majority of participants shared that they were using complementary approaches with their primary care provider (81.5%); and 4) significantly more participants who were satisfied with their complementary approach shared their usage with their specialty provider (84.2% vs. 58.8%, p=0.041).

Discussion of Resources that Cancer Survivors use to Decide on their Complementary Approaches

Satisfied cancer survivors report their complementary approach use to their health care team. The majority (81.5%) of our participants shared their complementary approaches with their primary care provider, which is a much higher rate than seen by other research teams (Huebner et al., 2014; K. Kim et al., 2018). We also saw higher reporting rates to specialty providers than observed in previous research (Kim et al., 2018). Additionally, those who were satisfied with their complementary approach reported their use to their specialty provider significantly more than those who were unsatisfied (84.2% vs. 58.8%, p=<0.05). These results differ from previous research, which found that even though the majority of their participants were satisfied with their complementary approach, only 22.5% reported their use to their care team (K. Kim et al., 2018). These results identify a potential strategy of linking cancer survivors to trusted resources to guide their complementary approach use and to potentially increase their reporting to their cancer care team.

Similar to previous studies, we found that there was very little agreement between cancer survivors' reason for consult and physician referral reasons for an IH consult (Samuels, 2015). This is an important finding as it may represent a key opportunity to help cancer survivors reach trusted resources to help them in their decisions to use complementary approaches. These results may allude to potential differences in communication styles. We found that cancer survivors'

reasons were more focused on symptoms, and that physician referrals were often more related to a medical diagnosis. Additionally, this lack of agreement could be due to a limited understanding of the role that Integrative Medicine and Health (IMH) Physicians can play in symptom management.

Discussion

We found that complementary approaches including natural products may influence psychologic and physiologic influencing factors as evidenced by the global assessment of change results, and that those who used complementary approaches reported improved performance defined as physical activity. Additionally, we confirmed high rates of use and satisfaction with complementary approach use among cancer survivors (K. Kim et al., 2018). We also found a higher rate of reporting complementary approach usage to care teams in this population of patients who received an integrative health consult (Huebner et al., 2014; Kim et al., 2018). The results of this dissertation supports continued research that 1) assesses natural products' safety and effects as a treatment for CRF, and 2) identifies interventions to assist both cancer survivors and cancer teams on how to navigate the complex world of complementary approaches in the setting of cancer and cancer treatment.

Theoretical Implications

This dissertation supported TOUS through its findings that natural products seem to influence both physiologic (i.e., inflammatory response) and psychologic factors (i.e., anxiety, stress) as evidenced by the significant findings for the global assessment of change questions. Additionally, we found that those reporting use of complementary approaches also reported improved performance (physical activity) (Barton et al., 2013; Lenz & Pugh, 2014; Yennurajalingam et al., 2015). These findings support the factors and performance concepts in

TOUS; however, due to the study design we were unable to test the change in the symptom itself (Lenz et al., 1997).

Direction for Future Research

This dissertation identified three key opportunities for future natural product research. First, natural product research should use strong research designs including blinding and randomization that mitigate multiple types of bias and increase internal validity. Additionally, results need to be replicated to build evidence that ensures they are safe and effective to aid treatment decisions. We need larger and more diverse samples to increase the generalizability of their results.

Furthermore, in the United States the natural product industry is not as regulated as the pharmaceutical industry, which results in variability in products. Due to this, we need to understand where cancer survivors are attaining their natural products, and how best to support cancer survivors and care teams to navigate this complex industry. Based on our results, which demonstrated a high percentage of cancer survivors reporting their complementary approach usage with their care teams, an integrative health consult may be an effective strategy.

Implications for Clinical Practice

Our results find that natural products may be a safe and acceptable treatment for CRF; however, there is not enough evidence to support them as a standard of practice to treat CRF. Currently, out of the natural products reviewed, ginseng has the most evidence to support its use as a treatment for CRF.

We found significantly more satisfied participants sought information from their integrative health provider and that significantly more participants who were satisfied with their complementary approach shared their usage with their specialty provider. This supports the use

of trusted resources like Integrative Health consultation and providers. Due to these results, coupled with cancer survivors' known high use of complementary approaches, it is recommended that cancer teams at minimum discuss complementary approach usage with cancer survivors—or, if available, cancer survivors should receive an Integrative Health consult.

Conclusion

Due to the rate of cancer, our aging population and the increasing success of cancer treatment, we are seeing the numbers of cancer survivors rise (American Cancer Society, 2016). During and after treatment, CRF is a distressing symptom that can impact many aspects of a cancer survivor's life (Centers for Disease Control and Prevention, 2017). Complementary approaches including natural products are a promising and acceptable treatment for CRF. In order to help mitigate this complex symptom we need to find safe, effective and acceptable treatments. The ultimate goals of this program of research are to 1) find safe and effective treatments for CRF; and 2) develop interventions that help abate the risk or potential risks posed by complementary approaches for cancer survivors.

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From: IRBe
To: Arring, Noel M., D.N.P., R.N., O.C.N.
Subject: 17-004274 - A study has been Approved by IRB
Date: Monday, June 05, 2017 11:03:01 AM

Principal Investigator Notification:

From: Mayo Clinic IRB
To: Noel Arring
CC: Noel Arring
Re: **IRB Application #:** 17-004274
Title: Why Do Patients Seek Integrative Health Consults?

IRBe Protocol Version: 0.03
IRBe Version Date: 6/2/2017 11:07 AM

IRB Approval Date: 6/5/2017
IRB Expiration Date: 6/4/2020

The above referenced application is approved by expedited review procedures (45 CFR 46.110, item 5). This approval is valid for a period of three years. The Reviewer conducted a risk-benefit analysis, and determined the study constitutes minimal risk research. The Reviewer determined that this research satisfies the requirements of 45 CFR 46.111.

The Reviewer approved the accrual of 1,200 subjects, and to review data that exist between January 1, 2013 and May 22, 2017.

The Reviewer approved waiver of the requirement to obtain informed consent in accordance with 45 CFR 46.116 as justified by the Investigator, and waiver of HIPAA authorization in accordance with applicable HIPAA regulations.

The investigator is reminded to contact Legal Contract Administration regarding appropriate agreement(s).

AS THE PRINCIPAL INVESTIGATOR OF THIS PROJECT, YOU ARE RESPONSIBLE FOR THE FOLLOWING RELATING TO THIS STUDY.

1) When applicable, use only IRB approved materials which are located under the documents tab of the IRBe workspace. Materials include consent forms, HIPAA, questionnaires, contact letters, advertisements, etc.

2) Submission to the IRB of any modifications to approved research along with any supporting documents for review and approval prior to initiation of the changes.

3) Submission to the IRB of all Unanticipated Problems Involving Risks to Subjects or Others

(UPIRTSO).

4) Compliance with Mayo Clinic Institutional Policies.

Mayo Clinic Institutional Reviewer

IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this document to the protocol section.

Modification: To modify this document after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points , save the template to your files

General Study Information

Principal Investigator: Noël Arring, DNP, RN, OCN

Study Title: Why Do Patients Seek Integrative Health Consults?

