

The Effect of Spiritual Intervention on the Concentration of Interleukin-1 β , Interleukin-6, Interleukin-8 and Tumor Necrosis Factor Alpha Cytokines in Patients with Breast Cancer: A Pretest–Posttest Experimental Study

Abstract

Background and Aim: Breast cancer (BC) has considerable effects on the immune system by modulating various psychological and biological aspects, especially hormonal function. Given the effectiveness of various psychological interventions on the overall health status of patients, we aimed to show the effect of the spiritual intervention on the immunological structure of patients with BC. **Subjects and Methods:** This was a pretest-posttest experimental study conducted from October 2017 to March 2018. There were three groups of patients with BC who referred to Shohada-e-Tajrish Hospital, Cancer Research Center, and Azar Clinic. The sample size based on Cohen's table for each group was at least 11 and taking into account the disadvantages of the subjects was 15. The selection of samples in the first stage was purposeful and based on the inclusion and exclusion criteria, but they were assigned to the groups randomly. They were assigned to the experiment group and two control groups. The first group received 12 sessions of spiritual intervention, the second group received 12 sessions of nonpsychological training focused on physical care related to their illness, and the third group received no intervention. The levels of interleukin (IL)-1 β , IL-6, IL-8, and tumor necrosis factor-alpha (TNF- α) were measured in all three groups by Enzyme-linked Immunosorbent Assay before, after, and 3 months after the intervention. The data were analyzed with SPSS software version 21 and the $P < 0.05$ was considered significant. **Results:** The level of cytokines was significantly changed at the time of follow-up. These changes were significant between the groups who received the spiritual intervention and nonpsychological training in comparison to the group that did not receive the intervention. Moreover, there was no significant difference between the intervention group and the training group. **Discussion/Conclusion:** Our findings showed that spiritual intervention can increase the success of the treatment process and the improvement of the patients. Spiritual intervention may significantly affect the physical health of patients with special needs, especially cancer patients in both treatment and recovery states.

Keywords: Breast cancer, breast neoplasms, cytokines, immune system, nonpsychological training, spiritual intervention

Introduction

The incidence of breast cancer (BC) in Iran is increasing from 16.7 per 100,000 women in 2000 to 33.6 in 2009, and likely increases to 63 per 100,000 in 2020.^[1] Development of cancers possibly is influenced by various stressors in life.^[2,3] Stressors cause rapid ACTH release and subsequently, release corticosteroids from the adrenal by causing emotional changes in the organism, which these corticosteroids usually decrease the activity of the immune system and consequently, cancer progression is accelerated.^[4] Negative emotions disrupt hormone secretion, while positive emotions stimulate the immune system by producing

favorable hormonal changes.^[5] High stress, in BC patients, disrupts white blood cell activity and disrupts body homeostasis, producing cortisol and impaired immune function; thus these adverse effects on the physiological system can affect certain parameters of the cellular immune system such as a reduction in the proliferation of T cells.^[6]

Although physical alterations in cancer can affect different aspects of an individual's emotions, attention to the effectiveness of various psychological interventions, especially strong parameters such as spirituality and religion, is increasing in the management of adverse effects of cancer

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Mehr SS, Pornour M, Movafagh A, Akbari ME, Vaziri S, Pourtoloei H, *et al.* The effect of spiritual intervention on the concentration of interleukin-1 β , interleukin-6, interleukin-8 and tumor necrosis factor alpha cytokines in patients with breast cancer: A pretest–posttest experimental study. *Clin Cancer Investig J* 2020;9:249-57.

Saeedeh Sarafranz Mehr,
Majid Pornour¹,
Abolfazl Movafagh²,
Mohammad Esmail Akbari³,
Shahram Vaziri⁴,
Hossein Pourtoloei⁵,
Hajar Vaseghi¹,
Farah Lotfi Kashani⁴,
Maliheh Entezari⁶

Cancer Research Center, Shahid Beheshti University of Medical Sciences, ¹Department of Photo Healing and Regeneration, Medical Laser Research Center; Yara Institute, Academic Center for Education, Culture, and Research, Departments of ³Surgical Oncology and ⁴Psycho-Oncology; Cancer Research Center; Shahid Beheshti University of Medical Sciences, ⁵Iran Management Industrial Institute (IMI), Management Industrial Institute, Tehran, Iran, ²Department of Medical Genetics, Cancer Research Center; School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran, ⁶Department of Genetic, Faculty of Advanced Science and Technology, Islamic Azad University, Tehran Medical Sciences, Tehran, Iran

Submitted: 13-Jun-2020

Revised: 20-Aug-2020

Accepted: 20-Sep-2020

Published: 28-Nov-2020

Address for correspondence:

Dr. Farah Lotfi Kashani,
Department of Psycho-Oncology,
Cancer Research Center,
Shahid Beheshti University of
Medical Sciences, Tehran, Iran.
E-mail: lotfi.kashani@gmail.com

Access this article online

Website: www.cci-j-online.org

DOI: 10.4103/ccij.cci_j_86_20

Quick Response Code:



on biological variables.^[7] Spirituality, by relying on the potential power of faith to heal and improve, can provide frameworks through which one can more fully understand the meaning, purpose, and values of one's own life as a consciousness.^[8] Therefore, the use of spiritual strategies is a psychological-enhancing factor and one of the most effective coping strategies that reduce mental distress and physical complaints,^[9] enhance the body's immunological ability and quality of life (QOL), and provide rest.^[10]

