

Is Stress a Contributor to Tumor Metastasis?

Sukarma Singh*

Delhi University, Benito Juarez Marg, South Campus, South Moti Bagh, New Delhi, Delhi 110021, India

*: All correspondence should be sent to: Dr. Sukarma Singh.

Author's Contact: Sukarma Singh, M.D., M.P.H., E-mail: sukarma.singh@gmail.com

DOI: <https://doi.org/10.15354/si.24.re1007>

Funding: No funding source declared.

COI: The author declares no competing interest.

AI Declaration: The author affirms that artificial intelligence did not contribute to the process of preparing the work.

Stress, often considered a silent yet pervasive force in our daily lives, has increasingly been recognized for its significant impact on human health. In the realm of oncology, the connection between stress and cancer development, particularly tumor metastasis, has become a subject of intense research and clinical interest. This review discusses the intricate relationship between stress and tumor metastasis, exploring the biological mechanisms, clinical implications, and potential therapeutic approaches at the intersection of these two complex phenomena. By understanding the role of stress in shaping cancer progression, we may uncover new avenues for improving patient outcomes and advancing cancer care.

Keywords: Stress; Tumor Metastasis; Mechanisms; Prevention; Prognosis

Science Insights, 2024 May 31; Vol. 44, No. 5, pp.1375-1380.

© 2024 Insights Publisher. All rights reserved.



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the [Creative Commons Attribution-NonCommercial 4.0 License](https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed by the Insights Publisher.

Introduction

IT HAS BEEN established for quite some time that stress contributes to a variety of health issues, including cancer. Tumor metastasis, which occurs when cancer cells travel from the site of origin to other organs and tissues, represents an especially perilous facet of the disease that is significantly impacted by stress. Studies have demonstrated that stress impairs the body's immune system, hinders its innate capacity to combat cancer cells, and facilitates the development and metastasis of malignancies (1, 2).

The influence of stress on tumor metastasis can be observed via the secretion of stress hormones, including cortisol and adrenaline. The immune system can be suppressed by these hormones, facilitating the spread of cancer cells and their ability

to evade detection (3). Moreover, chronic stress has the potential to induce inflammation, thereby fostering an environment that is more conducive to the development and spread of tumors (4).

In addition, stress can impair the body's capacity to repair DNA damage, a process that is pivotal in the progression and initiation of cancer (5). The dysfunction of DNA repair mechanisms caused by chronic stress can increase the likelihood of mutations, which are capable of promoting tumor metastasis and growth. Additionally, stress can disrupt the hormonal equilibrium of the body, which promotes the development of blood vessels that supply tumors with nutrients and facilitate their metastasis (6).

In both animal and human investigations, a correlation between stress and tumor metastasis has been established. As an

illustration, studies have established that chronic stress can facilitate the metastasis of breast cancer to distant organs, including the liver and lungs (3, 7). Likewise, research also has demonstrated that stress can promote the development and metastasis of melanoma tumors (8). The aforementioned results emphasize the criticality of stress management in the context of cancer prevention and treatment.

Fortunately, there exist strategies that can effectively mitigate the detrimental effects of stress on tumor metastasis. It has been demonstrated that mind-body practices, including yoga, meditation, and deep breathing exercises, reduce tension and enhance immune function (9). An additional benefit of sustaining a healthy lifestyle is that it supports the body's natural defenses against cancer and aids in stress reduction via regular exercise, a well-balanced diet, and sufficient sleep (10). By examining the relationship between stress and tumor metastasis, people can proactively enhance their well-being and health.

The Link Between Stress and Cancer Development

It is widely postulated that stress significantly contributes to the development of cancer, primarily by influencing the functioning of the immune system. It has been demonstrated that chronic stress impairs the immune system, thereby diminishing the body's capacity to combat cancer cells and other pathogens (3, 4). This may increase the risk of cancer progression and development in individuals who are subjected to protracted periods of stress. Additionally, research has demonstrated that stress hormones, including adrenaline and cortisol, can stimulate the development of cancer cells, thereby strengthening the link between stress and cancer (11).

An additional mechanism by which stress might contribute to the development of cancer is through its impact on systemic inflammation. There is a correlation between chronic stress and increased inflammation, a well-established cancer risk factor (4). The promotion of cancer cell proliferation and metastasis through inflammation can increase an individual's susceptibility to the disease. In addition, research has demonstrated that stress inhibits the body's innate mechanisms for repairing DNA damage, thereby increasing the risk of developing cancer (5).