Protocol version number and date: V3.1

Research Question and Aims

Aims, purpose, or objectives:

Aim 1: Describe the population seeking Integrative Health (IH) care consults at an academic medical center.

Aim 2: Evaluate relationship between the patient's reason for consulting IH, their reported symptoms and physician referral reasons

Aim 3: Determine if cancer patients seeking IH care consults differ from non-cancer patients seeking IH care consults.

H3a: Cancer patients seeking IH care consultation will report more symptoms (stress, pain, energy and anxiety) greater than 5 on 1-10 scale compared to non-cancer patients.

H3b: Increased energy levels will correlate with increased activity levels.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):

More than 60% of cancer survivors report using integrative health approaches [1, 2]. Integrative health is defined as incorporating complementary or non-western healthcare approaches with traditional

western or mainstream approaches [3]. Complementary health approaches include natural products like herbs and mind and body practices like yoga [3]. Worldwide over 30% of cancer patients report using complementary health approaches [4]. In the North America the rate of complementary health use in cancer patients rises to over 40% [4]. Cancer patients are using complementary health approaches; however, they are not likely to report this to their cancer teams [5]. Furthermore, there is evidence that demonstrates that they are seeking information about these interventions from potentially unreliable sources [6].

Current evidence on why cancer patients seek Integrative Health consults is limited. Often studies of IH consults do not assess why patients sought consultation and/or why they were referred for consultation [7, 8]. When patients' reasons were assessed, often they were reported in broad categories like physical symptoms [9, 10]. Furthermore, Samuels et al (2015) identified a mismatch between physician IH consult reason and patient expectations [10]. The current evidence highlights a gap in knowledge related to why patients are seeking IH consultations. The purpose of this study is to evaluate the relationship between the reasons why patients consult Integrative Health with their reported symptoms and physician referral reasons. It is critical to understand why patients seek IH approaches so IH providers can appropriately meet their needs, and cancer care providers can guide patients to trusted resources.

Theoretical Framework

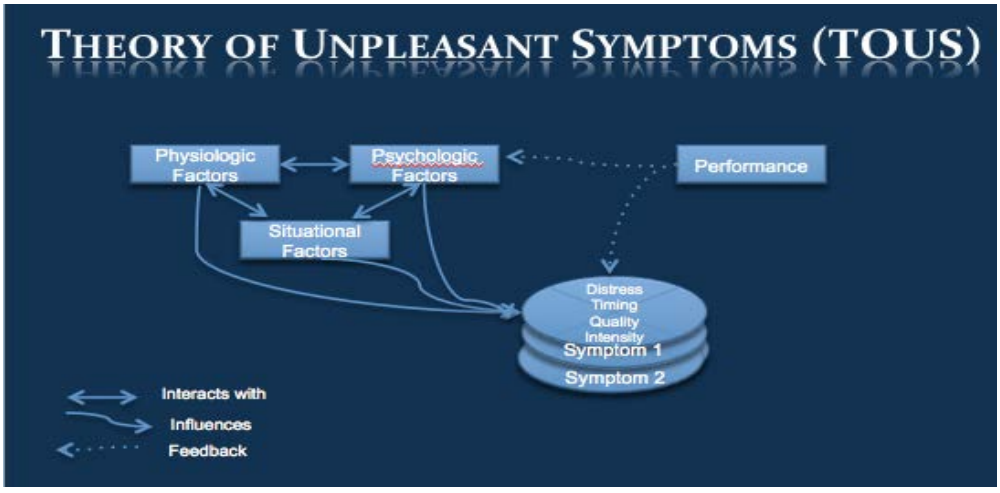


Figure 1: Theory of Unpleasant Symptoms

This research study is grounded in the Theory of Unpleasant Symptoms (TOUS) (Figure 1) [11]. TOUS has three key concepts: symptom, influencing factors and performance outcomes [11]. Influencing factors in TOUS include physiological factors, psychological factors (mood and cognitive variables) and situational factors (environment, social economic standing, social support, culture) that can impact the symptom experience [11]. In this study, we will be assessing the relationship between physiologic factors (i.e. diagnosis, medications, IH interventions), psychologic factors (i.e. anxiety level), situational factors (i.e. material status, payer source, physician referral), performance (i.e. overall health and physical activity) and reported symptoms.

Study Design and Methods

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:

A retrospective descriptive cross-sectional study will evaluate Integrative Health patient's reasons for seeking an initial consultation. This study will leverage an already collected Integrative Medicine Intake Form and the EHR. Additional information will be gathered from the EHR by a research team member, who is a Mayo Clinic employee.

Integrative Medicine Intake form variables:
Age
Sex
Reason for consult (Pain, Fatigue, Stress, Fibromyalgia, Sleep Problems, Cancer, Heart Disease, Other)
Type of referral: Self, Physician, Other
Stress level (0-10)
Pain level (0-10)
Energy level (0-10)
Anxiety level (0-10)
Diet (1- Excellent through 5-Poor)
Relationships (1- Excellent through 5-Poor)
Spiritual wellbeing (1- Excellent through 5-Poor)
Sleep (1- Excellent through 5-Poor)
Overall health (1- Excellent through 5-Poor)
Level of physical activity: sedentary, slight activity, moderately active, highly active
Relaxation practice (1 (not at all)- 5 (everyday))
Which relaxation program

Collected from EHR:
Marital status
Distance from Mayo Clinic
Length of time since diagnosis of chronic disease if selected participant (cancer, fibromyalgia, heart disease) to the integrative health consult
If cancer, type of cancer
If previous cancer, type of cancer, time since diagnosis, time since completion of treatment, type of treatment received

Payer source at time of services
Any previous and/or current use of IH interventions such as herbs, massage, acupuncture, yoga reported at IH consult
Ordering provider for Integrative Health Consult order
Medications at time of consult
Integrative Health recommendations

All materials related to this project will be maintained on a secured server, RedCap and/or locked file cabinet. Only limited dataset will be shared with external collaborators via secured/encrypted file transfers.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

Noël M. Arring, DNP, RN, OCN, is the Manager of Nursing Research, Department of Nursing at Mayo Clinic, Arizona. She received her DNP from the University of Massachusetts, Amherst, in Public Health Nurse Leadership and is pursuing a PhD from Oregon Health & Science University.

Lillian Nail, RN, PhD, FAAN, Rawlinson Distinguished Professor & Senior Scientist, School of Nursing and Member, OHSU Cancer Institute, Oregon Health & Science University is the chair of Dr. Arring's PhD committee and will mentor her through this project.

☐ (1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *When checked, describe in detail the research procedures or activities that will be conducted by Mayo Clinic study staff.*

☐ (1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 1200

Subject population (children, adults, groups): Adults

Inclusion Criteria: patient who sought Integrative Medicine Consults at Mayo Clinic, Arizona

Exclusion Criteria: Patients who sought Integrative Medicine Consults in Rochester or Florida.

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☐ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☐ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*.

_____

Biospecimens – Categories 2 and 3

(2) Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed

550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.)

_____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.)

_____

(3) Prospective collection of biological specimens other than blood:

_____

Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range: January 1, 2013- May 22, 2017

Check all that apply (data includes medical records, images, specimens).