In keeping with our model of an intimate relationship between the central nervous system and the immune system, religion serves as an example of how a pervasive cognitive system, influences interactions with one's environment, may modulate the effects of stress on the immune system.^[11,12] It was shown in a study that higher levels of religious attendance in a nondisabled population of older adults were prospectively related to lower mortality up to 12 years later and that these effects appear to be mediated by IL-6.^[13] Among studies reviewed, Mindfulness-Based Stress Reduction (MBSR) interventions have been the most utilized spiritual-based interventions in BC 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. Findings suggest that in general, spiritual-based interventions are associated with improved neuroendocrine-immune function, particularly cortisol and cytokine activity.^[14] The humoral system is weakened by reducing the production of cytokines such as tumor necrosis factor-alpha (TNF- α), which is one of the factors that induce programmed cell death in cancer cells. Hence, a reduction in the number of T cells is associated with decreased production of TNF- α , which may induce proliferation of tumor cells in the absence of such cytokines and immune cells.^[15] The primary aim of therapies is to improve the immune system function, eradicate tumors, or prevent tumor recurrence through robust, specific, long-term antitumor immune responses, and focus on the function of cytokines and activation. They have been one of the most successful forms of immune-based therapeutic approaches for cancer patients to date.^[16] Accordingly, more focus has been placed on the treatment of individuals based on the four physical, mental, social, and spiritual dimensions in the medical care system.^[17] Therefore, given the role of mental health in human health, enhancing the immunity of patients with cancer, and preventing them from reducing their immunity, this study aimed to find a suitable solution for promoting mental health to improve the immune system in patients with BC.

Subjects and Methods

This was a pretest-posttest experimental designed study from October 2017 to March 2018. The study population consisted of all women with BC referred to

Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences Cancer Research Center, and Azar Clinic. Inclusion criteria were the patients at clinical stage 1 and 2 of BC, aged between 25 and 65 years, having minimal reading and writing literacy to complete and sign a consent form. We selected patients with stage 1 and 2 because there were not any metastasis and recurrences in these two stages.^[18] The first treatment for patients was surgery first, then chemotherapy and radiation therapy if necessary (were not neoadjuvant). By the end of their radiotherapy and chemotherapy, it had been at least 6 months and a maximum of 1 year. Exclusion criteria were advanced and metastatic cancer, neoadjuvant (those who had undergone chemotherapy and then surgery), a significant clinical disorder, psychiatric drug use for the past 3 months, participation in other therapies or their current membership, their reluctance to donate blood and to discontinue any cooperation.

The sample size of the study was determined based on Cohen's table,^[19] with an effect size of 0.5 and the power of 0.8 for each group, which was at least 11 and considering the subjects' dropout was estimated by 15 individuals per group. For allocating the patients to the groups, after calculating the sample size, they were randomly assigned to the experiment group and two control groups in which the participants were measured three times.

The first measurement is called pretest, the second measurement is posttest and the third measurement is followed-up. The level of serum cytokines was measured in these three phases. There were eligibility criteria for performing this study. The spiritual intervention was performed by a psychologist under the supervision of a tutor. Nonpsychological classes were held by specialists in each field under the supervision of the Cancer Research Center of Shahid Beheshti University of Medical Sciences. Blood samples were collected by skilled and experienced nurses of Shohada-e-Tajrish Hospital.

The experiment group was the patients with BC who underwent 12 sessions of spiritual intervention. The first control group consisted of the patients with BC who completed 12 sessions of training (except psychological content), the second control group included the patients with BC who did not receive any intervention or training. Educational and spiritual intervention sessions were held once a week for 90 min. Serum levels of IL1- β , IL-6, IL-8, and TNF- α were measured in all groups before, after, and 3 months after the last session of the intervention. In order to evaluate the serum level of cytokines, 5 ml of venous blood was taken from the patients and their serum was separated and stored at -20°C until the day of the test. Serum levels of cytokines were measured and quantified by Enzyme-linked Immunosorbent Assay (IBL Company, Germany) with the minimum detection limit of pg/ml.

The protocol of spiritual intervention

In spiritual intervention, the therapist invites the patient to explore spiritual issues and issues in order to improve and restore health along with other therapies such as medication and emphasizes spiritual issues by means of mental approaches. Spiritual intervention means considering cultural-religious beliefs and the intrinsic relationship with divine power, beyond the boundaries of religious beliefs in different religions that guide patients toward God's divine power.^[20] Training stress management strategies with spiritual resources and attention to the meaning and QOL are useful in helping patients "personal independence and awareness in improving their treatment process. Therefore, we can use patients' spiritual beliefs and traditional ethnic values as a spiritual and supportive resource to improve the spiritual health of patients with cancer."^[21] Spiritual intervention in the present study was based on a twelve-session spiritual intervention package standardized by Vaziri *et al.* At Shahid Beheshti University Cancer Research Center.^[22] The contents of the package are listed in Table 1.

Ethical committee

This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences with ethics number: IR.SBMU.RETECH.REC.1397.562.

Statistical analysis

Data were analyzed with Statistical Package for the Social Sciences (SPSS) software version 21 www.ibm.com/products/spss-statistics. The normality was assessed by the Kolmogorov–Smirnov test with $P < 0.05$. To compare the significance level of intergroup changes, the independent *t*-test was used, the ANOVA test was used to evaluate the significance level of the data in the follow-up stage, and the Bonferroni test was used for intragroup changes. In the present study, $P < 0.05$ was considered statistically significant.

Results

The results showed that IL-1 β level was different in the intervention group between the pretest and follow-up phases ($P = 0.001$). The intervention group was also different in the posttest and follow-up phases ($P = 0.001$). There was a difference in pretest and follow-up of the training group ($P = 0.001$). Furthermore, there was a significant difference between the follow-up phase of the group under spiritual intervention and in the follow-up group without intervention and training ($P = 0.001$). There was a significant difference between the follow-up phase of the training group and the follow-up group without any intervention and training ($P = 0.001$) [Figure 1].

