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A Systematic Review of Spiritually Based Interventions and Psychoneuroimmunological Outcomes in Breast Cancer Survivorship

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Abstract

Objective. This is a review of spiritually based interventions (eg, mindfulness-based stress reduction) that utilized psychoneuroimmunological (PNI) outcome measures in breast cancer survivors. Specifically, this review sought to examine the evidence regarding relationships between spiritually based interventions, psychosocial-spiritual outcomes, and biomarker outcomes in breast cancer survivors. *Methods*. A systematic search of 9 online databases was conducted for articles of original research, peer-reviewed, randomized and nonrandomized control trials from 2005-2015. Data were extracted in order to answer selected questions regarding relationships between psychosocial-spiritual and physiological measures utilized in spiritually based interventions. Implications for future spiritually based interventions in breast cancer survivorship are discussed. *Results*. Twenty-two articles were reviewed. Cortisol was the most common PNI biomarker outcome studied. Compared with control groups, intervention groups demonstrated positive mental health outcomes and improved or stable neuroendocrine-immune profiles, although limitations exist. Design methods have improved with regard to increased use of comparison groups compared with previous reviews. There are few spiritually based interventions that specifically measure religious or spiritual constructs. Similarly, there are few existing studies that utilize standardized religious or spiritual measures with PNI outcome measures. Findings suggest that a body of knowledge now exists in support of interventions with mindfulness-breathing-stretching components; furthermore, these interventions appear to offer potential improvement or stabilization of neuroendocrine-immune activity in breast cancer survivors compared to control groups. *Conclusion*. From a PNI perspective, future spiritually based interventions should include standardized measures of religiousness and spirituality in order to understand relationships between and among religiousness, spirituality, and neuroendocrine-immune outcomes. Future research should now focus on determining the minimum dose and duration needed to improve or stabilize neuroendocrine-immune function, as well as diverse setting needs, including home-based practice for survivors who are too ill to travel to group sessions or lack economic resources.

Keywords

breast cancer, interventions, oncology, psychoneuroimmunology, religious, review, spirituality

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Introduction

Despite the vast amount of research that has been conducted in breast cancer, the extended survivorship trajectory for breast cancer survivors remains unpredictable and complicated by breast cancer recurrence or treatment-related physical effects (ie, secondary lymphedema).[1] The incidence of secondary lymphedema in breast cancer survivors ranges from 6% to 94% and is associated with a lifetime risk.[2] Because of these posttreatment late effects, as many as 30% of breast cancer survivors have reported physical function decline, poorer mental health, social difficulties, and a poorer quality of life.[3-5] When considering interventions appropriate for symptom management in breast cancer

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survivorship, it is recognized that breast cancer survivors are now an aging population with multifaceted problems beyond physiological symptoms, including economic, psychosocial, and spiritual stress.[6-8]

According to Pew Forum Research data, 92% of Americans believe in God or a higher power and 56% report religion is very important in their lives.[9] Previous research has shown that older adults rely on religious practices (ie, prayer) while seeking treatment for chronic symptoms.[10] To cope with chronic physical and psychological symptoms, studies have shown that 80% to 90% of breast cancer survivors report using spiritually based complementary and alternative medicine (CAM) therapies (eg, mindfulness, meditation, yoga, Tai Chi, Qigong, guided imagery, and affirmations) to manage long-term breast cancer treatment–related symptoms.[11-15]

Religious coping has shown an association with spiritual growth, better mental health, and positive outcomes following stressful life events.[16,17] Studies of chronically ill populations, including breast cancer survivors, have reported that religious and spiritual factors (eg, relationship with God/higher power, prayer, and congregational/social support) are used for comfort and coping with cancer survivorship experiences.[10,18,19] In the past 10 years, a number of CAM interventions have been conducted in breast cancer populations to examine changes in psychological and physiological outcomes in those receiving the interventions.[20,21] Although many of these CAM interventions (eg, mindfulness-based interventions and Qigong) had a spiritual component, the relationships between the spiritual basis of these interventions and health outcomes have remained unclear. Moreover, previous data suggest that religious and spiritual variables influence mental health outcomes; however, a gap exists in the psychoneuroimmunological (PNI) research regarding the evidence linking religious and spiritual variables and physiological health outcomes.

The purpose of this article is to review PNI-based interventions for health outcomes associated with religious and spiritually based interventions in breast cancer survivors. Despite numerous CAM interventions reported in the breast cancer literature, there remain few reported findings regarding the relationships between religious and spiritual variables and neuroimmune function changes associated with these religious and spiritual interventions. This article is divided into 2 sections: (1) An overview of the relationships between and among religious and spiritual variables related to health outcomes and (2) a systematic review of spiritually based interventions with PNI health outcomes in breast cancer survivors.

Literature Review

Religious and Spiritual Variables Related to Health

Many terms have been used to describe spirituality for health research purposes including meaning, purpose in life, the mystical, the numinous, hope, value, optimism, emotional connectedness, transcendence, gratitude, and forgiveness.[22-24] Religious and spirituality researchers have conceptualized spirituality based on their own cultural and philosophical traditions that may have either a religious or a secular basis.[25,26] Consequently, the constructs of religiousness and spirituality have been difficult to clarify for health research purposes due to the lack of agreement among contemporary researchers who have viewed the 2 constructs as complex with overlapping aspects (i.e. searching for the sacred).[27-29]

In general, *religion* refers to denomination affiliation, religious identity, public religious practice (eg, attendance and group prayer) and specific beliefs in religious tenets (eg, afterlife).[22,30] *Religious practices* are culturally based practices such as prayer, church attendance, meditation, or reading religious texts. *Spirituality* is viewed as a subjective experience of the sacred and refers to an emotional connectedness or relationship with God or the transcendent beyond the self.[31-33] Additionally, recent data suggest that spirituality may be a dimension of personality.[23,24]

Self-transcendence refers to the ability to stand outside one's immediate sense of time and place to view life from a larger perspective.[24,34] Spiritual self-transcendence is further characterized by recognition that a synchronicity to life exists and fosters a sense of commitment to helping others.[35] Three common themes have been represented in the literature regarding spirituality: a relationship with the transcendent and to others, the existence of a higher being, and an appreciation for the greater world.[36]

Although it has been generally agreed that religion and spirituality are separate constructs, the literature discusses these two constructs as interchangeable; furthermore, religious and spiritual variables have often been denoted as "RS." Extending from this trend, religious and spirituality research now reflects measures with religious and spiritual construct overlap. It is recognized that there remains a lack of a "gold standard" definition providing separation of religious and spiritual constructs for health care research purposes.[25,37] Therefore, for purposes of this discussion and where appropriate, religious and spiritual variables will hereafter be denoted as "RS."

Spiritual Experiences, Religious Practices, and Congregational Support. Findings from a recent factor analysis of religious measures, spiritual measures, and health outcomes suggested that 3 dimensions represent the religious and spiritual variables related to health outcomes: spiritual experiences (ie, emotional connectedness to the transcendent), religious practices (ie, behaviors), and congregational support (ie, social support).[27] Moreover, religious and spiritual dimensions are viewed as separate constructs that can be distinguished as positive and negative (eg, loving God/higher power vs a punishing God/higher power and positive/negative congregational support).[27,38,39] Positive

spiritual experiences are associated with better physical health in individuals with chronic disabilities, and negative spiritual experiences are associated with worse health. Among religious and spiritual variables, forgiveness appears to be a greater predictor of health outcomes.[23]

RS Variables and Health Outcomes in Breast Cancer

Observation of breast cancer survivors (n = 763) over 10 years demonstrated that although a diagnosis of cancer was associated with a sense of vulnerability, there was a positive change in survivor participants' worldview and perceptions of life's meaning that persisted even 10 years postdiagnosis.[40] A growing consensus in the literature has suggested that the presence of a spiritual dimension is an indicator of positive adaptation to cancer treatment and coping with cancer.[41,42] Data have also shown that social isolation among women with newly diagnosed breast cancer was associated with higher mortality risk.[43] Breast cancer survivors who reported positive perceptions of social support (eg, emotional reassurance, personal assistance, and advice) also demonstrated positive immune system benefits and decreased psychological distress.[44,45]

Data from breast cancer populations have suggested that increased stress correlates with decreased immune function (ie, natural killer [NK] cell activity and T cell response), resulting in a decreased ability to destroy cancerous tumors.[46] Data have also shown that emotional distress experienced by breast cancer survivors correlated with impaired NK cell and cytokine function and further suggested that emotional distress negatively influenced the immune profile of breast cancer survivor participants.[47] Pilot data from mindfulness-based interventions have shown that mindfulness exerted a positive influence on NK cell cytotoxicity, cytokine function,[48-50] and cortisol patterns.[49,51-54] These relationships between psychosocial and RS (eg, mindfulness) variables and health outcomes in populations with immune dysregulation (ie, breast cancer) are consistent with a psychoneuroimmunological (PNI) model of health.