☒ (5a) Only data that exists before the IRB submission date will be collected.

☐ (5b) The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol.*

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____
☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff. **External** refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name		
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data		
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	X	X
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		

Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes	X	
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☐ None

Data Analysis

Power analyses and study endpoints are not required for minimal risk research, pilot or feasibility studies.

☐ No statistical information. *If checked, please explain*:

Power Statement:

Data Analysis Plan:
The data will be summarized by the descriptive statistics (mean, standard deviation, median, percentage and frequency). The demographic and clinical characteristics of the two study groups (cancer vs. other) will be compared by the two-sample t-test or Chi-square test. The test of normality on the continuous variables will be performed, and the non-parametric test will be applied if there is evidence of non-normality. Logistic regression modeling of reasons for seeking IH consultation will be applied to evaluate possible factors associated with seeking consultation. Both univariate and multivariable analysis will be performed.

References

1. Bower, J.E., *Cancer-related fatigue--mechanisms, risk factors, and treatments.* Nat Rev Clin Oncol, 2014. **11**(10): p. 597-609.
2. Weymann, K.B., et al., *A role for orexin in cytotoxic chemotherapy-induced fatigue.* Brain Behav Immun, 2014. **37**: p. 84-94.
3. National Center for Complementary and Integrative Health. *Complementary, Alternative, or Integrative Health: What's In a Name?* 2016; Available from: https://nccih.nih.gov/health/integrative-health.
4. Horneber, M., et al., *How many cancer patients use complementary and alternative medicine: a systematic review and metaanalysis.* Integr Cancer Ther, 2012. **11**(3): p. 187-203.
5. Frenkel, M., Sierpina, V., *The Use of Dietary Supplements in Oncology.* Curr Oncol Rep, 2014. **16**(411).
6. Adams, M. and A.P. Jewell, *The use of Complementary and Alternative Medicine by cancer patients.* Int Semin Surg Oncol, 2007. **4**: p. 10.
7. Ben-Arye, E., Schiff, E., Raz, O. G., Samuels, N., Lavie, O., *Integrating a complementary medicine consultation for women undergoing chemotherapy.* International Journal of Gynecology and Obstetrics, 2014. **124**: p. 51-54.
8. Ben-Arye, E., Kruger, D., Samuels, N., Keinan-Boker, L., Shalom, T., Schiff, E., *Assessing patient adherence to a complementary medicine treatment regimen in an integrative supportive care setting.* Support Care Cancer, 2014. **22**: p. 627-634.
9. Frenkel, M., Cohen, L., Peterson, N., Palmer, J. L., Swint, K., Bruera, E., *Integrative Medicine Consultation Service in a Comprehensive Cancer Center: Findings and Outcomes.* Integrative Cancer Therapies, 2010. **9**(3): p. 276-283.
10. Samuels, N., Schiff, E., Lavie, O., Raz, O. G., Ben-Arye, E., *Expectations from an integrative medicine consultation in breast cancer care: a registry protocol-based study.* 2015, 2015. **23**: p. 317-324.
11. Meterko, M., D.C. Mohr, and G.J. Young, *Teamwork Culture and Patient Satisfaction in Hospitals.* Medical Care, 2004: p. 492-498.

From: IRBe
To: Arring, Noel M., D.N.P., R.N., O.C.N.
Subject: 17-006802 - A study has been Approved by IRB
Date: Monday, August 14, 2017 5:35:56 AM

Principal Investigator Notification:

From: Mayo Clinic IRB
To: Noel Arring
CC: Noel Arring

Re: **IRB Application #:** 17-006802
Title: Integrative Health and Reasons for Using Complementary Interventions.

IRBe Protocol Version: 0.03
IRBe Version Date: 8/12/2017 6:26 PM

IRB Approval Date: 8/14/2017
IRB Expiration Date: 8/13/2018

The above referenced application is approved by expedited review procedures (45 CFR 46.110, item 5,7). This approval is valid for a period of one year. The Reviewer conducted a risk-benefit analysis, and determined the study constitutes minimal risk research. The Reviewer determined that this research satisfies the requirements of 45 CFR 46.111.

The Reviewer approved the accrual of 930 subjects and to review data that exist between January 1, 2013 and May 22, 2017.

The Reviewer noted that oral consent with HIPAA authorization is appropriate for this study. The oral consent script/contact letter was reviewed and approved as written. The written HIPAA form was reviewed and approved as written. The Reviewer approved waiver of the requirement for the Investigator to obtain a signed consent form in accordance with 45 CFR 46.117 as justified by the Investigator.

The investigator is reminded to contact Legal Contract Administration regarding appropriate agreement(s).

AS THE PRINCIPAL INVESTIGATOR OF THIS PROJECT, YOU ARE RESPONSIBLE FOR THE FOLLOWING RELATING TO THIS STUDY.

1) When applicable, use only IRB approved materials which are located under the documents tab of the IRBe workspace. Materials include consent forms, HIPAA, questionnaires, contact letters, advertisements, etc.

2) Submission to the IRB of any modifications to approved research along with any supporting documents for review and approval prior to initiation of the changes.

3) Submission to the IRB of all Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO) and major protocol violations/deviations within 5 working days of becoming aware of the occurrence.

4) Compliance with applicable regulations for the protection of human subjects and with Mayo Clinic Institutional Policies.

Mayo Clinic Institutional Reviewer

(Date}

{ Name}
{Street Address}
{City, State Zip}

RE: *{ first name} { last name}*
MC#: *{mc #}*

Protocol Title: Integrative Health and Reasons for Using Complementary Interventions
IRB #: 17-006802
Principal Investigator: Noël Arring, DNP, RN, OCN

Dear *{Mr., Ms, or Mrs.}*

You are being asked to participate in a research study about the use of complementary health approaches. The purpose of this study is to inform Integrative Health providers about the services that are being sought and to help inform treatment teams so they can guide patients to appropriate resources. We are conducting a short survey of patients who have had a consultation with Integrative Medicine. The survey is estimated to take 5-10 minutes.

If you agree to participate you will be asked to respond to a short (less than 10 minute) survey about your use complementary approaches. All information gathered will be securely maintained. You will not receive payment for your participation. We have mailed a questionnaire for you to complete. If you would like to, you may fill it out and return in the enclosed stamped envelope.

There are no known risks to you from taking part in this research study and you may refuse to answer any question(s) that you do not wish to answer.

This study will not make your health better. However, your responses will help to inform the Integrative Health and medical communities about the use of complementary approaches to help develop awareness and services to meet these needs.

Please understand your participation is voluntary and you have the right to withdraw your consent or discontinue participation at any time without penalty. Specifically, your current or future medical care at Mayo Clinic will not be jeopardized if you choose not to participate.

If you decide to participate, you will need to read and sign the Authorization to Use and Disclose Protected Health Information (HIPAA) form and return it with the questionnaire. We are not allowed to use the answers without your signature on the HIPAA form. An extra copy is included for your records.