The level of IL-6 in pretest and follow-up groups was significantly different ($P = 0.001$); it was different in posttest and follow-up group ($P = 0.001$). Moreover, there

was a significant difference between the posttest phase and the follow-up groups ($P = 0.001$). Pretest phase of the training group and follow-up group were different and this value was higher in follow-up group ($P = 0.001$). There was a significant difference between the follow-up phase of the training group and the follow-up group without intervention and training ($P = 0.001$) [Figure 2].

The level of IL-8 in the pretest phase of the group undergoing spiritual intervention and follow-up was higher ($P = 0.001$). In the pretest phase of the training group and follow-up group, there is a difference between the two groups ($P = 0.001$). In the posttest phase, the intervention group did not receive any intervention, and this difference was higher in the follow-up group without intervention and training ($P = 0.001$). There was a significant difference between the follow-up phase of the group undergoing spiritual intervention and the follow-up group without intervention and training ($P = 0.001$) [Figure 3].

The level of TNF- α was significantly different in the posttest group in the spiritual intervention and follow-up group and this value was higher in the follow-up group in the spiritual intervention group ($P = 0.001$). Moreover, there was a significant difference between the posttest group without intervention and training and follow-up group ($P = 0.001$). In addition, we found a significant difference between the follow-up phase of the group under spiritual intervention and the follow-up group without intervention and training ($P = 0.001$) [Figure 4].

Discussion

This study aimed to evaluate the effectiveness of spiritual intervention on altering the function of cytokines in improving immune function. In other words, our hypothesis study was that spiritual intervention could help improve immune function by altering the function of cytokines. There are conflicting reports on the role of inflammatory cytokines such as IL-8, IL-6, IL-1 β , and TNF- α in

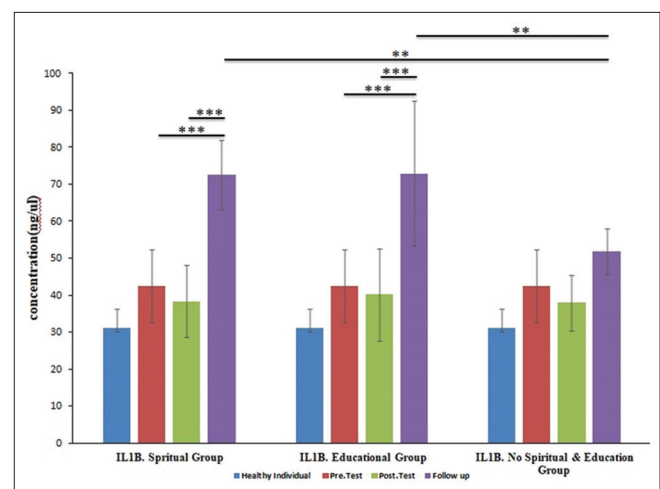


Figure 1: Comparison of interleukin-1 β levels in the experimental and control groups

Table 1: Protocol of spiritual intervention, the twelve-session spiritual intervention package

First session	Understanding and grounding the re-experience of spirituality
Target	Acquaintance of members with each other, knowledge of the reasons for the formation of the challenge group (awareness of the implicit and personal meaning of spirituality and its definition in terms of each member, examination of the belief in superior and sacred power in the members, and recall of perceptions and beliefs of therapists about spirituality)
Second session	Introspection
Target	Introspection 1. Overview of the first session; 2. Individual/medical examination of the group; 3. Meeting preparation; 4. Group status; 5. Introducing the subject of the second session; 8. Presenting homework and reminding the day and time of the next meeting
Third session	The sources of fear and anxiety and our resources in front of them
Target	Finding sources of fear and anxiety and resolving it 1. Meeting preparation; 2. Group status review; 3. Third session review; 4. Reflection on assignments; 5. Introducing a third session (sources of fear and anxiety and coping with them); 6. Reflection on assignments; Practice recognizing fear, anxiety, and relaxation. 8. Providing homework and reminding the day and time of the next meeting
Fourth Session	Infinity and inheritance
Target	Understanding our endlessness and inheritance 1. Session preparation; 2. Group status review; 3. Third session review; 4. Reflection on assignments; Session 8. Presenting homework and reminding the day and time of the next meeting
Fifth meeting	Inheritance on the seal circuit and Inheritance on the hate circuit
Target	Understanding the results of malice and affection 1. Meeting preparation; 2. Prayer at the beginning; 3. Group status review; 4. Review of the fourth session; 5. Reflection on assignments; 6. Introducing the fourth session (inheritance on the seal circuit and inheritance on the Keane circuit); 7. Sealing and abstinence from the Kane; 8. Summing up the session; Meeting
Sixth session	Understanding meditation and calculation
Target	Understanding meditation and calculation 1. Meeting preparation; 2. Prayer at the beginning; 3. Group status review; 4. Review of the fifth session; 5. Meditation; 6. Introducing the sixth session (meditation and calculation); Meeting Session 9. Presenting Homework; Reminding the Day and Hour of the Next Meeting and Praying for the End of the Meeting
Seventh session	Meditation and calculation
Target	Performing meditation and meditation 1. Preparing a meeting; Initial prayer; 2. Studying group status; 3. Reviewing the sixth session; 4. Reflecting on assignments; 5. Introducing the seventh session (meditation and calculation); 6. Meditation and calculation practice; Session 8; Homework Presentation; Form Distribution; Reminder of Next Session Date and End of Prayer Meeting
Eighth session	Understanding forgiveness and resolving anger
Target	Increasing forgiveness and resolving anger toward oneself and others and the world, acceptance, patience, perseverance, responsible action, and personal and social benefit 1. Session Preparation; Prayer at the beginning; 2. Studying Group Status; Reviewing Seventh Session; 3. Reflecting on Tasks; 4. Introducing Seventh Session (Forgiveness and Resolution of Anger); Meeting Summary; 7. Homework Presentation; Form Distribution; Day and Hour Reminder of the Next Meeting and Prayer End of the Meeting
Ninth session	Forgiveness and resentment of anger
Target	Increasing forgiveness and resolving anger toward oneself and others and the world, acceptance, patience, perseverance, responsible action, and personal and social benefit 1. Meeting preparation; 2. Group status review; 3. Eighth session review; 4. Assignment; 5. Introducing the ninth session (anger forgiveness and resolving); 6. Anger forgiveness and resolving practice; Homework assignment; reminder of the day and time of the next session and prayer for the end of the session
Tenth meeting	Computation and meditation and stability
Target	Increased self-control in maintaining awareness, hope and expectation; acceptance, patience, persistence, tolerance; responsible action; and personal and social benefit 1. Session preparation; Prayer at the beginning; 2. Group status review; 3. Ninth session review; 4. Meditation; 5. Introducing the ninth session: Computation and Meditation and Stability. 6. Computation and Meditation Practice (Self-care); 7. Meeting Summary; 8. Homework Presentation; Remembrance Day and Hours of the Next Meeting and Prayer End of the Meeting