The PNI Model of Health

The PNI model of health seeks to explain causal relationships between and among stress, brain function (ie, mind/thoughts), psycho-social-behavioral components (eg, spirituality), and physiological components (ie, neuroendocrine-immune system interactions).[55-57] As stress influences perceptions, the resulting thought processes are then communicated from the brain to the immune system via neuroendocrine and hormonal pathways. The subsequent adaptive immune system response then manifests as a psychological or physiological symptom (ie, mental or physical illness) or health maintenance (ie, wellness).[58,59]

Psychoneuroimmunological research has established that neuroendocrine-immune function can be studied through measures of biomarker levels obtained in saliva and serum specimens. The 2 primary neuroendocrine-immune pathways associated with stress are the sympatho-adrenomedullary (SAM) axis, which includes the sympathetic nervous system (SNS); and the hypothalamic-pituitary-adrenocortical axis (HPAA).[60] Chronic stress results in dysregulation of both axes.[61] During acute stress the SAM axis activates the SNS to release norepinephrine which induces a "fight or flight" response.[62] The HPAA responds by releasing endocrine-based glucocorticoids, primarily in the form of cortisol hormone.[63] Repeated activation of the HPAA system results in increased allostatic load and has been shown to cause chronic immunosuppression associated with negative health outcomes.[61,64,65] In chronically ill populations, suppressed immune function associated with long-term stress is further associated with increased susceptibility to illness, delayed wound healing, and prolonged recovery from illness.[66] After prolonged HPAA vigilance, elevated cortisol activity becomes detrimental, as it becomes immunosuppressive and ultimately contributes to persistent immune dysregulation.[58,67]

Mindfulness-Based Interventions and Moving Meditations as Spiritually Based Interventions

Among the most commonly reported psychosocial interventions in breast cancer research literature, mindfulness-based interventions (eg, mindfulness-based stress reduction [MBSR] and mindfulness-based cognitive therapies [MBCT]) have become prolific as adjunct treatments for post–cancer treatment–related symptoms.[68,69] Traditional forms of MBSR stem from the contemplative, spiritually based Buddhist philosophy, which promotes the development of a nonjudgmental, accepting, and patient worldview and teaches relaxation through focused awareness on breathing.[48] MBSR and MBCT interventions use meditation and gentle Yoga stretching to "maintain awareness moment by moment, disengaging oneself from strong attachment to beliefs, thoughts or emotions, and thereby developing a greater sense of emotional balance or well-being."[70(p1350)] Similarly, there are other movement-meditative-breathing interventions (eg, Qigong and Tai Chi) that include encourage mindfulness and self-awareness. Since spiritual self-transcendence involves viewing life from a larger perspective beyond the self, mindfulness and meditation practices facilitate spiritual change.[24] From this perspective, interventions that encourage mindfulness, meditation, and self-awareness through breath work and movement are viewed as facilitating spiritual transformation.

Relaxation and Visualization Therapy. Relaxation and visualization therapy (RVT) involves the induction of a relaxation using mental imagery of a desired object or outcome and

includes progressive muscle relaxation, continued guided imagery, meditation, and deep breathing.[71] RVT involves imagery of peaceful scenery and focused sensory awareness on individual muscle groups. RVT has been reported to improve quality of life, mood, reduced social conformity, and enhanced emotional expression.[72,73]

Guided Imagery. Similar to RVT, guided imagery utilizes progressive relaxation of muscle groups combined with focused breathing techniques intended to calm the mind and prepare it for guided imagery.[74] Guided imagery is a consciousness-focused practice intended to increase awareness with a relaxed, open mind for the purpose of confronting a specific concern or issue. Guided imagery is viewed as a way to allow patients to participate in their own healing and has been reportedly used for healing, symptom management, promotion of positive health behaviors, and making positive life changes. Guided imagery also includes aspects involving the "unconscious mind" including intuition, emotions, feelings, memories, values, beliefs, perceptions, and goals.[75]

Tai Chi. In Western culture, Tai Chi is a moving meditation or a form of low-level exercise, which involves a sequence of fluid, graceful movements, focused breathing, posturing movement, and consciousness directed at relaxation.[76,77] However, for some traditions, Tai Chi is a Chinese martial art, a Shamanic religious ritual, an exercise, and a relaxation technique that has been in existence for at least 5000 years.[76] The practice of Tai Chi is meant to increase the participant's mind-body connection through the awareness of the body's energy and potential for self-healing, resulting in self-empowerment. The meanings of the Tai Chi movements and philosophy are conveyed using the 5 elements (ie, fire, earth, minerals, water, and wood) and seasons of the year to represent (spiritual) transformation.[77]

Yoga. Yoga is an ancient Eastern traditional mind-body practice.[78] Yoga is also considered a moving meditation and consists of breathing exercises, postures, relaxation, and meditation.[79] Yoga encourages increased self-awareness and relaxation and has been observed to alter the stress response associated with thoughts and emotions, subsequently reducing psychological distress.[79]

Qigong. Qigong, also a 5000 year-old Chinese mind-body tradition, conceptualizes health as the result of unimpeded flow of "qi" (ie, energy, spirit or life force) through "gong" (ie, achievement).[80,81] The focus of Qigong is the prevention and healing of diseases by harmonizing the mind, body, and spirit.[82] Specifically, 4 main components are involved in the stimulation and manipulation of the qi: consciousness, mindful focus on the body, breathing techniques, and specific movements.[83] Unlike other moving meditations, Qigong can be practiced internally or externally. In external Qigong practice, a Qigong master may facilitate the clearing of qi blockages or balancing of qi for an individual.[83]

Given the preceding definitions, mindfulness-based interventions, RVT, guided imagery, Tai Chi, yoga, and Qigong all suggest common themes of mindfulness, self-awareness, and self-transcendence (ie, viewing life from a larger perspective beyond the self).[24] Therefore, because these practices involve themes of spirituality and spiritual transformation, they were included in this review and are referred to as spiritually based interventions.

Summary of Previous Spiritually Based Interventions and Health Outcomes

MBSR Interventions and Health Outcomes. Early pilot studies demonstrated that MBSR improves mindfulness,[84-86] stress,[50,87] mood, and psychological distress.[49,84,88] MBSR has been shown to decrease depression and anxiety,[89-91] and rumination among breast cancer survivors.[92,93] Data have shown that MBSR improved sleep quality,[54,85] reduced fatigue,[21,54] improved quality of life,[52,92] and improved perceptions of life being more meaningful.[94] Although 2 studies have reported MBSR improves perceptions of spiritual growth in breast cancer survivors,[94,95] few studies have examined relationships between mindfulness-based practices and RS constructs (ie, positive and negative spiritual experiences, congregational support, and religious practices).