Contact me at Noël Arring, DNP, RN at 480-342-0282 if you have any questions about:

- Study procedures
- Withdrawing from the research study
- Materials you receive

If you prefer, you may write to me at the address given below:

5777 E Mayo Blvd
Phoenix, AZ 85054
arring.noel@mayo.edu

Contact the Mayo Institutional Review Board (IRB) to speak to someone independent of the research team at 507-266-4000 or toll free at 866-273-4681 if you have questions about:

- Rights of a research participant
- Use of your Protected Health Information
- Stopping your authorization to use your Protected Health Information

Research-related questions not listed above, or any research-related complaints may also be addressed to me. If you prefer to speak with someone independent of the research team, you may contact the Mayo Institutional Review Board (IRB).

If you prefer to complete the survey over the phone, or if you do not wish to participate, please indicate on the next page and return this letter since it will make a follow-up telephone call unnecessary. Thank you very much for your time and consideration.

Sincerely,

_____
Noël Arring, DNP, RN, OCN

RE: *{first name} {last name}*
MC#: *{mc #}*

Protocol Title:
IRB #:
Principal Investigator:

Noël Arring, DNP, RN, OCN
5777 E Mayo Blvd
Phoenix, AZ 85054
arring.noel@mayo.edu

☐ I would prefer to complete the survey over the phone. I am **enclosing** the **Authorization to Use and Disclose Protected Health Information form** only. Please call me.

Your name: _____
Telephone number: (___) ___-_____
Today's date: __/__/__
Best time to call: ☐ Morning ☐ Afternoon ☐ Evening
Best day(s) to call: _____

☐ I am **not** willing to participate in this research study.

Study Title: Integrative Health and Reasons for Using Complementary Interventions

IRB#: 17-006802

Principal Investigator: Noël Arring, DNP, RN, OCN and Colleagues

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission. You will be given a copy of this form.

Health information may be collected about you from:

- Past, present and future medical records.
- Research procedures, including research office visits, tests, interviews and questionnaires.

This information will be used and/or given to others to:

- Do the research.
- Report the results.
- See if the research was done correctly.

If the results of this study are made public, information that identifies you will not be used.

Your health information may be used or shared with:

- Mayo Clinic research staff involved in this study.

Your health information may also be shared with:

- The Mayo Clinic Institutional Review Board that oversees the research.
- Researchers involved in this study at other institutions.
- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research.
- A group that oversees the data (study information) and safety of this research.

Protection of your health information after it has been shared with others:
Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Privacy Rights
You do not have to sign this form, but if you do not, you cannot take part in this research study. Your decision won't change the access to medical care or any other benefits you get at Mayo Clinic now or in the future.

If you cancel your permission to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

You can cancel your permission to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
200 1st Street SW
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing the Mayo Clinic Research Subject Advocate at: researchsubjectadvocate@mayo.edu.

Please be sure to include in your letter or email:
- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission lasts until the end of this study, unless you cancel it. Because research is an ongoing process, we cannot give you an exact date when the study will end.

Your signature documents your permission to use your protected health information for this research.

	/ /	: AM/PM
Printed Name	Date	Time

Signature

Protocol Title: Integrative Health and Reasons for Using Complementary Interventions
IRB #:17-006802
{Date}

{Name}
{Street Address}
{City, State Zip}

RE: *{ first name} { last name}*
MC#: *{mc #}*

Dear *{Mr., Ms., or Mrs.}*

Thank you for your recent participation in Integrative Health and Reasons for Using Complementary Interventions a research project about the use of complementary health approaches.

We are mailing you the Authorization to Use and Disclose Protected Health Information (HIPAA) form to read and sign. We are not allowed to use your health information or survey responses without your signature on the Authorization to Use and Disclose Protected Health Information form. An extra copy is included for your records.

Please return the signed form using the enclosed return stamped envelope to enable us to use your medical information that you kindly shared with us when answering the survey questions.

If you have any questions about this research study you can contact me at Noël Arring, DNP, RN at 480-342-0282. If you have any concerns, complaints, or general questions about research or your rights as a participant, please contact the Mayo Institutional Review Board (IRB) to speak to someone independent of the research team at 507-266-4000 or toll free at 866-273-4681.

Thank you very much for your time and consideration.

Sincerely,

_____
Noël Arring, DNP, RN, OCN

Mayo Clinic: Office for Human Research Protection
Oral Consent Script

Protocol Title: Integrative Health and Reasons for Using Complementary Interventions
IRB #:17-006802
Principal Investigator: Noël Arring, DNP, RN, OCN

The purpose of this study is to inform Integrative Health providers about the services that are being sought and to help inform treatment teams so they can guide patients to appropriate resources. We are conducting a short survey of patients who have had a consult with Integrative medicine. The survey is estimated to take 5-10 minutes.

If you agree to participate you will be asked to respond to a short (less than 10 minute) survey about your use complementary approaches. All information gathered will be securely maintained. You will not receive payment for your participation.

If you decide to participate, you will need to read and sign the Authorization to Use and Disclose Protected Health Information (HIPAA) form and return it with the questionnaire. We are not allowed to use the answers without your signature on the HIPAA form. An extra copy is included for your records.

There are no known risks to you from taking part in this research study and you may refuse to answer any question(s) that you do not wish to answer.

This study will not make your health better. However your responses will help to inform the Integrative Health and medical communities about the use of complementary approaches to help develop awareness and services to meet these needs.

Please understand your participation is voluntary and you have the right to withdraw your consent or discontinue participation at any time without penalty. Specifically, your current or future medical care at the Mayo Clinic will not be jeopardized if you choose not to participate.

If you have any questions about this research study you can contact the principle investigator Noël Arring, DNP, RN, OCN at 480-342-0282. If you have any concerns, complaints, or general questions about research or your rights as a participant, please contact the Mayo Institutional Review Board (IRB) to speak to someone independent of the research team at 507-266-4000 or toll free at 866-273-4681.

Mayo Clinic: Office for Human Research Protection
Telephone Script

Protocol Title: Integrative Health and Reasons for Use Complementary Interventions
IRB #:17-006802
Principal Investigator: Noël Arring, DNP, RN, OCN

Introduction:

Hello, this is _____ calling from the Mayo Clinic in Arizona (if out of state). May I please speak to _____?

***If the participant is there continue with the script.

***If the participant is not there, ask when it would be a good time to speak with _____?

Enrollment into the study:

We are following up on survey that was sent to you about the different complementary approaches, like herbs, and yoga our patients are using and why. Have you already responded to this survey?

If yes: *Thank you for participating in this important study. Did you mail it back? (if so when) Have you sent in your signed HIPAA Authorization to Use and Disclose Protected Health Information form? If not, do you need us to send you another one?*

If no: *Would you be willing to complete the survey now over the phone? Please understand that your current or future medical care at the Mayo Clinic will not be jeopardized if you choose not to participate.*

If no*: Thank them for their time and stop the recruitment process.*

If yes*:* Use **ORAL CONSENT SCRIPT**.

Following Up on a Returned Survey without a HIPPA Form:

We are following up on survey that you participated in about the different complementary approaches, like herbs, and yoga our patients are using and why. Thank you for your response to our survey. We are following up because we have not yet received your signed HIPAA Authorization to Use and Disclose Protected Health Information form. Without this form we are not allowed to use your responses. Have you sent us this form?