Contd...

Table 1: Contd...

First session	Understanding and grounding the re-experience of spirituality
Eleventh session	Computation and Meditation and Stability
Target	Self-care in maintaining awareness, hope and expectation; acceptance, patience, resilience, tolerance; responsible action; and personal and social benefit
	1. Meeting preparation; prayer at the beginning; studying group status; reviewing tenth session; reflecting on tasks; introducing eleventh session, calculating and meditating and stability (self-estimation); homework presentation; remembrance day and hours of next meeting and end of prayer
Twelfth session	Together, the sustainability stabilization sessions and the announcement of course completion
Target	Self-care in maintaining awareness, hope and expectation; acceptance, patience, persistence, tolerance; responsible action; and personal and social benefit

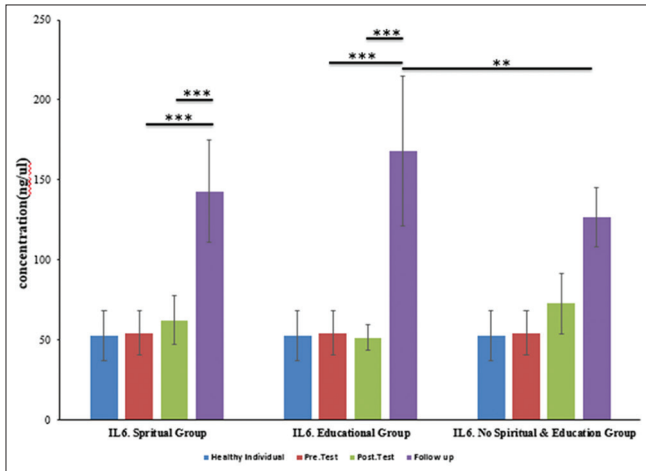


Figure 2: Comparison of interleukin-6 levels in the experimental and control groups

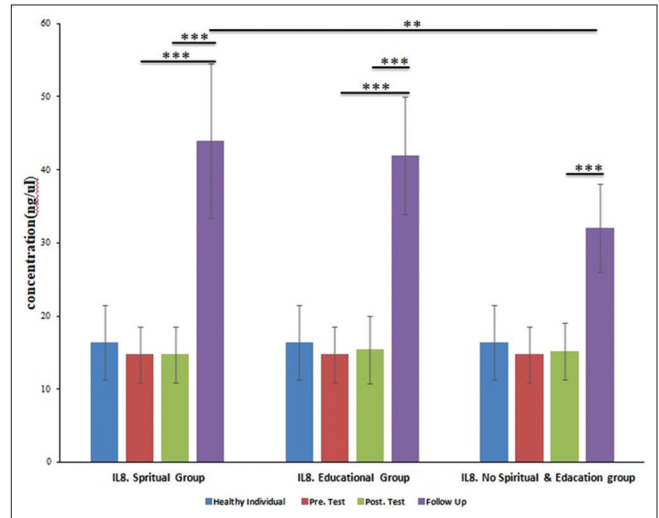


Figure 3: Comparison of interleukin-8 levels in the experimental and control groups

enhancing the immune system or progressing to various stages of cancer or inducing apoptosis.^[23-25] Studies show that at high tumor stages, the presence of such cytokines will induce tumor growth by inducing apoptosis, but cellular studies indicate the inhibitory role of inflammatory cytokines such as TNF- α *in vitro*.^[26,27]

In this regard, there are detailed suggestions about the role of immune cells in inhibiting tumor genesis and cancer, one of which is the role of M1 macrophages.^[28] Neutrophil and macrophages these cells control and inhibit cancer cell proliferation, indicating that innate immunity plays an important role in the inhibition of cancer.^[29] It is noteworthy that the M1 macrophage phenotype is directly related to inflammatory conditions. They facilitate inflammation and a decrease in the secretion of these pro-inflammatory factors leads to a switch to other macrophage phenotypes such as M2, which leads to the growth and proliferation of tumor cells.^[30] The secretion of cytokines such as IL-1 β activates innate immune cells such as natural killer (NK) cells and cellular immunity cells such as CD8+.^[31] In addition, it polarizes CD4+ cells to Th1 cells. The activation of the immune system is attenuated after a period of chemotherapy in cancer patients.^[32] However, studies have shown that the persistent presence of these cytokines in the cancerous environment stimulates the secretion of

cytokines such as interferon-gamma (IFN- γ) by NK cells and cells involved in immunity and induces the expression of PD-L1 and PD-L2 molecules.^[33] IL-6 plays an important role in activation, maintenance, survival and proliferation of T cells independent of IL-2 and differentiates and maintains the balance between Th1/Th2 cells.^[34] On the other hand, IL-8 is also an inflammatory cytokine and is secreted by phagocytic cells and plays an important role in the chemo taxis of phagocytic cells such as neutrophils, and its concomitant elevation along with three other factors may indicate inflammatory cell activity.^[35]