A previous meta-analysis and review revealed that the majority of early MBSR studies utilized exploratory, pilot designs, with small samples, varied intervention design, and lacked information regarding intervention therapy protocols.[96,97] A more recent meta-analysis of MBSR studies (n = 9) with psychological measures in breast cancer survivors reported that MBSR interventions had a moderate to large effect ($d = 0.76$) on mental health outcomes.[98] In a narrative review of MBSR interventions (n = 43) with PNI measures in heterogeneous cancer populations, Carlson[69] noted that strong level 1 evidence offered support that MBSR improved anxiety, quality of life, depression, stress, spiritual growth, and well-being in cancer populations. Moreover, quantitative findings suggested MBSR improved PNI biomarker levels in cancer survivors (ie, decreased inflammatory cytokines and cortisol levels), but relationships remain unclear and the overall evidence was weak.[69]

Subnis et al[99] conducted a systematic review of randomized control trials (RCTs), nonrandomized control trials (non-RCTs), and pretest/posttest designs (n = 24) among heterogeneous cancer populations who received cognitive-behavioral interventions or spiritually based interventions (eg, MBSR, yoga) and the associated PNI-based outcome measures. Analyses revealed that most of the psychosocial measures were measures of negative psychological states,

with mood as the most common psychosocial measure of interest (11 of 24 studies) and cortisol as the most common biomarker of interest (11 of 24 studies). Moreover, effectiveness of interventions on PNI outcomes among cancer patients could not be determined due to lack of longitudinal designs, small sample sizes, wide variation in intervention protocols, and lack of adherence data. Finally, the review by Subnis et al[99] was one of the first to address the lack of biomarker measures representing the SAM (ie, SNS) response to stress. The majority of PNI studies to date have investigated only the HPAA by using cortisol as a proxy measure of chronic stress.

Qigong and Tai Chi Interventions. In a systematic review of 23 studies (RCT and non-RCT), Chan et al[100] reported that Qigong had a statistically significant effect on quality of life, symptom improvement, improved fatigue, improved well-being, and improved immune function. However, the overall quality of studies was ranked as poor in methodology, with 3 studies rated "A" and 9 studies rated as "B" (based on Oxford Centre for Evidence-Based Medicine's levels of evidence).[100,101] Moreover, half of the studies were not peer-reviewed and had numerous methodological flaws, including small sample sizes, lack of randomization designs, and disparities in intervention protocols (eg, duration, dose).[100]

In a meta-analysis by Zeng et al,[102] Qigong (n = 5) and Tai Chi (n = 8) intervention data showed that Qigong did not have a statistically significant effect on depression or anxiety; however, it was associated with improved fatigue (P = .04) and improved quality of life (P = .008). Additionally, both Qigong and Tai Chi intervention data demonstrated reduction of cortisol levels (P < .05) and offered limited, but supportive, data suggesting positive associations with improved C-reactive protein and cytokine function. Zeng et al[102] also found limitations in intervention designs and methodologies, as well as limited ability to pool data from multiple studies due to lack of heterogeneity between trials.

Specific RS Interventions. In a meta-analysis of RCTs and non-RCTs, Oh and Kim[103] examined interventions (n = 14), including protocol descriptions of religious interventions, spiritual nursing care, spiritual counseling, spiritually focused meditation, and meaning-centered psychotherapy, in heterogeneous cancer patients (n = 889). Analyses of RS intervention data revealed significant effects on spiritual well-being (d = −0.48), meaning of life (d = −0.58), depression (d = −0.62), and anxiety (d = −0.82), as well as supported associations between RS interventions and improved mental health outcomes. However, findings and conclusions were limited by a lack of physiological measures, overlap of religious and spiritual constructs, heterogeneous samples, and varied intervention protocols.[103]

Gaps in the Literature. Breast cancer survivors report perceived therapeutic benefits from using mindfulness-based (ie, spiritual) practices (ie, MBSR and yoga) to cope with posttreatment sequela, although there has been limited empirical evidence to support how spiritual practices influence physiological outcomes. A major gap in current PNI research is the limitations regarding the evidence linking objective measures of neuroendocrine-immune function (eg, biomarkers) to self-report measures of stress and RS variables (eg, religious and spiritual beliefs). The purpose of this review is to address the following questions:

1. What psychosocial and RS measures have been used in spiritually based interventions in breast cancer survivors; and what were the associated mental health outcomes?
2. What PNI outcome measures have been used in spiritually based interventions in breast cancer survivors, and what were the associated physiological biomarker outcomes?
3. What is the evidence regarding the relationships between and among spiritually based interventions, psychosocial-spiritual outcomes, and PNI-based outcomes in breast cancer survivors?
4. What are the implications for future research studies regarding spiritually based interventions, measures of RS, and PNI-based outcome measures?

Methods

Articles from 2005 through 2015 were retrieved from the following databases: PubMed, Medline, PsycInfo, PsycArticles, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Academic Search Complete, American Theological Library Association (ATLA) Religion, Educational Resources Information Center (ERIC), and Google Scholar. Additionally, a hand search of peer-reviewed journals with a PNI focus (eg, *Brain, Behavior, and Immunity* [*BBI*], *Psychoneuroendocrinology*, and *Psycho-Oncology*), an ancestry search of references from selected articles, and a personal library search were done.

Keywords

The keywords search was developed from 6 main categories with related subcategories noted in parentheses: (1) spirituality (spiritual, spirituality, spiritual beliefs, spiritual practices), (2) religious (religious, religion, religiosity, religiousness, religious beliefs, religious practices), (3) cancer (neoplasm, oncology, breast, lymphedema), (4) stress, (5) intervention (spiritual, psychosocial, spiritual healing, spiritual therapies, faith healing, CAM, psychological therapy/therapies, spiritual coping, mind-body-therapies, Qigong, group therapy, mindfulness, and (6) PNI-based measures