The influence of stress on the body's hormones and neurotransmitters, according to some researchers, might contribute to the development of cancer. Stress has the potential to disturb the equilibrium of hormones, including testosterone and estrogen, both of which have been implicated in the pathogenesis of cancer (12). Moreover, stress has the potential to disrupt the synthesis of neurotransmitters, including serotonin and dopamine, thereby influencing the viability and proliferation of cells (13). The presence of these hormonal and neurotransmitter imbalances within the body may foster an environment that is malignant.

Psychological stressors, including anxiety and depression, have been linked to the development of cancer. There is a correlation between elevated levels of stress and the development of mental health disorders, both of which can negatively affect an individual's physical health (14). Anxiety and depression have the potential to impact hormone levels, inflammation, and immune function—all of which are factors that may contribute to

the development of cancer (15). Moreover, individuals grappling with mental health concerns may partake in activities that elevate their cancer risk, including but not limited to smoking, consuming alcohol, and making unfavorable dietary decisions (16).

Research has additional evidence to support the correlation between stress and the development of cancer, as individuals who have encountered traumatic events or chronic stress have a higher incidence of cancer. As discovered, a significant correlation exists between childhood traumatic experiences and the subsequent development of cancer (17). In a similar way, a study discovered a correlation between elevated stress levels and an increased risk of developing breast cancer (18). These results indicate that stress may affect cancer risk in the long run.

Although the relationship between stress and the development of cancer is intricate and multifarious, there are measures that individuals can adopt to alleviate the adverse effects of stress on their well-being. The implementation of relaxation techniques, including but not limited to yoga, meditation, and deep breathing exercises, can effectively mitigate the physiological consequences of stress. In addition to obtaining sufficient sleep, engaging in regular physical activity, and adhering to a healthy diet, these practices can help mitigate the effects of stress on cancer risk.

Impact of Stress on Tumor Growth and Spread

Stress hormones can promote the growth and metastasis of tumors by stimulating the development of blood vessels that supply them (19). Adrenaline and noradrenaline, among other stress hormones, can impede the capability of the immune system to identify and eliminate malignant cells, thereby facilitating the evasion of tumors from the body's defenses.

In addition, hormonal equilibrium can be disrupted by chronic stress, which can result in elevated cortisol levels. Cortisol is recognized for its pro-inflammatory properties within the body, a milieu that may facilitate the development and metastasis of tumors (20). An investigation established a correlation between elevated cortisol levels and heightened tumor size and aggressiveness among individuals diagnosed with breast cancer (21). Additionally, stress has the potential to impair the body's capacity to rectify DNA damage, a critical determinant in the progression of cancer. Chronic stress can impair the body's repair mechanisms and cause DNA damage, thereby increasing the risk of developing cancer (5).

Moreover, alterations in the microbiome, which comprises the assemblage of bacteria and other microorganisms residing in the gastrointestinal tract, can be influenced by stress-induced modifications. Accordingly, stress has the potential to modify the microbiome's composition, resulting in an overabundance of pro-inflammatory bacteria that facilitate the development of tumors (22).

Beyond its direct implications for tumor growth and metastasis, stress has the potential to influence the efficacy of cancer treatments. Stress hormones have the potential to impede the efficacy of radiation therapy and chemotherapy, thereby diminishing their capacity to eradicate cancer cells and diminish tumor size (23).

In addition, stress can influence a person's sleep patterns,

diet, and exercise regimens, all of which have the potential to affect cancer risk and treatment outcomes. It is well established that chronic stress increases the desire for high-sugar, high-fat diets and decreases the motivation to engage in physical activity; both of these are risk factors for the development and progression of cancer. Furthermore, stress may induce disruptions in sleep patterns, which may impair the body's capacity to combat cancer. Studies discovered a correlation between chronic stress and reduced sleep duration and quality, both of which were associated with an elevated risk of developing cancer (24, 25).

Stress Management Strategies for Cancer Patients

Psychological Interventions to Reduce Stress

Cognitive-behavioral therapy (CBT) is a highly prevalent psychological intervention that is utilized to alleviate tension among individuals diagnosed with cancer (26). CBT assists individuals in recognizing and altering their anxiety-inducing and stress-involved negative thought patterns and behaviors. By acquiring stress management skills, cognitive restructuring, and relaxation training, cancer patients can develop the ability to contend with the emotional challenges of the disease and enhance their mental health.