Based on the results of this study, it seems that spiritual intervention can affect the secretion of inflammatory cytokines and consequently, the effect of these cytokines on the cellular and humoral immune system in cancer patients. Previous surgery and chemotherapy play a supporting role in the homeostasis and strengthening the immune system. On the other hand, given the different and sometimes contradictory effects of these cytokines in the metastasis of cancer and the need for continuous and unnecessary presence of these cytokines, it seems that it is better to perform effective interventions at specific intervals rather than permanent courses. It is advisable to perform effective interventions at specified intervals, rather than permanently,

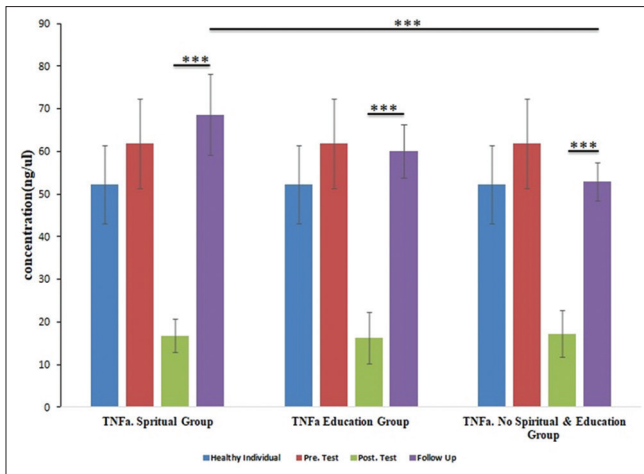


Figure 4: Comparison of tumor necrosis factor-alpha levels in the experimental and control groups

depending on the amount of cytokine secretion in different individuals. In other words, appropriate interventions should be optimized based on the type of cytokines and concentrations of cytokines at different stages of the disease.

Afterward, we examine the effects of cytokines in terms of their synergistic effects. For example, the only presence of transforming growth factor-beta (TGF- β) in the environment does not mean that Treg cells have increased. This may, in fact, be partially beneficial to cancer and make the environment readier for cancer progression. On the other hand, if Th17 cells are present in the environment (presence of TGF- β and IL-6), they can provide an inflammatory environment, which may augment the elimination of the tumor. Therefore, it is advisable to perform effective interventions at specified intervals, rather than permanently, depending on the amount of this cytokine secretion in different individuals and depending on the needs of individuals, which, of course, may be useful in further studies. The results showed that there was no significant difference in the levels of cytokines between the intervention and nonpsychological training groups. However, there was a significant difference between the intervention group and the group received no intervention. In relatively similar studies, the results are considerable. For example, Jim *et al.* (2015) in their study with the meta-analysis model showed that greater R/S is associated with better patient-reported physical health. These results underscore the importance of attending to patients' religious and spiritual needs as part of comprehensive cancer care.^[36] Or in the study of Alexander *et al.* with a significant sample size of 398 people is expressed that women experience distinctly different physical well-being, social well-being, and total QOL outcomes during and after BC surgery. The genetic associations identified suggest that cytokine dysregulation influences QOL outcomes. However, specific QOL domains may be impacted by different cytokines.^[37] On the other hand Fallath *et al.* stated that Multivariate

analysis of variance of serum levels of cytokine IFN- γ and TNF- α revealed that spiritual therapy is effective in reducing serum levels of cytokine IFN- γ and TNF- α in women with BC and has relative endurance over time.^[38] Finally we can say the level of some cytokines in tumors' microenvironment was high and blocking these cytokines can be effective in the eradication or prevention of the recurrence of the tumor. However, in the present study, we did not encounter an inflammatory state because the tumor was removed from the patients' bodies and inflammatory cytokines decrease after surgical intervention. Therefore, spiritual therapy might improve immune responses in terms of either cellular or humoral responses, which needs further studies to be clarified.^[24,39,40] Similar to other studies, this study showed that the gathering people and their group-participation in purposeful and reciprocal activities and learning concepts that create a sense of happiness in people and improve their overall health undoubtedly affects other aspects of their existence as well.^[41,42] Although spiritual intervention sessions, according to previous studies, and in particular, in this study has influenced the spiritual and psychological structure of individuals, and the nature of its function has also been shown the purpose of allocating the second group, namely the group without interfering with the spiritual and psychological content, was to neutralize the effect of the group in the study, but the elements of a group that showed the effectiveness of a group consisted of "empathy."^[43] Empathy leads to improved mental health for those patients with BC who are experiencing higher levels of anxiety about their cancer diagnosis and subsequent treatments.^[44] After empathy, the social support that interacts with the provider and the recipient of the support may prevent unnecessary adverse effects, In addition, it has a positive effect on physical, mental, and social well-being, and ultimately enhances one's overall performance and is effective in maintaining and enhancing hope.^[45] Leading to increased mental health, reduced distress, increased QOL, and even increased sexual self-esteem in women with BC.^[46,47] The originality of group efficacy has been proven in many studies, and this has attracted more research from researchers to enhance therapies based on this model. Numerous studies have been conducted to compare the different types of therapies that have shown that each approach has been effective. For example, a study by Garland *et al.* (2007) comparing MBSR programs and improving traumatic growth and spirituality in cancer patients showed that both programs may have positive growth after injury experiences. Improvement of life for those who participate in group therapy.^[48] But what is the effectiveness of spiritual intervention is that although the differences in the levels of cytokines in the intervention group and in the training group were not significant, the same level of effectiveness of the intervention was not neglected. In the experience of living with cancer, spirituality is considered an important and prominent aspect of a healthy life and it seems that the