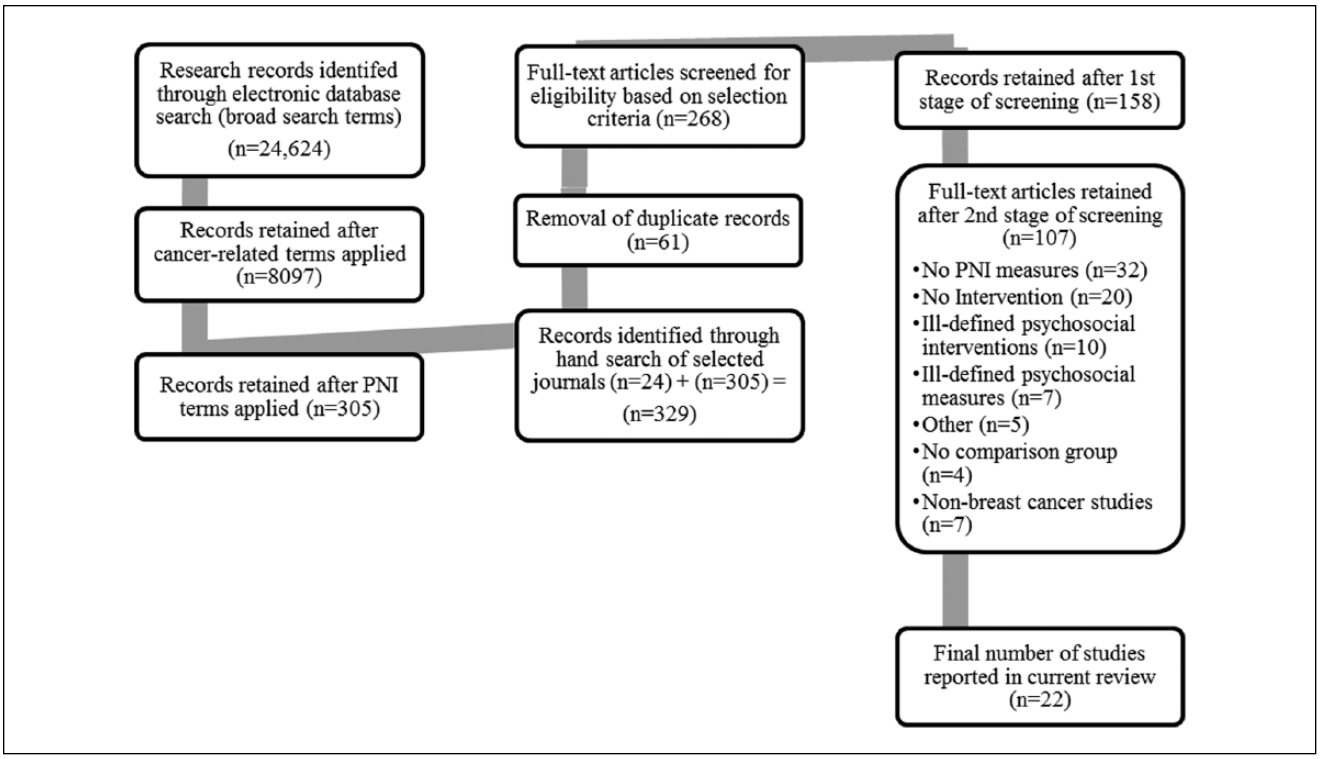

Figure 1. Flowchart of article identification, screening, and selection process.

(biomarkers, immune function, immune system, leukocyte, lymphocyte, cytokines, natural killer cell, interferon-gamma, interleukin, tumor necrosis factor- alpha, cortisol, salivary alpha-amylase, neuroendocrine, neuroimmune, hormonal, and inflammatory/inflammation).

Inclusion Criteria

The inclusion criteria included the following: original research in peer-reviewed journals, full-text available online, clearly stated descriptions of samples and methodology, randomized control trials (RCTs), nonrandomized control trials (non-RCTs), human subjects, adults, and articles available in English. The initial search yielded 268 articles. Articles were further screened in several stages. First, titles of articles and abstracts were evaluated based on the inclusion criteria, which resulted in the selection of 158 articles. Next, selected articles were further evaluated by reading the full-text which resulted in 107 articles. Finally, articles were excluded for the following reasons: lack of PNI-based measures (n = 32), lack of RS-based PNI interventions (n = 20), poorly defined or highly customized psychosocial interventions (ie, difficult to replicate based on information provided (n = 10), lack of standardized psychosocial measures (ie, subjective measures) (n = 7), small sample size (n < 10) (n = 3), healthy participant sample (n = 2), and lack of a comparison group (n = 4).

Article Selection. Figure 1 provides a flowchart of the identification, screening, and article selection process, which resulted in 22 articles original articles with RS interventions in breast cancer survivors. Article data selected for extraction and summary included (1) first author and year of publication, (2) study design, (3) cancer stage, (4) sample size of intervention and control groups, (5) type and description of interventions, (6) psychosocial measure data, (7) RS measure data, (8) PNI measures, and (9) conclusion of findings.

Results and Discussion

Studies reviewed included RCTs (n = 19) and non-RCTs (n = 3). The majority of studies were from the United States (n = 12), followed by Canada (n = 3), India (n = 2), China (n = 1), Brazil (n = 1), Taiwan (n = 1), Sweden (n = 1), and the United Kingdom (n = 1). Participant sample sizes in the research studies ranged from 28 to 271 participants. RS interventions were a majority MBSR (n = 8), followed by yoga (n = 5), cognitive based stress management (CBSM) (n = 2), guided imagery (n = 2), relaxation visualization therapy (RVT) (n = 1), mindfulness-based cancer recovery (MBCR) (n = 1), Qigong (n = 1), Tai Chi/spiritual growth group (n = 1), and body-mind-spirit (n = 1). Interventions were described as lasting from 5 to 37 weeks in duration. The majority of research designs used a single intervention

Table 1. Spiritually Based Interventions and Psychosocial-Spiritual Outcomes in Breast Cancer Survivors.

Study Number (See Table 3)	Spiritually Based Interventions	Psychosocial-Spiritual Outcomes (↓ or ↑)[a]
1,4, 6, 8, 15, 18	CBSM, MBSR, Qigong, RVT, Yoga	↓ Depression
1, 4, 6, 8, 12	CBSM, MBSR, RVT, Yoga	↓ Anxiety
2, 4, 14, 15, 18, 19, 20	MBCR, MBSR, Qigong, Yoga	↑ Quality of life/vitality/vigor
4	Yoga	↓ Distress
4, 17	MBSR, Yoga	↓ Symptoms
2	MBSR	↑ Coping
5, 7	CBSM	↑ Relaxation
1, 6, 8, 12, 14, 18	CBSM, MBCR, MBSR,RVT, Yoga	↓ Stress
16	Tai Chi	↑ Stress
9, 12, 13	MBSR	↑ Mindfulness
11	BMS	↑ Spiritual growth/spiritual well-being
13	MBSR	↓ Rumination
14	MBCR	↑ Social support
15, 17, 18, 19, 20	MBSR, Qigong, Stretching, Yoga	↓ Fatigue
9, 14	MBCR, MBSR	↑ Mood
17	MBSR	↑ Cognitive function (postchemotherapy)

Abbreviations: CBSM, cognitive-based stress management; MBCR, mindfulness-based cancer recovery; MBSR, mindfulness-based stress reduction; RVT, relaxation visualization therapy; BMS, body-mind-spirit.
[a]↓ indicates decreased and ↑ indicates increased.

group with a wait list or usual care control group (n = 13). All studies utilized physiological measures, with cortisol being the most common biomarker measure (n = 12; 54.5%).

Question 1: What psychosocial and RS measures have been used in spiritually based interventions in breast cancer survivors; and what were the associated health outcomes?

The majority of studies (n = 20) included standardized, self-report psychosocial measures, with an average of 3 to 4 psychosocial instruments administered per study. The most common self-report psychosocial measures included depression (n = 8), stress (n = 7), quality of life (n = 7), anxiety (n = 6), fatigue (n = 5), mindfulness (n = 4), and mood (n = 2). Importantly, only 1 study examined specific RS measures: spiritual growth (ie, meaning of life).[104] Because many of the studies reviewed have psychosocial (subjective) and PNI (objective) outcomes, the findings are separated and presented in 2 tables to illustrate the relationships between subjective and objective variables. Table 1 provides a brief summary of the statistically significant psychosocial-spiritual findings associated with each spiritually based intervention, while Table 2 focuses on the respective PNI outcomes associated with each spiritually based intervention. Both Tables 1 and 2 utilize upward- or downward-pointing arrows, respectively, to illustrate the reported direct or inverse relationships between the variables. Additionally, the number of studies in this review are noted in Tables 1 and 2 by their corresponding order of presentation in Table 3 where highlights of the reviewed studies are provided.

The majority of spiritually based intervention studies demonstrated positive changes in one or more of the psychosocial-spiritual outcome measures examined. The most common positive psychosocial outcomes associated with spiritually based interventions were observed in measures of quality of life, depression, stress, anxiety, fatigue, and mood. The exception was a study by Robins et al[77] in which measures of stress at study conclusion demonstrated an overall decrease in perceived stress among Tai Chi, spiritual intervention, and control groups compared with preintervention measures, however, the Tai Chi group continued to report more perceived stress compared to those in the spiritual intervention group and control group at postintervention. Of note, all participants, including the control group, were receiving adjuvant chemotherapy. Robins et al[77] suggested that greater perceived stress among the Tai Chi participants may have indicated psychological distress that occurred due to increased self-awareness or "centering" secondary to the interventions. Moreover, the authors noted that although Tai Chi encourages mindfulness, an unintended initial effect of increased mindfulness may be temporary depression-like symptoms (ie, psychological distress) that occur during stressful life events (eg, post–cancer chemotherapy treatment sequela). Additionally, Robins et al[77] noted that psychological distress may have been secondary to chemotherapy sequela (eg, fatigue) and/or secondary to learning Tai Chi movement; however, these potential confounders were not measured. Finally, 2 studies examined relationships between mindfulness-based

Table 2. RS Interventions and Biomarker Outcomes in Breast Cancer Survivors.