If yes: *Thank you. How long ago was this mailed to us?*

If no: *Are you willing to sign the HIPAA Authorization to Use and Disclose Protected Health Information form?*

If yes: *Do you need an additional copy? (if they agree confirm mailing address)*

If no: *Without this form we are not allowed to use your responses, so you will be withdrawn from this study.*

Closing

If they participated: *Thank you for participating in our research study. Please understand that your answers will remain confidential. Please contact Noël Arring at 480-342-0282 if you have any questions regarding this study.*

If they did not participate: *Thank you for your time today. Please contact Noël Arring at 480-342-0282 if you have any questions regarding this study.*

Name:_____

1) Have you used complementary approaches like herbs, fish oil or yoga before seeking your IH consult?

☐Yes ☐No

If so, which ones (select all that apply)

☐Multivitamin	☐Coenzyme Q10	☐Cranberry (pills, capsules)
☐Echinacea	☐Fish oil/omega-3 fatty acids	☐Garlic supplements
☐Ginkgo biloba	☐Ginseng	☐Glucosamine
☐ Turmeric	☐Green tea	☐Medicinal marijuana
☐Melatonin	☐Probiotics	☐Chiropractic manipulation
☐Massage	☐Meditation	☐Yoga
☐Acupuncture	☐Therapeutic touch	☐Biofeedback
☐Progressive muscle relaxation	☐Guidance Therapy (i.e. counseling, religion, prayer)	☐Laughter therapy
☐Traditional Chinese medicine	☐Cranial sacral therapy	☐Mindfulness based stress reduction
☐Qi Gong	☐Breathing exercises	☐Reiki
☐Guided imagery	☐Aromatherapy	☐Homeopathy
☐Hypnosis	☐Tai Chi	

☐Other: Please specify: _____

2) Primary reason for seeking your Integrative Health Consultation?

_____

3) Do you have **fatigue**? ☐Yes ☐No

If no, continue to question 4.

If yes, on a scale of 1-10, 10 being the worst how would you rate your **fatigue**?

A) How long have you been **fatigued**?

☐less than 1 month
☐1-2 months
☐3-5 months
☐6-11 months
☐1-4 years
☐5-9 years
☐greater than 10 years

B) How do you manage your **fatigue**?

☐Medical management like prescription medications
If yes, please specify which one(s) _____

☐Do not treat

☐Other: Please specify _____

☐Complementary approach (if selected please answer question below)

C) What complementary approaches do you use to treat your **fatigue**? (select all that apply)

☐Multivitamin
☐Echinacea
☐Ginkgo biloba
☐ Turmeric
☐Melatonin
☐Massage
☐Acupuncture
☐Progressive muscle relaxation
☐Traditional Chinese medicine
☐Qi Gong
☐Guided imagery
☐Hypnosis
☐Coenzyme Q10
☐Fish oil/omega-3 fatty acids
☐Ginseng
☐Green tea
☐Probiotics
☐Meditation
☐Therapeutic touch
☐Guidance Therapy (i.e. counseling, religion, prayer)
☐Cranial sacral therapy
☐Breathing exercises
☐Aromatherapy
☐Tai Chi
☐Cranberry (pills, capsules)
☐Garlic supplements
☐Glucosamine
☐Medicinal marijuana
☐Chiropractic manipulation
☐Yoga
☐Biofeedback
☐Laughter therapy
☐Mindfulness based stress reduction
☐Reiki
☐Homeopathy

☐Other: Please specify: _____

D) Since beginning the complementary approach, the overall quality of my life is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

E) Since beginning the complementary approach, my **fatigue** is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

F) Since beginning the complementary approach, my emotional state is:

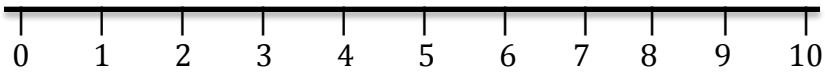
-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

G) Were you satisfied with the effect this treatment had on your **fatigue**?

☐Yes ☐No

4) Do you have **pain**? ☐Yes ☐No
If no, continue to question 5.

If yes, on a scale of 1-10, 10 being the worst how would you rate your **pain**?



A) How long have you had **pain**?

☐less than 1 month
☐1-2 months
☐3-5 months
☐6-11 months
☐1-4 years
☐5-9 years
☐greater than 10 years

B) How do you manage your **pain**?

☐Medical management like prescription medications
If yes, please specify which one(s) _____

☐Do not treat

☐Other: Please specify _____

☐Complementary approach (if selected please answer question below)

C) What complementary approaches do you use to treat your **pain**? (select all that apply)

☐Multivitamin
☐Echinacea
☐Ginkgo biloba
☐ Turmeric
☐Melatonin
☐Massage
☐Acupuncture
☐Progressive muscle relaxation
☐Traditional Chinese medicine
☐Qi Gong
☐Guided imagery
☐Hypnosis
☐Coenzyme Q10
☐Fish oil/omega-3 fatty acids
☐Ginseng
☐Green tea
☐Probiotics
☐Meditation
☐Therapeutic touch
☐Guidance Therapy (i.e. counseling, religion, prayer)
☐Cranial sacral therapy
☐Breathing exercises
☐Aromatherapy
☐Tai Chi
☐Cranberry (pills, capsules)
☐Garlic supplements
☐Glucosamine
☐Medicinal marijuana
☐Chiropractic manipulation
☐Yoga
☐Biofeedback
☐Laughter therapy
☐Mindfulness based stress reduction
☐Reiki
☐Homeopathy

☐Other: Please specify: _____

D) Since beginning the complementary approach, the overall quality of my life is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

E) Since beginning the complementary approach, my **pain** is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

F) Since beginning the complementary approach, my emotional state is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

G) Were you satisfied with the effect this treatment had on your **pain**?

☐Yes ☐No

5) Do you have **numbness and tingling**? ☐Yes ☐No
If no, continue to question 6.

If yes, on a scale of 1-10, 10 being the worst how would you rate your **numbness and tingling**?

A) How long have you had **numbness and tingling**?

☐less than 1 month
☐1-2 months
☐3-5 months
☐6-11 months
☐1-4 years
☐5-9 years
☐greater than 10 years

B) How do you manage your **numbness and tingling**?