threatening nature of this disease increases the spiritual needs of patients. Spirituality can lead to greater psychological adjustment by providing supportive resources for the individual and more indirectly through affecting hope.^[48] Spiritual interventions in the treatment of cancer patients are, in fact, capable of utilizing their spiritual resources and resources in addressing physical and psychological problems and making life better by accepting the environment, purpose and orientation in life and make it possible to fill the semantic vacuum.^[49] In addition to the effectiveness of spiritual intervention on improving the psychological and social functioning of individuals, recent studies have assessed the effectiveness of spiritual interventions on physiological dimensions.^[50] Prayer and communication with God and spiritual care can reduce the symptoms of pain and improve the patient's physical function by arousing the sympathetic nervous system.^[51] For example, a study of 16 studies reported that spirituality significantly is positively related to cardiovascular functions or outcomes.^[52] It has been repeatedly reported that those who were more spiritual or experienced spiritual intervention had lower blood pressure.^[53] Moreover, in a study aimed at observing the relationship between cortisol levels, levels of spiritual well-being, and suicidal tendencies in Croatian war veterans suffering from Post-Traumatic Stress Disorder, the results showed that veterans with higher spiritual well-being scores have lower cortisol levels.^[54] Studies on spirituality and communication or their effects on endocrine functions, positive relationships or positive effects have been reported and no studies showed any negative association or negative effects,^[55] in the area of cancers, individuals who are more spiritual likely have a lower risk of experiencing cancer or a better prognosis.^[56] In addition, the changes in the time-based groups were also significant because, in this study, the changes in all three groups at the time of follow-up were more significant than the pretest and posttest, and this finding confirms that besides the valuable short-term effectiveness of interventions and training, achieving therapeutic sustainability is a more important achievement. Sustainable effects are the effects that an individual experiences outside of their training and intervention experience. Thus, the emergence of psychological perception of time as a component of the neurodevelopmental process is particularly important in the social functioning and adaptive behavior of the individual. According to psychologists' opinions, it seems that long-term estimates of survival have the highest survival value during evolution, as this process is essential for internal representations of the external environment.^[57] The passage of time gradually reduces the stresses of the individual and by providing the necessary cognitive processing, leads to an understanding of the reality of the event and subsequently to a new worldview and change of the dysfunctional schemas of the individual. Numerous studies have found a significant relationship between positive changes and the passage of time, even in cancer patients.^[58,59]

The current study was carried out with great care. Selection of three groups of patients with BC who can evaluate both spiritual intervention and nonspiritual intervention groups and no intervention is a noteworthy feature of this study, which led many researchers to answer the question of the effectiveness of group content or function in the treatment. The next reliable item was blood sampling in three stages, which clearly indicated the issue of time without intervention in the stability of the interventions. In the end, the limitations of the study include the difficulty of finding samples and trying to keep the samples in the study for three blood sampling stages. Cytokines and complete blood count testing and lack of access to patient tissue samples are the other important limitations in this study for more accurate tissue studies.

Weaknesses and the strength of the study

Measuring psychological variables at biological level and showing these changes in the level of immune system function is one of the most strengths of the study. Studying two control groups of subjects instead of one control group and in three stages instead of two stages are also of the strongest points of the study. However, small sample size and inability to further study at the cell line level can be mentioned as its weaknesses.

Conclusion

The study revealed that the health of a cancer patient is not limited to complete medical treatment and that we showed that holistic treatment can increase the success of the treatment process and improvement of the patients. Nowadays, psychologists have realized that spiritual intervention may have significant positive effects on the physical health of patients with special needs, especially cancer patients, in both treatment and recovery states. IL-1 β and TNF have antitumor activity and inhibit tumor growth. IL-6 has also inflammatory effects and controls the differentiation of T cells and balance between Th1/Th2 cells, especially Treg cells, which have negative effects on tumor inhibition; IL-8 recruits neutrophils and MDSCs into the tumor environment, which are capable of attenuating antitumor immune responses. Although the attitudes of the medical system have shifted from being one-dimensional to multi-dimensional in treating the disease, it still requires more effort to intervene in the humanities to maintain and enhance the overall health of individuals. The path of progress in the field of therapy is through the interconnection of the sciences with different perspectives and the common goal that may lead to avoidance of biased views and openness to accepting healthy and rational attitudes.

Acknowledgments

This work was supported by the, Shahid Beheshti University of Medical Sciences Cancer Research Center, Tehran, Iran.

Financial support and sponsorship

This work was supported by, Shahid Beheshti University of Medical Sciences Cancer Research Center, grant no: 1397.562, Tehran, Iran.

Conflicts of interest

There are no conflicts of interest.