Study Number (See Table 3)	RS Intervention	Biomarker Outcomes (↓, ↑, or Stable)[a]
18	Yoga	↓ Interleukin (IL)-1
7, 20	GI, Yoga	↓ IL-1β
3, 6	GI, CBSM	↑ (IL)-2
2, 17	MBSR	↓ IL-4
6	CBSM	↑ IL-4
2, 20	MBSR, Yoga	↓ IL-6
2	MBSR	↓ IL-10
2, 3, 7	GI, MBSR	↑Natural killer (NK) cell activity
4	Yoga	↓ Immunoglobulin A (IgA)
4	Yoga	↑ CD56 %
2, 5, 6, 8, 9[b], 11, 14, 19	BMS, CBSM, MBCR, MBSR,Yoga	↓ Cortisol
1, 12, 15, 18	MBSR, Qigong, RVT, Yoga	Stable or no change in cortisol
18, 20	Yoga	Stable or ↓ tumor necrosis factor–α (TNF-α)
9, 13	MBSR	↓ Blood pressure
9	MBSR	↓ Pulse
9	MBSR	↓ Respirations
2, 6, 10, 17	CBSM, MBSR	↑ Lymphocyte subsets; T cells, Th1/Th2
7, 17	GI, MBSR	↑ CD4+/CD8+
2, 6, 17	CBSM, MBSR	↑ Interferon-γ (IFN-γ)
21, 22	MBSR	Stable (preserved) telomere length
17	MBSR	Stable/no change in CD4+ T lymphocytes
17	MBSR	Stable/no change CD3+ subsets (T1/T2)

Abbreviations: RS, religious and spiritual; GI, guided imagery; CBSM, cognitive-based stress management; MBSR, mindfulness-based stress reduction; BMS, body-mind-spirit; RVT, relaxation/visualization therapy; MBCR, mindfulness-based cancer recovery.
[a]↓ indicates decreased and ↑ indicates increased.
[b]Decreased cortisol not sustained at 1 month follow-up.

interventions, psychosocial measures (eg, mood and stress), and telomere variables; however, the psychosocial relationships very small and were not statistically significant.[117,118]

Question 2: What PNI outcome measures have been used in spiritually based interventions in breast cancer survivors; and what were the associated physiological biomarker outcomes?

Table 2 provides an overview of the spiritually based intervention studies with PNI-based biomarker outcomes. In this review, cortisol is the most commonly studied biomarker outcome studied in the spiritually based interventions. An interesting finding was that among the cortisol studies reviewed, 8 studies reported positive changes in cortisol activity (ie, decreased levels or healthier diurnal slope patterns compared to control groups), while 4 studies reported "no change" or "stable" cortisol levels compared with control groups. These can be somewhat mixed findings to interpret, as "no change" in cortisol levels is occasionally noted in studies in which elevated levels of cortisol are observed in the control group. These findings suggested that in some instances, "no change" or "stable" cortisol levels after a spiritually based intervention may reflect a positive buffering effect associated with the intervention. Additionally, some cortisol studies reported significant changes immediately postintervention, but not sustained at 1-month,[109] 3-month,[110] and 6-month follow-up.[111]

Two biomarkers of emerging PNI interest, telomere length and telomere activity are noteworthy for this discussion. Recent data suggest that shorter telomere length is associated with poorer outcomes in chronic lymphocytic leukemia populations[119] and may be predictive or poor prognosis in cancer patients.[120] In this review, Carlson et al[118] reported that MBSR appeared to preserve telomere length in breast cancer survivors in the intervention group, while telomere length in the control group was shortened. Interestingly, Lengacher et al[117] did not report preserved telomere length among MBSR breast cancer survivor participants; instead, their study demonstrated that those receiving the MBSR intervention had increased telomerase activity. Of note, duration of these MBSR interventions ranged from 6 to 8 weeks. These studies offer significant direction to PNI research as both provide early data regarding the potential relationship between mindfulness-based interventions and telomere length/telomere activity in breast cancer populations. Although more empirical data are required, these studies are some of the first studies to

Table 3. RS Interventions With PNI Measures in Breast Cancer Survivors.

No.	Study (First Author, Year)	Design	Cancer Stage	Intervention Group (IG) (n) vs Control Group (CG) (n)	Intervention Duration	Psychosocial and RS Measures	Objective (PNI) Measures	Key Health Outcomes
1	Nunes (2007)[71]	RCT	I-II	Relaxation/visualization (IG) (RVT)* (n = 20) vs CG: Assessment only* (n = 14) *All participants undergoing concurrent radiotherapy	24 consecutive days, 30-min sessions	Stress, Anxiety, Depression (ISSL, STAI, BAI, BDI)	Cortisol	RVT improved depression and anxiety scores ($P < .05$). Change in anxiety negatively correlated with cortisol ($r = -0.38$). RVT had no effect on cortisol levels
2	Witek-Janusek (2008)[105]	Non-RCT	0-II	MBSR (IG) (n = 38) vs CG: Assessment only (n = 28)	8 weeks; 150 min/wk	Quality of Life, Coping, Mindfulness (QOLI-cv3, JCS, MAAS)	Lymphocytes, NKCA, Cytokines (Interleukin [IL])-2, IL-4, IL-6, IL-10, and interferon-gamma (IFN-γ), cortisol	MBSR group had lower levels of NKCA, IL-4, IL-6, IFN-γ (all $P < .04$) compared with CG. cortisol was lower in MBSR group ($P = .002$) than CG. No effect on mindfulness ($P > .05$). Treatment group reestablished positive immune function while control group had continued immune dysregulation
3	Lengacher (2008)[74]	RCT	0-II	Guided imagery (IG) (n = 15) vs Usual care CG (n = 13)	6-7 weeks (2-3 weeks preop through 4 weeks postop)	None	Natural killer (NK) cells, cytokine (IL-2)	Guided imagery positively influenced NK cell cytotoxicity after IL-2 activation at 4 weeks postoperative compared with CG ($P < .05$)
4	Rao (2008)[79]	RCT	II-III	Yoga (IG) (n = 33) vs Supportive therapy and exercise CG (n = 36)	4 weeks	(Anxiety, Depression, Function) (STAI, BDI, FLIC)	T-lymphocyte subsets, CD4%, CD8%, NK cells, and immunoglobulin (IgA, IgG, IgM)	Yoga group demonstrated decreased anxiety ($P = .04$), depression ($P = .01$), decreased symptom severity ($P = .01$), decreased distress ($P < .01$) and improved QOL ($P = .01$) compared with CG. Less immune dysfunction was observed in yoga group (decreased CD56%, $P = .02$) and (decreased IgA, $P = .001$) compared with CG
5	Phillips (2008)[106]	RCT	0-III	CBSM (IG) (n = 65) vs 1-day education CG (n = 63)	10 weeks; repeat measures over 12 months	Current Status (MOCS-Relaxation)	Cortisol	Greater reductions in cortisol levels across 12 months in CBSM compared with CG, although effect was small ($d = 0.20$).
6	Antoni (2009)[107]	RCT	0-III	CBSM (IG) (n = 65) vs Usual care CG: 1-day education (n = 63)	10 weeks	Stress, Anxiety & Depression, & Negative Mood (IES, HADS, ABS)	Cortisol, lymphocyte subsets, cytokines (IL-2, IFN-γ, IL-4)	CBSM had improved cortisol patterns ($P < .01$), improved IL-2 ($P < .05$), and improved IFN-γ ($P < .01$) function compared with CG during the first 6 months. Results suggest CBSM group may have experienced a buffering effect of adjuvant therapy compared with the CG. Improved trends observed in psychosocial measures; however, no significant effects observed between changes in psychosocial measures and biomarker measures

(continued)