☐Medical management like prescription medications
If yes, please specify which one(s) _____

☐Do not treat

☐Other: Please specify _____

☐Complementary approach (if selected please answer questions below)

C) What complementary approaches do you use to treat your **numbness and tingling**? (select all that apply)

☐Multivitamin
☐Echinacea
☐Ginkgo biloba
☐ Turmeric
☐Melatonin
☐Massage
☐Acupuncture
☐Progressive muscle relaxation
☐Traditional Chinese medicine
☐Qi Gong
☐Guided imagery
☐Hypnosis
☐Coenzyme Q10
☐Fish oil/omega-3 fatty acids
☐Ginseng
☐Green tea
☐Probiotics
☐Meditation
☐Therapeutic touch
☐Guidance Therapy (i.e. counseling, religion, prayer)
☐Cranial sacral therapy
☐Breathing exercises
☐Aromatherapy
☐Tai Chi
☐Cranberry (pills, capsules)
☐Garlic supplements
☐Glucosamine
☐Medicinal marijuana
☐Chiropractic manipulation
☐Yoga
☐Biofeedback
☐Laughter therapy
☐Mindfulness based stress reduction
☐Reiki
☐Homeopathy

☐Other: Please specify: _____

D) Since beginning the complementary approach, the overall quality of my life is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

E) Since beginning the complementary approach, my **numbness and tingling** is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

F) Since beginning the complementary approach, my emotional state is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

G) Were you satisfied with the effect this treatment had on your **numbness and tingling**?

☐Yes ☐No

6) Do you have **nausea**? ☐Yes ☐No
If no, continue to question 7.

If yes, on a scale of 1-10, 10 being the worst how would you rate your **nausea**?

A) How long have you had **nausea**?

☐less than 1 month
☐1-2 months
☐3-5 months
☐6-11 months
☐1-4 years
☐5-9 years
☐greater than 10 years

B) How do you manage your **nausea**?

☐Medical management like prescription medications
If yes, please specify which one(s) _____

☐Do not treat

☐Other: Please specify _____

☐Complementary approach (if selected please answer questions below)

C) What complementary approaches do you use to treat your **nausea**? (select all that apply)

☐Multivitamin
☐Echinacea
☐Ginkgo biloba
☐ Turmeric
☐Melatonin
☐Massage
☐Acupuncture
☐Progressive muscle relaxation
☐Traditional Chinese medicine
☐Qi Gong
☐Guided imagery
☐Hypnosis
☐Coenzyme Q10
☐Fish oil/omega-3 fatty acids
☐Ginseng
☐Green tea
☐Probiotics
☐Meditation
☐Therapeutic touch
☐Guidance Therapy (i.e. counseling, religion, prayer)
☐Cranial sacral therapy
☐Breathing exercises
☐Aromatherapy
☐Tai Chi
☐Cranberry (pills, capsules)
☐Garlic supplements
☐Glucosamine
☐Medicinal marijuana
☐Chiropractic manipulation
☐Yoga
☐Biofeedback
☐Laughter therapy
☐Mindfulness based stress reduction
☐Reiki
☐Homeopathy

☐Other: Please specify: _____

D) Since beginning the complementary approach, the overall quality of my life is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

E) Since beginning the complementary approach, my **nausea** is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

F) Since beginning the complementary approach, my emotional state is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

G) Were you satisfied with the effect this treatment had on your **nausea**?

☐Yes ☐No

7) Do you have **memory problems or difficulty concentrating**?

☐Yes ☐No

If no, continue to question 8.

If yes, on a scale of 1-10, 10 being the worst how would you rate your **memory problems or difficulty concentrating**?

A) How long have you had **memory problems or difficulty concentrating**?

☐less than 1 month
☐1-2 months
☐3-5 months
☐6-11 months
☐1-4 years
☐5-9 years
☐greater than 10 years

B) How do you manage your **memory problems or difficulty concentrating**?

☐Medical management like prescription medications
If yes, please specify which one(s) _____

☐Do not treat

☐Other: Please specify _____

☐Complementary approach (if selected please answer questions below)

C) What complementary approaches do you use to treat your **memory problems or difficulty concentrating**? (select all that apply)

☐Multivitamin
☐Echinacea
☐Ginkgo biloba
☐ Turmeric
☐Melatonin
☐Massage
☐Acupuncture
☐Progressive muscle relaxation
☐Traditional Chinese medicine
☐Qi Gong
☐Guided imagery
☐Hypnosis
☐Coenzyme Q10
☐Fish oil/omega-3 fatty acids
☐Ginseng
☐Green tea
☐Probiotics
☐Meditation
☐Therapeutic touch
☐Guidance Therapy (i.e. counseling, religion, prayer)
☐Cranial sacral therapy
☐Breathing exercises
☐Aromatherapy
☐Tai Chi
☐Cranberry (pills, capsules)
☐Garlic supplements
☐Glucosamine
☐Medicinal marijuana
☐Chiropractic manipulation
☐Yoga
☐Biofeedback
☐Laughter therapy
☐Mindfulness based stress reduction
☐Reiki
☐Homeopathy
☐Other: Please specify: _____

D) Since beginning the complementary approach, the overall quality of my life is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

E) Since beginning the complementary approach, my **memory problems or difficulty concentrating** is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

F) Since beginning the complementary approach, my emotional state is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

G) Were you satisfied with the effect this treatment had on your **memory problems or difficulty concentrating**?

☐Yes ☐No

8) Do you have **hot flashes**? ☐Yes ☐No
If no, continue to question 9.

If yes, on a scale of 1-10, 10 being the worst how would you rate your **hot flashes**?

A) How long have you had **hot flashes**?

☐less than 1 month
☐1-2 months
☐3-5 months
☐6-11 months
☐1-4 years
☐5-9 years
☐greater than 10 years

B) How do you manage your **hot flashes**?

☐Medical management like prescription medications
If yes, please specify which one(s) _____

☐Do not treat

☐Other: Please specify _____

☐Complementary approach (if selected please answer questions below)

C) What complementary approaches do you use to treat your **hot flashes**? (select all that apply)

☐Multivitamin
☐Echinacea
☐Ginkgo biloba
☐ Turmeric
☐Melatonin
☐Massage
☐Acupuncture
☐Progressive muscle relaxation
☐Traditional Chinese medicine
☐Qi Gong
☐Guided imagery
☐Hypnosis
☐Coenzyme Q10
☐Fish oil/omega-3 fatty acids
☐Ginseng
☐Green tea
☐Probiotics
☐Meditation
☐Therapeutic touch
☐Guidance Therapy (i.e. counseling, religion, prayer)
☐Cranial sacral therapy
☐Breathing exercises
☐Aromatherapy
☐Tai Chi
☐Cranberry (pills, capsules)
☐Garlic supplements
☐Glucosamine
☐Medicinal marijuana
☐Chiropractic manipulation
☐Yoga
☐Biofeedback
☐Laughter therapy
☐Mindfulness based stress reduction
☐Reiki
☐Homeopathy

☐Other: Please specify: _____

D) Since beginning the complementary approach, the overall quality of my life is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

E) Since beginning the complementary approach, my **hot flashes** are:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

F) Since beginning the complementary approach, my emotional state is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

G) Were you satisfied with the effect this treatment had on your **hot flashes**?

☐Yes ☐No

9) Do you have **sleeping disturbances**? ☐Yes ☐No

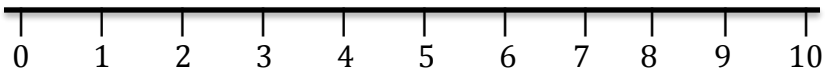
If yes, select all that apply

☐Sleeping too much ☐Difficulty falling asleep
☐Insomnia ☐Difficulty staying asleep

Other: Please specify _____

If no, continue to question 10.