References

- Zahmatkesh B, Keramat A, Alavi N, Khosravi A, Kousha A, Motlagh AG, et al. Breast cancer trend in Iran from 2000 to 2009 and prediction till 2020 using a trend analysis method. *Asian Pac J Cancer Prev* 2016;17:1493-8.
- Nourazarian AR, Kangari P, Salmaninejad A. Roles of oxidative stress in the development and progression of breast cancer. *Asian Pac J Cancer Prev* 2014;15:4745-51.
- Sawada T, Nishiyama T, Kikuchi N, Wang C, Lin Y, Mori M, et al. The influence of personality and perceived stress on the development of breast cancer: 20-year follow-up of 29,098 Japanese women. *Sci Rep* 2016;6:32559.
- Handa RJ, Weiser MJ. Gonadal steroid hormones and the hypothalamo-pituitary-adrenal axis. *Front Neuroendocrinol* 2014;35:197-220.
- Morey JN, Boggero IA, Scott AB, Segerstrom SC. Current directions in stress and human immune function. *Curr Opin Psychol* 2015;5:13-7.
- Diangong H, Feng G, Zaifu L, Helland T, Weixin F, Liping C. Sea buckthorn (*Hippophae rhamnoides* L.) oil protects against chronic stress-induced inhibitory function of natural killer cells in rats. *Int J Immunopathol Pharmacol* 2016;29:76-83.
- Ochoa C, Casellas-Grau A, Vives J, Font A, Borràs JM. Positive psychotherapy for distressed cancer survivors: Posttraumatic growth facilitation reduces posttraumatic stress. *Int J Clin Health Psychol* 2017;17:28-37.
- Soundy A, Liles C, Stubbs B, Roskell C. Identifying a framework for hope in order to establish the importance of generalised hopes for individuals who have suffered a stroke. *Adv Med* 2014;2014:2014;2014:471874.
- Sarafraz Mehr S, Saberian N, Akbaei M, ModarresiAsem F. A study on the effectiveness of spiritual intervention on perception of god and attitude toward death in women with breast cancer. *Europ J Med Natl Sci* 2018;2:116-25.
- Rosenkranz MA, Lutz A, Perlman DM, Bachhuber DR, Schuyler BS, MacCoon DG, et al. Reduced stress and inflammatory responsiveness in experienced meditators compared to a matched healthy control group. *Psychoneuroendocrinology* 2016;68:117-25.
- Koenig HG, Ames D, Youssef NA, Oliver JP, Volk F, Ellen J Teng et al. The Moral Injury Symptom Scale-Military Version. *J Relig Health* 2018 Feb;57:249-65.
- Terrizzi JA Jr., Shook NJ, McDaniel MA. The behavioral immune system and social conservatism: A meta-analysis. *Evolution Human Behav* 2013;34:99-108.
- Lucchetti G, Lucchetti AL, Koenig HG. Impact of spirituality/religiosity on mortality: Comparison with other health interventions. *Explore (NY)* 2011;7:234-8.
- Hulett JM, Armer JM. A systematic review of spiritually based interventions and psychoneuroimmunological outcomes in breast cancer survivorship. *Integr Cancer Ther* 2016;15:405-23.
- Watson AM, Lam LM, Klimstra WB, Ryman KD. The 17D-204 vaccine strain-induced protection against virulent yellow fever virus is mediated by humoral immunity and CD4+ but not CD8+ T cells. *PLoS Pathogens* 2016;12:e1005786.
- Waldmann TA. Cytokines in cancer immunotherapy. *Cold Spring Harb Perspect Biol* 2018 Dec 3;10:a028472.
- Pearce MJ, Coan AD, Herndon JE 2nd, Koenig HG, Abernethy AP. Unmet spiritual care needs impact emotional and spiritual well-being in advanced cancer patients. *Support Care Cancer* 2012;20:2269-76.
- Millar EK, Graham PH, O'Toole SA, McNeil CM, Browne L, Morey AL, et al. Prediction of local recurrence, distant metastases, and death after breast-conserving therapy in early-stage invasive breast cancer using a five-biomarker panel. *J Clin Oncol* 2009;27:4701-8.
- Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Psychol Bull. 1992 Jul;112:155-9. doi: 10.1037//0033-2909.112.1.155.
- Richards PS, Worthington EL Jr. The need for evidence-based, spiritually oriented psychotherapies. *Prof Psychol* 2010;41:363.
- Renaud J, Bédard E. Depression in the elderly with visual impairment and its association with quality of life. *Clin Interv Aging* 2013;8:931-43.
- Vaziri S, LotfiKashani F, Akbari M. Spirituality Intervention; 2018.
- de Visser KE, Eichten A, Coussens LM. Paradoxical roles of the immune system during cancer development. *Nat Rev Cancer* 2006;6:24-37.
- Esquivel-Velázquez M, Ostoa-Saloma P, Palacios-Arreola MI, Nava-Castro KE, Castro JI, Morales-Montor J. The role of cytokines in breast cancer development and progression. *J Interferon Cytokine Res* 2015;35:1-6.
- Rose-John S, Schooltink H. Cytokines are a therapeutic target for the prevention of inflammation-induced cancers. *Recent Results Cancer Res* 2007;174:57-66.
- Lu L, Shi W, Deshmukh RR, Long J, Cheng X, Ji W, et al. Tumor necrosis factor- α sensitizes breast cancer cells to natural products with proteasome-inhibitory activity leading to apoptosis. *PLoS One* 2014;9:e113783.
- Scott DL, Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. *N Engl J Med* 2006;355:704-12.
- Lippitz BE. Cytokine patterns in patients with cancer: A systematic review. *Lancet Oncol* 2013;14:e218-28.
- Qiu J, Xiao J, Han C, Li N, Shen X, Jiang H, et al. Potentiation of tumor necrosis factor- α -induced tumor cell apoptosis by a small molecule inhibitor for anti-apoptotic protein hPEBP4. *J Biol Chem* 2010;285:12241-7.
- Grecian R, Whyte MKB, Walmsley SR. The role of neutrophils in cancer. *Br Med Bull* 2018;128:5-14.
- Bent R, Moll L, Grabbe S, Bros M. Interleukin-1 beta-A friend or foe in malignancies? *Int J Mol Sci* 2018 Jul 24;19:2155. doi: 10.3390/ijms19082155.
- Ostroumov D, Fekete-Drimusz N, Saborowski M, Kühnel F, Woller N. CD4 and CD8 T lymphocyte interplay in controlling tumor growth. *Cell Mol Life Sci* 2018;75:689-713.
- Maimela NR, Liu S, Zhang Y. Fates of CD8+ T cells in tumor microenvironment. *Comput Struct Biotechnol J* 2019;17:1-3.
- Dienz O, Rincon M. The effects of IL-6 on CD4 T cell responses. *Clin Immunol* 2009;130:27-33.
- Todorović-Raković N, Milovanović J. Interleukin-8 in breast cancer progression. *J Interferon Cytokine Res* 2013;33:563-70.
- Jim HS, Pustejovsky JE, Park CL, Danhauer SC, Sherman AC, Fitchett G, et al. Religion, spirituality, and physical health in cancer patients: A meta-analysis. *Cancer* 2015;121:3760-8.
- Alexander K, Conley YP, Levine JD, Cooper BA, Paul SM,