Table 3. (continued)

No.	Study (First Author, Year)	Design	Cancer Stage	Intervention Group (IG) (n) vs Control Group (CG) (n)	Intervention Duration	Psychosocial and RS Measures	Objective (PNI) Measures	Key Health Outcomes
7	Eremin (2009)[72]	RCT	II-IV	Relaxation and guided imagery (IG) (n = 40) vs Standard care CG (n = 40)	37 weeks	None	T-cell subsets and lymphokine activated killer cells, B lymphocytes and monocytes; cytokines IL-1beta (1β), IL-2, IL-4 and IL- 6 and TNF-α	At 8 weeks, significant correlations observed between imaging ratings and natural killer cell activity (r = 0.319, P = .02). Relaxation frequency (r = 0.308, P = .018) and imagery ratings (r = 0.308, P = .019) correlated significantly with blood IL-1β, CD4+, and CD8+ levels.
8	Vadiraja (2009)[108]	RCT	I-III	Yoga (IG) (n = 44)* vs Supportive therapy CG* (n = 44) *All participants undergoing concurrent radiotherapy	6 weeks (3) 1-hour sessions per week	Anxiety & Depression, Stress (HADS, PSS)	Cortisol	Positive correlations between decreased AM cortisol levels and decreased anxiety (Cohen's f = 0.31), depression (f = 0.31), and stress (f = 0.36) in yoga group compared with CG
9	Matchim (2010)[109]	Non-RCT	0-II	MBSR (IG) (n = 15) vs Wait list CG (n = 17)	8 weeks 90 min/wk Repeat measures at 1 month	Mood, Stress, Mindfulness (POMS, C-SOSI, FFMQ)	Salivary cortisol, blood pressure (BP), pulse, and respirations	Increased mindfulness decreased BP, pulse, and respirations observed in MBSR compared with CG (P = .05 to P = .001). Initial decrease in AM cortisol within MBSR group was statistically significant (P < .05), but was not sustained at 1-month follow-up
10	Lengacher (2013)[50]	RCT	0-III	MBSR (IG) (n = 42) vs Usual care CG (n = 40)	6 weeks 2 h/wk Repeat measures at 12 weeks	None	Lymphocyte subsets, T helper 1 and 2 cells (Th1/Th2), NK cells, IFN-γ, IL-4	Positive associations between all immune subset recoveries in MBSR group compared with CG. Women who received MBSR had T cells more readily activated by the mitogen phytohemagglutinin and an increase in the Th1/Th2 ratio (P = .002). MBSR associated with a more rapid return to normal immune function compared with CG, particularly in early posttreatment recovery periods
11	Hsiao (2012)[104]	RCT	0-III	Body-mind-spirit (BMS) (IG) (n = 26) vs Education CG (n = 22)	8 weeks 2 h/wk Repeat measures at 5 and 8 months	Depression Meaning in Life (Purpose, Search) (BDI, MLQ-P, MLQ-S)	Cortisol	At 5 months, BMS was related to greater spiritual growth (search for meaning in life) (P < .01). At 8 months, the BMS group demonstrated healthier cortisol patterns compared with CG (P < .05).

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Table 3. (continued)

No.	Study (First Author, Year)	Design	Cancer Stage	Intervention Group (IG) (n) vs Control Group (CG) (n)	Intervention Duration	Psychosocial and RS Measures	Objective (PNI) Measures	Key Health Outcomes
12	Branstrom (2012; 2013)[110,111]	RCT	Data not provided	MBSR (IG) (n = 32) vs Wait list CG (n = 39)	8 weeks 2 h/wk Repeat measures at 3 and 6 months	Stress, Anxiety & Depression, Mood, Coping; Mindfulness (PSS, HADS, IES-R, PSOM, CSES, FFMQ)	Cortisol	MBSR associated with lower stress ($P = .06$), lower anxiety ($P = .09$), and increased mindfulness ($P < .01$). Although not quite significant ($r = -0.38$, $P = .06$) a trend was observed that MBSR demonstrated a moderate effect on awakening cortisol levels and was sustained at 6-month follow-up. Nonsignificant effects between stress and cortisol ($P = .06$) were observed
13	Campbell (2012)[92]	NonRCT	Data not provided	MBSR (IG) (n = 19) vs Wait list CG (n = 16)	8 weeks 90 min/wk	Mindfulness, Rumination (MAAS, RRQ-rs)	Blood pressure (BP)	MBSR may improve mindfulness, moderate effect between decreased rumination and decrease systolic BP ($r = 0.35$), no main effects observed
14	Carlson (2013)[68]	RCT	0-IV	MBCR (IG) (n = 113) vs Supportive emotional therapy (SET) (IG) (n = 104) vs Usual care CG: 1-day stress management seminar (n = 54)	8 weeks 90 min/wk	Mood, Stress, Quality of Life, Social Support (POMS-TMD, C-SOSI, FACT-B, FACT-G, MOS-SSS)	Cortisol	Cortisol patterns were stable over time in both SET ($P = .003$) and MBCR ($P = .014$) groups relative to the CG, who had more flattened cortisol slopes. Women in MBCR improved more over time on stress symptoms compared with both SET ($P = .009$) and control ($P = .023$) groups. Greater improvements in MBCR group in quality of life compared with SET ($P = .006$) and CG ($P = .005$); and in social support compared with the SET ($P = .012$)
15	Chen (2013)[112]	RCT	0-III	Qigong (IG) (n = 49)* vs Wait list CG (n = 47)* *Participants currently undergoing radiotherapy	5 weeks 40 min/wk with 1- and 3-month repeat measures	Depression, Fatigue, Quality of Life, Sleep Disturbance (CES-D, BFI, FACT-G, PSQI)	Cortisol	Qigong group reported less depression over time than women in CG ($P = .05$). Women who had elevated depressive symptoms at the start of radiotherapy reported less fatigue ($P < .01$) and better overall quality of life ($P < .05$) in the Qigong group compared with the CG. No significant changes observed in cortisol slopes
16	Robins (2013)[77]	RCT	I-IIIa	(n = 109)* (no further data) Tai Chi (IG) vs Spiritual growth group (IG) vs Usual care CG *Concurrent chemotherapy	10 weeks 90 min/wk Repeat measures at 1 week, 4.5 months, 6 months	Stress, Quality of Life, Depression (IES, FACT-B, CES-D)	Cytokine panel (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, TNF-α)	Interesting patterns in biomarkers observed; however, no statistically significant effects observed between intervention and control groups while *currently* receiving chemotherapy

(continued)

Table 3. (continued)