If yes, on a scale of 1-10, 10 being the worst how would you rate **sleeping disturbances**?



A) How long have you had **sleeping disturbances**?

☐less than 1 month
☐1-2 months
☐3-5 months
☐6-11 months
☐1-4 years
☐5-9 years
☐greater than 10 years

B) How do you manage your **sleeping disturbances**?

☐Medical management like prescription medications
If yes, please specify which one(s) _____

☐Do not treat

☐Other: Please specify _____

☐Complementary approach (if selected please answer questions below)

C) What complementary approaches do you use to treat your **sleeping disturbances**? (select all that apply)

☐Multivitamin	☐Coenzyme Q10	☐Cranberry (pills, capsules)
☐Echinacea	☐Fish oil/omega-3 fatty acids	☐Garlic supplements
☐Ginkgo biloba	☐Ginseng	☐Glucosamine
☐ Turmeric	☐Green tea	☐Medicinal marijuana
☐Melatonin	☐Probiotics	☐Chiropractic manipulation
☐Massage	☐Meditation	☐Yoga
☐Acupuncture	☐Therapeutic touch	☐Biofeedback
☐Progressive muscle relaxation	☐Guidance Therapy (i.e. counseling, religion, prayer)	☐Laughter therapy
☐Traditional Chinese medicine	☐Cranial sacral therapy	☐Mindfulness based stress reduction
☐Qi Gong	☐Breathing exercises	☐Reiki
☐Guided imagery	☐Aromatherapy	☐Homeopathy
☐Hypnosis	☐Tai Chi	

☐Other: Please specify: _____

D) Since beginning the complementary approach, the overall quality of my life is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

E) Since beginning the complementary approach, my **sleeping disturbances** are:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

F) Since beginning the complementary approach, my emotional state is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

G) Were you satisfied with the effect this treatment had on your **sleeping disturbances**?

☐Yes ☐No

10) Do you have **any other problems you are using complementary approaches for?** ☐ Yes ☐No

Please specify _____

If yes, on a scale of 1-10, 10 being the worst how would you rate your **problem**?

A) How long have you had **your problem**?

☐less than 1 month
☐1-2 months
☐3-5 months
☐6-11 months
☐1-4 years
☐5-9 years
☐greater than 10 years

B) How do you manage your **problem**?

☐Medical management like prescription medications
If yes, please specify which one(s) _____

☐Do not treat

☐Other: Please specify _____

☐Complementary approach (if selected please answer questions below)

C) What complementary approaches do you use to treat your **problem?** (select all that apply)

☐Multivitamin
☐Echinacea
☐Ginkgo biloba
☐ Turmeric
☐Melatonin
☐Massage
☐Acupuncture
☐Progressive muscle relaxation
☐Traditional Chinese medicine
☐Qi Gong
☐Guided imagery
☐Hypnosis
☐Coenzyme Q10
☐Fish oil/omega-3 fatty acids
☐Ginseng
☐Green tea
☐Probiotics
☐Meditation
☐Therapeutic touch
☐Guidance Therapy (i.e. counseling, religion, prayer)
☐Cranial sacral therapy
☐Breathing exercises
☐Aromatherapy
☐Tai Chi
☐Cranberry (pills, capsules)
☐Garlic supplements
☐Glucosamine
☐Medicinal marijuana
☐Chiropractic manipulation
☐Yoga
☐Biofeedback
☐Laughter therapy
☐Mindfulness based stress reduction
☐Reiki
☐Homeopathy
☐Other: Please specify: _____

D) Since beginning the complementary approach, the overall quality of my life is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

E) Since beginning the complementary approach, my **problem** is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

F) Since beginning the complementary approach, my emotional state is:

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

G) Were you satisfied with the effect this treatment had on your **problem**?

☐Yes ☐No

11) On average how would you describe your health?

Excellent	Very Good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

12) On average, what is your usual level of physical activity?

☐Sedentary (no physical activity that raises your heart rate)

☐Slightly active (about 30 minutes a week of activity that raises your heart rate)

☐Moderately active (45-60 minutes a week of activity that raises your hear rate)

☐Highly active (over 60 minutes a week of activity that raises your heart rate)

11) Where did you get information about the complementary approaches you use? (select all that apply)

☐Primary treating physician
☐ Integrative Medicine physician
☐Naturopathic physician
☐Hematologist/Oncologist
☐At your local health food store
☐Certified life or wellness coach
☐ Nurse
☐Registered dietician
☐Online
☐Integrative Health provider (i.e. acupuncturist, massage therapist)
☐Television
☐Friends or family

☐Other: Please specify: _____

12) Which helped you to decide to use the complementary approaches you chose? (select all that apply)

☐Primary treating physician
☐ Integrative Medicine physician
☐Naturopathic physician
☐Hematologist/Oncologist
☐At your local health food store
☐Certified life or wellness coach
☐ Nurse
☐Registered dietician
☐Online
☐Integrative Health provider (i.e. acupuncturist, massage therapist)
☐Television
☐Friends or family

☐Other: Please specify: _____

13) Do you share your complementary approach usage with your primary medical providers?

☐Yes ☐No

14) Do you share your complementary approach usage with your specialty medical providers (i.e. heart doctor, cancer doctor)? ☐Yes ☐No

If yes, please select:

☐Hematologist/Oncologist ☐Cardiologist (heart doctor) ☐Surgeon (cancer doctor)

☐Neurologist ☐Transplant doctor

☐Other: Please specify _____

14) How much do you spend per month on Integrative Healthcare?_____

IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this document to the protocol section.

Modification: To modify this document after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points , save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

General Study Information

Principal Investigator: Noël Arring, DNP, RN, OCN

Study Title: Integrative Health and Reasons for Using Complementary Interventions

Protocol version number and date: V1 5.18.17

Research Question and Aims

Hypothesis:

Aims, purpose, or objectives:

Aim 1: Determine which complementary approaches are being used and why in patients who sought IH consults.

Aim 2: Explore the relationship between reported symptoms, complementary approaches, and participant demographics.

H2a: Participants with prolonged or chronic symptom (greater than 12 weeks) [1] will report using more than 1 complementary intervention.

Aim 3: Assess resources utilized to make decisions to use complementary approaches.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc.*):

More than 60% of cancer survivors report using integrative health approaches [2, 3]. Integrative health is defined as incorporating complementary or non-western healthcare interventions with traditional western or mainstream approaches [4]. Complementary health interventions include natural products like herbs and mind and body practices like yoga [4]. Cancer patients are using complementary health interventions; however, they are not likely to report this to their cancer teams [5, 6]. Furthermore, there is evidence that demonstrates that they are seeking information about these interventions from potentially unreliable sources [7]. This leads to a dynamic where cancer patients can unwittingly be taking complementary interventions, like St. Johns Wart, which can interfere with their cancer treatments.