- Mastick J, *et al.* Cytokine gene polymorphisms associated with various domains of quality of life in women with breast cancer. *J Pain Symptom Manage* 2018;55:334-50000.
38. Fallath L, Lotfi KF, Masjedi AA. Effectiveness of Group Spiritual Therapy on Serum Levels of Cytokine Interferon-Gamma and Tumor Necrosis Factor Alpha among Patients (WOMEN) with Breast Cancer; 2017.
 39. Goldberg JE, Schwertfeger KL. Proinflammatory cytokines in breast cancer: Mechanisms of action and potential targets for therapeutics. *Curr Drug Targets* 2010;11:1133-46.
 40. Standish LJ, Sweet ES, Novack J, Wenner CA, Bridge C, Nelson A, *et al.* Breast cancer and the immune system. *J Soc Integrative Oncol* 2008;6:158.
 41. Lambert D'raven LT, Moliver N, Thompson D. Happiness intervention decreases pain and depression, boosts happiness among primary care patients. *Prim Health Care Res Dev* 2015;16:114-26.
 42. Ul-Haq Z, Mackay DF, Martin D, Smith DJ, Gill JM, Nicholl BI, *et al.* Heaviness, health and happiness: A cross-sectional study of 163066 UK Biobank participants. *J Epidemiol Community Health* 2014;68:340-8.
 43. Dehning S, Gasperi S, Krause D, Meyer S, Reiß E, Burger M, *et al.* Emotional and cognitive empathy in first-year medical students. *ISRN Psychiatry* 2013;2013:801530. doi: 10.1155/2013/801530. eCollection 2013.
 44. Fang SY, Chang HT, Shu BC. The moderating effect of perceived partner empathy on body image and depression among breast cancer survivors. *Psychooncology* 2015;24:1815-22.
 45. Paterson C, Jones M, Rattray J, Lauder W, Nabi G. What is the mechanism effect that links social support to coping and psychological outcome within individuals affected by prostate cancer? Real time data collection using mobile technology. *Eur J Oncol Nurs* 2016;21:126-33.
 46. Akbari M, Lotfi Kashani F, Vaziri S. The efficacy of four-factor psychotherapy on increasing sexual self-esteem in breast cancer survivors. *Iran J Breast Dis* 2017;10:48-60.
 47. Dimino K, Horan KM, Stephenson C. Leading Our Frontline HEROES Through Times of Crisis With a Sense of Hope, Efficacy, Resilience, and Optimism. *Nurse Leader*; 2020.
 48. Garland SN, Carlson LE, Cook S, Lansdell L, Specia M. A non-randomized comparison of mindfulness-based stress reduction and healing arts programs for facilitating post-traumatic growth and spirituality in cancer outpatients. *Support Care Cancer* 2007;15:949-61.
 49. Ando M, Morita T, Akechi T, Okamoto T, Japanese Task Force for Spiritual Care. Efficacy of short-term life-review interviews on the spiritual well-being of terminally ill cancer patients. *J Pain Symptom Manage* 2010;39:993-1002.
 50. Russ TC, Stamatakis E, Hamer M, Starr JM, Kivimäki M, Batty GD. Association between psychological distress and mortality: Individual participant pooled analysis of 10 prospective cohort studies. *BMJ* 2012;345:e4933.
 51. Akhbardeh M. Role of spiritual beliefs and prayer in health promotion of chronic patients: A qualitative study. *Quran Med* 2011;1:5-9.
 52. Balboni MJ, Sullivan A, Enzinger AC, Epstein-Peterson ZD, Tseng YD, Mitchell C, *et al.* Nurse and physician barriers to spiritual care provision at the end of life. *J Pain Symptom Manage* 2014;48:400-10.
 53. Holt-Lunstad J, Steffen PR, Sandberg J, Jensen B. Understanding the connection between spiritual well-being and physical health: An examination of ambulatory blood pressure, inflammation, blood lipids and fasting glucose. *J Behav Med* 2011;34:477-88.
 54. Gillum RF, Ingram DD. Frequency of attendance at religious services, hypertension, and blood pressure: The Third National Health and Nutrition Examination Survey. *Psychosom Med* 2006;68:382-5.
 55. Paul-Labrador M, Polk D, Dwyer JH, Velasquez I, Nidich S, Rainforth M, *et al.* Effects of a randomized controlled trial of transcendental meditation on components of the metabolic syndrome in subjects with coronary heart disease. *Arch Intern Med* 2006;166:1218-24.
 56. Mihaljević S, Vuksan-Ćusa B, Marčinko D, Koić E, Kušević Z, Jakovljević M. Spiritual well-being, cortisol, and suicidality in Croatian war veterans suffering from PTSD. *J Relig Health* 2011;50:464-73.
 57. Schnall E, Wassertheil-Smoller S, Swencionis C, Zemon V, Tinker L, O'Sullivan MJ, *et al.* The relationship between religion and cardiovascular outcomes and all-cause mortality in the Women's Health Initiative Observational Study. *Psychol Health* 2010;25:249-63.
 58. Phillips I. Attention to the passage of time. *Philosop Perspect* 2012;26:277-308.
 59. Allen TD, French KA, Braun MT, Fletcher K. The passage of time in work-family research: Toward a more dynamic perspective. *J Vocational Behav* 2019;110:245-57.