No.	Study (First Author, Year)	Design	Cancer Stage	Intervention Group (IG) (n) vs Control Group (CG) (n)	Intervention Duration	Psychosocial and RS Measures	Objective (PNI) Measures	Key Health Outcomes
17	Reich (2014)[113]	RCT	0-III	MBSR (IG) (n = 17) vs Usual care/wait list CG (n = 24)	6 weeks 2 hs/wk Measures at baseline and 6 weeks	Symptoms (MDASI)	Lymphocyte subsets, mitogen-stimulated subsets, cytokines	After 6 weeks, multiple baseline biomarkers were significantly positively improvement in GI symptoms ($P = .035$) and fatigue ($P = .035$) in MBSR group. Regression modeling identified B-lymphocytes and IFN-γ as the strongest predictors of gastrointestinal symptom improvement ($P < .01$). CD4+, CD8+ were predictive of strongest predictor of cognitive/psychological improvement ($P = .02$). Lymphocytes and IL-4 were strongest predictors of fatigue improvement ($P < .01$)
18	Bower (2012; 2014)[78,114]	RCT	0-II	Iyengar yoga (IG) (n = 14) vs Usual care CG (n = 15)	12 weeks 90 min, twice weekly Repeat measures at baseline, 12 weeks, and 24 weeks	Fatigue, Depression, Sleep, Stress, Vigor (FSI, BDI-II, PSQI, PSS, MSFI)	Cortisol, tumor necrosis factor-alpha (TNF-α), IL-1, IL-6, CRP	Decreased fatigue in yoga group from baseline to posttreatment and sustained at 3-month follow-up compared to CG ($P = .032$). Yoga group had significant increases in vigor compared with CG ($P = .011$). Both groups had positive changes in depressive symptoms and perceived stress ($P < .05$). Yoga group showed improved immune biomarker functioning compared with controls ($P < .05$). Tumor necrosis factor patterns remained stable in yoga group, while CG levels increased ($P = 0.28$). Similar trend observed with IL-1, but nonsignificant ($P = .16$). No significant changes in CRP, IL-6 or diurnal cortisol patterns
19	Chandwani (2014)[115]	RCT	0-III	Yoga (IG) (n = 53)* vs Stretching (IG) (n = 56)* vs Wait list CG (n = 54)* *Concurrently undergoing radiotherapy	6 weeks Up to 180 min/wk Repeat measures at 1, 3, and 6 months postintervention	Quality of Life, Fatigue, Depression, Sleep (MO-SF 36, BFI, CES-D, PSQI)	Cortisol	Yoga group demonstrated greater increases in physical component scale scores compared with CG at 1 and 3 months after radiotherapy ($P = .01$ and $P = .01$, respectively). At 1, 3, and 6 months, the yoga group had greater increases in physical functioning compared with both stretching and CG ($P < .05$), with stretching and CG differences at only 3 months ($P < .02$). Yoga and stretching groups had reduced fatigue ($P < .05$) at radiotherapy completion. No group differences for mental health and sleep quality. Cortisol slope was steepest for the yoga group compared with the stretching and CG at the end ($P = .023$ and $P = .008$, respectively) and 1 month after radiotherapy completed ($P = .05$ and $P = .04$, respectively)

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Table 3. (continued)

No.	Study (First Author, Year)	Design	Cancer Stage	Intervention Group (IG) (n) vs Control Group (CG) (n)	Intervention Duration	Psychosocial and RS Measures	Objective (PNI) Measures	Key Health Outcomes
20	Kiecolt-Glaser (2014)[116]	RCT	0-IIIa	Yoga (IG) (n = 100) vs Wait list CG (n = 100)	12 weeks 90 min/twice weekly Repeat measures at 3 months postintervention	Fatigue, Quality of Life, Depression, Sleep, Activity, Diet (MFSI-SF, MO SF-36, CES-D, PQSI, CHAMPS, FFQ)	Cytokines (IL-1β, IL-6, TNF-α)	At posttreatment, fatigue was not lower in yoga compared with CG ($P > .05$) but vitality was higher ($P = .01$). At 3 months posttreatment, fatigue was lower in the yoga group ($P = .002$), vitality was higher ($P = .01$), and IL-6 ($P = .027$), TNF-α ($P = .027$), and IL-1 ($P = .037$) were lower for yoga group compared with CG. No group differences in depression at either time points ($P > .20$). Frequency of yoga practice showed a stronger association with fatigue and vitality, but not depression; greater changes associated with more frequent practice. At 3 months posttreatment, increased yoga practice was associated with decreased IL-6 ($P = .01$) and IL-1 ($P = .03$), but not TNF-α production ($P > .05$)
21	Lengacher (2014)[117]	RCT	0-III	MBSR (IG) (n = 74) vs Usual care (n = 68)	6 weeks intervention Repeat measures at 12 weeks	Recurrence Concerns, Mindfulness, Stress, Anxiety, Depression (CARS,CAMS, PSS, STAI, CES-D)	Telomere length, telomere activity	Telomere activity (TA) increased steadily over 12 weeks in MBSR group (17%) compared with minimal increase in CG (approximately 3%, $P < .01$). No effects observed on Telomere length ($P = .92$). MBSR appears to increase TA in peripheral blood mononuclear cells. TA was not associated with change in mindfulness, stress, anxiety, or fear of recurrence
22	Carlson (2015)[118]	RCT	I-III	MBCR (IG) (n = 53) vs Supportive emotional therapy group (SET) (IG) (n = 49) vs Usual care (n = 26) (1-day seminar)	8 weeks 90 min/wk plus 6-hour, 1-day retreat 12 weeks 90 min/wk 1-day, 6-hour, stress management seminar	Mood, Stress (POMS, C-SOSI)	Telomere length	No correlations between measures of mood ($P = .80$) and stress ($P = .24$) and changes in telomere length between MBCR and SET groups and the CG ($P = .28$), or across the 2 intervention conditions ($P = .31$) and ($P = .55$). Telomere length in the MBCR and SET groups remained preserved (positive outcome) while a decrease among the CG was significant ($P = .04$)

Abbreviations: RS, religious and spiritual; PNI, psychoneuroimmunological; RCT, randomized control trial group; IG, intervention group; CRP, C-reactive protein; CG, control group; RVT, relaxation and visualization therapy; ISSL, Inventory of Stress Symptoms Lipp; STAI, State-Trait Anxiety Inventory; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; non-RCT, nonrandomized control trial group; MBSR, mindfulness-based stress reduction; QOLI-v3, Quality of Life Index Cancer Version 3, JCS, Jaloweic Coping Scale; MAAS, Mindfulness Attention Awareness Scale; FLIC, Functional Living Index of Cancer; MOCS-R, Measure of Current Status–Relaxation; IES, Impact of Events Scale; HADS, Hospital Anxiety and Depression Scale; ABS, Affects Balance Scale; PSS, Perceived Stress Scale; POMS, Profile of Mood States; C-SOSI, Calgary Symptoms of Stress Inventory; FFMQ, Five Facet Mindfulness Questionnaire; MDASI, MD Anderson Symptom Inventory; MLQ-P, Meaning in Life Questionnaire, Presence; MLQ-S, Meaning in Life Questionnaire; IES-R, Impact of Events Scale–Revised; PSOM, Positive State of Mind; CSES, Coping Self-Efficacy Scale; RRQ-rs, Rumination Reflection Questionnaire—revised; MBCR, mindfulness-based cancer recovery; POMS-TMD, Profile of Mood States–Total Mood Disturbance; FACT-B, Functional Assessment of Cancer Therapy–Breast; FACT-G, Functional Assessment of Cancer Therapy–General; MOS-SSS, Medical Outcomes Study–Social Support Survey; SOSI, Symptoms of Stress Inventory; NK, natural killer; IFN-γ, interferon-gamma; IL, interleukin; DHEA, dehydroepiandrosterone sulfate; FACIT-G, Functional Assessment of Cancer Illness Therapy–General; CES-D, Center for Epidemiological Studies–Depression Scale; BFI, Brief Fatigue Inventory; PSQI, Pittsburg Sleep Quality Index; FSI, Fatigue Symptom Inventory; BDI-II, Beck Depression Inventory–II; MFSI, Multidimensional Fatigue Symptom Inventory; MO SF-36, Medical Outcomes Short-Form 36; CHAMPS, Community Healthy Activities Model Program for Seniors; FFQ, Food Frequency Questionnaire; CARS, Concerns About Recurrence Scale; CAMS, Cognitive and Affective Mindfulness Scale–Revised.

report observations between spiritually based practices and physiological outcomes.

Overall, a wide variety of neuroendocrine-immune biomarker measures represented in the studies were observed in this review. Positive and negative associations between the spiritually based interventions and PNI outcome variables for the intervention studies were examined and these relationships are depicted in Table 2 with upward- or downward-pointing arrows. Moreover, the studies reporting these associations in Table 2 are linked with their corresponding study number as presented in Table 3. Among studies reviewed, MBSR interventions have been the most utilized spiritually based interventions in breast cancer survivors. MBSR is associated with improved inflammatory cytokine activity, improved lymphocyte function, improved or stabilization of cortisol levels, and increased or preservation of telomere activity. Moreover, interventions similar to MBSR, including CBSM, MBCR, and yoga all demonstrated similar influences on cytokine function, lymphocyte production, and improved or stabilized cortisol activity. While the remaining interventions, including Qigong, body-mind-spirit, and relaxation visualization therapy showed preservation or improved cortisol function in breast cancer survivors, there are few of these studies to date and conclusions are limited. Findings suggest that in general, spiritually based interventions are associated with improved neuroendocrine-immune function, particularly cortisol and cytokine activity.