Current evidence on why cancer patients seek Integrative Health consults is limited. Many studies do not discuss which complementary interventions patients are using and/or why the specific interventions are being used [8-11]. Often studies of Integrative Health consults do not assess why patients sought consultation and/or why they were referred for consultation [12, 13]. When patients' reasons were assessed, often they were reported in broad categories like physical symptoms [11, 14]. The current evidence highlights a gap in knowledge related to why patients who seek an Integrative Health consults are using complementary interventions. It is critical to understand what complementary interventions cancer patients are seeking so Integrative Health providers can appropriately provide education and resources to meet these needs. Furthermore, identifying why cancer patients are seeking complementary interventions can aid cancer care providers so they can guide patients to trusted resources and address any concerns of compatibility with their cancer treatment. The purpose of this study is to inform Integrative Health providers about the services that are being sought and to help inform our treatment teams so they can guide patients to appropriate resources.

Theoretical Framework

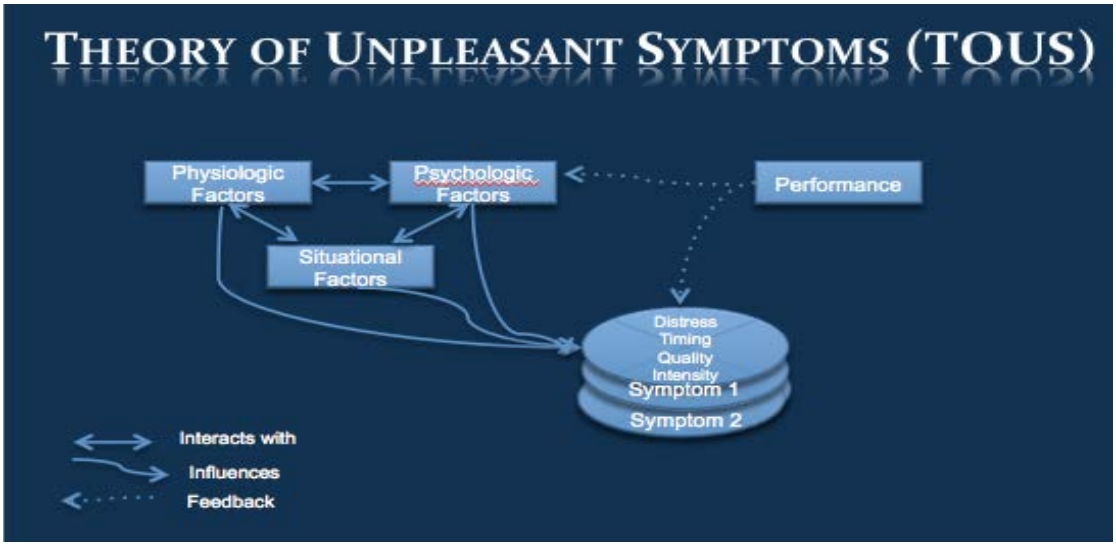


Figure 1: Theory of Unpleasant Symptoms

This research study is grounded in the Theory of Unpleasant Symptoms (TOUS) (Figure 1) [15]. TOUS has three key concepts: symptom, influencing factors and performance outcomes [15]. Influencing factors in TOUS include physiological factors, psychological factors (mood and cognitive variables) and situational factors (environment, social economic standing, social support, culture) that can impact the symptom experience [15]. In this study, we will be assessing the relationship between physiologic factors (i.e. diagnosis, medications, complementary interventions), psychologic factors (i.e. anxiety level), situational factors (i.e. material status, payer source, physician referral), performance (i.e. overall health and physical activity) and reported symptoms.

Study Design and Methods

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:

This is a prospective descriptive cross-section study, which will use the Integrative Health Symptom and Complementary Interventions Inventory. The study inventory will be sent via postal mail to potential participants with the study contact letter and HIPAA form with a prepaid

return envelope. The inventory is estimated to take less than 10 minutes to complete. If after 10 days the study materials have not been returned a study team member, who is a Mayo employee, will call potential participants who meet study inclusion criteria using the Enrollment into the study phone script to request their participation. If a potential participant agrees to participate then the research team member will attain verbal consent and remind participants to send in their signed HIPAA forms. If unsuccessful at reaching potential participant via the phone the study team will try to reach the participant via the phone 2 additional times due to the expected travel of this population during the study period. If participants respond to the survey, but does not return the HIPAA form the HIPAA form letter along with 2 additional copies of the HIPAA form will be mailed to participants. If the HIPAA form is not returned within 10 days of being mailed a study team member, who is a Mayo Clinic employee, will call using the telephone script for Following Up on a Returned Survey without a HIPAA Form.

Integrative Health Symptom and Complementary Interventions Inventory is a study team developed questionnaire, which has under gone content validity. It leverages Visual Analogue Scales for symptom assessment which has been shown to be reliable measure of symptoms [16, 17] and the clinically relevant global assessment of change [18].

Additionally already collected data from IRB# 17-004274 will be utilized to capture additional patient data.

All materials related to this project will be maintained on a secured server, RedCap and/or locked file cabinet. Only Limited datasets will be shared with external collaborators via secured/encrypted file transfers.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

Noël M. Arring, DNP, RN, OCN, is the Manager of Nursing Research, Department of Nursing at Mayo Clinic, Arizona. She received her DNP from the University of Massachusetts, Amherst, in Public Health Nurse Leadership and is pursuing a PhD from Oregon Health & Science University.

Lillian Nail, RN, PhD, FAAN, Rawlinson Distinguished Professor & Senior Scientist, School of Nursing and Member, OHSU Cancer Institute, Oregon Health & Science University is the chair of Dr. Arring's PhD committee and will mentor her through this project.

☐ (1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *When checked, describe in detail the research procedures or activities that will be conducted by Mayo Clinic study staff.*

☐ (1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 930

Subject population (children, adults, groups): Adults

Inclusion Criteria: patient who sought Integrative Medicine Consults at Mayo Clinic, Arizona

Exclusion Criteria: Patients who sought Integrative Medicine Consults in Rochester or Florida.

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☐ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☐ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo,

ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☒ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*.

_____

Biospecimens – Categories 2 and 3

(2) Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.)

_____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.)

_____

(3) Prospective collection of biological specimens other than blood:

_____

Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range: January 1, 2013- May 22, 2017

Check all that apply (data includes medical records, images, specimens).

☐ (5a) Only data that exists before the IRB submission date will be collected.

☐ (5b) The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☒ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol.*

Enter one IRB number per line, add more lines as needed

☒ Data ☐ Specimens ☐ Data & Specimens IRB# 17-004274

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff. **External** refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name		
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	X	X
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	X	X
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes	X	
Phone or fax numbers		
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☐ None

Data Analysis

Power analyses and study endpoints are not required for minimal risk research, pilot or feasibility studies.

☐ No statistical information. *If checked, please explain*:

Power Statement:

Data Analysis Plan:

The data will be summarized by the descriptive statistics (mean, standard deviation, median, percentage and frequency). The demographic and clinical characteristics of the two study groups (cancer vs. other) will be compared by the two-sample t-test or Chi-square test. The test of normality on the continuous variables will be performed, and the non-parametric test will be applied if there is evidence of non-normality. Logistic regression modeling of reasons for using IH interventions will be applied to evaluate possible factors associated with IH usage. Both univariate and multivariable analysis will be performed.

Endpoints
Primary:
Secondary:

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