Question 3: What is the evidence regarding the relationships between spiritually based interventions, psychosocial-spiritual outcomes, and PNI-based outcomes in breast cancer survivors?

Details of each reviewed intervention study are provided in Table 3, including designs, sample sizes, intervention and control group descriptions, psychosocial-spiritual measures, PNI measures, and the statistical significance of the outcome variables. The comparison of findings is challenging due to the wide variation in intervention duration and the wide range of psychosocial measures, as well as variation in PNI measures outcomes. However, there is a growing body of evidence to suggest a positive pattern is emerging between spiritually based interventions and physiological health outcomes. The majority of studies in this review report positive psychosocial and mindfulness-spiritual outcomes, as well as positive biomarker outcomes across differing spiritually based interventions.

While the immune system response to spiritually based interventions during chemotherapy and/or radiotherapy was not an initial question for the review, it was observed that five spiritually based intervention studies were conducted while participants were concurrently undergoing chemotherapy or radiotherapy for breast cancer treatment. These interventions included RVT, yoga, Qigong, Tai Chi/spiritual growth, and yoga/stretching. It was observed that yoga interventions report a limited, but positive, trend on immune function during chemotherapy and radiotherapy treatments.[108,115] While comparison is limited due to differing designs and treatments, both yoga interventions utilized the same intervention dose and duration (6 weeks, 180 min/wk) and utilized cortisol measures in breast cancer participants with stage III or lower.

Question 4: What are the implications for future research studies regarding spiritually based interventions, measures of RS, and PNI outcome measures?

Although interventions with a spiritual basis were the primary focus of this review, only one breast cancer study reported utilization of actual RS measures. Hsiao et al[104] reported an association between an 8-week body-mind-spirit intervention, spiritual growth, and healthier cortisol patterns among breast cancer participants, compared with the control group ($P < .05$). While there were no other breast cancer body-mind-spirit intervention studies for comparison in this review, a similar study in patients with chronic depression and anxiety reported no association between prayers and cortisol levels.[121] These findings contrast with those reported by Bormann et al,[122] who did find an association between prayer and decreased cortisol levels in HIV-positive individuals. There are few studies examining specific RS measures and associated PNI biomarker outcomes in breast cancer survivorship; therefore, the nature of these relationships remain unclear.

Table 3 provides the differences in the spiritually based interventions, including duration and dosing protocols (ie, frequency of practice). Similar to findings by Subnis et al,[99] little has been reported regarding intervention practice adherence. Additionally, it should be noted that spiritually based interventions with fewer weeks of duration have shown positive benefits similar to those with longer durations. This is important because intervention designs need to consider examination of the minimum dose and duration required to achieve a positive effect on immune function. Furthermore, these interventions add a degree of burden to chronically ill participants who may not feel well enough to leave home and travel to a group setting. Future intervention design should consider modifying spiritually based interventions for use in personal (ie, home-based) settings.

Previously, spiritually based interventions with PNI measures were of exploratory design, cross-sectional, and lacking a comparison arm. This review found that studies reviewed were generally more rigorous in approach than previous studies as a growing number of interventions (n = 6) were greater than 10 weeks in duration and the majority performed repeat measures ranging from 3 to 24 months

postintervention. Moreover, it was feasible to find a number of studies with comparison groups (22 RCTs/non-RCTs) that satisfactorily met review criteria, allowing a more comprehensive examination of findings than earlier reviews that lacked comparison groups.

Findings from this review are consistent with other reviews that found spiritually based interventions exerted a positive influence on psychological health, particularly on symptoms of depression, anxiety, mood, stress, and perceptions of quality of life. However, previous reviews have been mixed on the extent to which spiritually based interventions influence PNI outcome measures. This review revealed a positive pattern between spiritually based interventions and a number of PNI biomarker outcomes, suggesting that spiritually based interventions offer positive mental and physiological health benefits. For breast cancer survivors, these studies suggested that engaging in spiritually based practices may improve or stabilize the immune profile dysregulation that occurs with breast cancer.

Future questions to be answered based on these findings include the following: which components of the interventions are most influential on outcomes (eg, mindfulness, breathing, stretching); and, are all components necessary to achieve the immune profile benefits? Additionally, what could the minimum dose (eg, frequency and length of practice) and duration (eg, weeks, months, or lifetime) be for achieving and sustaining neuroendocrine-immune benefits? Moreover, which spiritually based interventions are most predictive of biomarker outcomes?

Limitations

This review found that spiritually based interventions utilized disease-specific variables (ie, treatment-type, stage) for study inclusion criteria. However, this design does not allow for individual differences in psychosocial-spiritual variables (eg, perceptions of distress, spiritual beliefs, coping skills, and lifestyle behavior patterns). For these reasons, and as Carlson[69] indicated previously, recruitment of a study population based on disease characteristics rather than psychosocial-spiritual considerations may result in unintended participant stress and impede measurement of the intervention's therapeutic value.

Similar to previous reviews, there remains a continued need for larger sample sizes and the inclusion of study power calculations. The direction of future spiritually based intervention design needs to standardize methods for intervention dosing, frequency, and duration of treatment. This review observed an increase in the numbers of study designs with randomization and longitudinal measures. However, because of the relative "newness" of spiritually based interventions in health care research, a variety of methods and study protocols exist between these interventions. Subsequently, these study methods and protocols vary in the reporting of details, resulting in a lack of guidance for prospective researchers wishing to reproduce intervention findings. A recent National Institutes of Health[123] mandate for grant submissions highlights the need for reporting detailed study protocols and statistical computation methods in order to facilitate scientific validation of study findings.

Finally, this review did not utilize a standard measure of study quality as this was beyond the focus of the review. Additionally, rigor of study randomization and blinding practices were not examined. However, screening and selection of intervention studies reviewed were limited to studies with comparison groups; and the majority of studies reviewed were randomized control trials.

Conclusion

This review found a positive pattern of relationships between spiritually based interventions, mental health outcomes, and neuroendocrine-immune function in breast cancer survivors. However, there were limited and uncertain benefits regarding the impact of spiritually based interventions on neuroendocrine-immune function among individuals receiving chemotherapy and/or radiotherapy. There is a growing body of evidence supporting relationships between RS self-report measures and mental health outcomes; however, RS self-report measures were rarely utilized when psychosocial-spiritual and PNI outcome measures (ie, biomarkers) were examined. Specifically, the trend in PNI intervention studies has been to measure a wide variety of psychosocial variables, with minimal measures of specific RS variables. Therefore, future research must clarify how best to address the issue regarding overlap of RS constructs in order for intervention outcomes to be more meaningful.

Additional biomarker studies are needed with specific and standardized measures of RS in order to understand the relationships between RS variables and PNI health outcomes. Similarly, future studies should examine which biomarkers offer the most utility in predicting breast cancer survivorship outcomes including biomarkers associated with the risk of post–breast cancer treatment late effects. Future psychosocial-spiritual healthcare research might consider intervention designs that personalize treatment based on psychosocial-spiritual needs, as well as diverse participant setting considerations. Additionally, research that can inform on the minimum necessary spiritual-intervention dose and duration will serve to reduce survivors' burden in managing post-breast cancer treatment-related symptoms. Finally, intervention designs will need to consider home-based delivery options, which remain important for survivors who are too ill to travel, have a preference for private/individual practice settings, or lack economic resources for traveling and transportation for group interventions.

Authors' Note

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, The University of Utah, or the University of Missouri.

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