Additionally, it has been demonstrated that mindfulness-based stress reduction (MBSR) effectively reduces tension in cancer patients (27). Body scanning, meditation, and deep breathing are examples of mindfulness practices that assist individuals in developing an awareness of the present moment and acceptance of their thoughts and emotions. Through consistent mindfulness practice, cancer patients can cultivate a sense of inner tranquility and serenity amidst the turmoil of their illness and learn to manage their stress more efficiently.

Support groups are another psychological intervention that can help reduce tension among cancer patients (28). Individuals are afforded the opportunity to interact with others who are undergoing comparable circumstances, express their emotions and concerns, and receive encouragement and emotional support through participation in support groups. Through active engagement in support groups, individuals afflicted with cancer can mitigate feelings of isolation and solitude, thereby fostering a sense of community and belonging that positively impacts stress levels and mental health.

An additional efficacious psychological intervention that can aid cancer patients in mitigating tension and enhancing their emotional state is art therapy. By engaging in artistic endeavors such as painting, drawing, writing, or music, individuals are afforded a secure and encouraging setting in which to delve into and navigate their emotions, anxieties, and sentiments pertaining to cancer (29). Art therapy facilitates patients' nonverbal self-expression, enabling them to access their latent creativity and resilience. This process fosters a sense of empowerment and self-exploration, which in turn may contribute to stress reduction and improved coping mechanisms.

Lifestyle Changes and Supportive Therapies

A healthy diet is one of the most essential lifestyle modifications a person confronting cancer can make (30). A diet abundant in

fruits, vegetables, whole cereals, and lean protein can support the body's ability to combat cancer cells and strengthen the immune system. Red meat consumption, sugary beverages, and processed foods should be avoided in order to reduce inflammation, which has been associated with an increased risk of cancer.

Cancer patients can benefit from regular exercise in addition to consuming a nutritious diet. Cancer patients can experience an overall improvement in quality of life, a reduction in fatigue, and an enhancement in energy levels (31). Physically beneficial exercises such as walking, swimming, and yoga can also offer patients a psychological and emotional release that is significantly required during a trying time.

In addition to acupuncture, massage, and meditation, research has demonstrated that these practices are beneficial for cancer patients. Cancer treatments are associated with pain, vertigo, and fatigue; acupuncture can alleviate these symptoms; massage therapy can promote relaxation and alleviate muscle tension (32, 33). Engaging in mindfulness and meditation can aid individuals in managing tension and anxiety while also cultivating a profound sense of tranquility and fortitude.

Additionally, counseling and support groups can be invaluable resources for cancer patients. Connecting with others who are undergoing comparable circumstances can foster an indispensable sense of community and assistance that is fundamental for the process of emotional recovery (34). Patients can develop coping mechanisms and process their emotions and concerns in order to better manage the challenges of cancer treatment through the use of counseling services.

As supplementary cancer treatments, complementary therapies such as aromatherapy, herbal supplements, and homeopathy are gaining popularity. Although these alternative therapies should be utilized in conjunction with conventional cancer treatment, they have been reported to provide alleviation from symptoms such as pain, nausea, and anxiety for numerous patients.

In conjunction with conventional cancer treatments, lifestyle modifications and supportive therapies have the potential to empower patients and grant them a sense of agency throughout their process of recovery. Patients can increase their likelihood of effectively managing their disease and enhance their physical, emotional, and spiritual well-being by adopting a holistic approach to cancer care. Collaborating closely with their healthcare team to ascertain the optimal combination of treatments and therapies that align with their specific requirements and objectives is of paramount importance for cancer patients.

Pharmacological Interventions for Stress Reduction

Benzodiazepines

Benzodiazepines are a category of drugs frequently prescribed for the treatment of anxiety and stress-related conditions. These drugs function by augmenting the efficacy of gamma-aminobutyric acid (GABA), a neurotransmitter in the brain that aids in the regulation of stress and anxiety. Benzodiazepines have been found to be efficacious in alleviating stress and inducing relaxation in cancer patients, especially those who are experiencing acute discomfort or anxiety (35). Nevertheless, the

extended use of benzodiazepines is not advisable due to the potential for addiction and the development of tolerance (36).

Antidepressants

Antidepressants are a pharmacological category of drugs that can be utilized to alleviate stress and enhance mood in individuals diagnosed with cancer. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are frequently recommended medications for treating stress and anxiety, as they effectively relieve symptoms (37). These drugs function by augmenting the concentrations of serotonin and norepinephrine in the brain, which are neurotransmitters involved in the regulation of mood and emotions. Antidepressants can be especially beneficial for cancer patients who are experiencing depression in addition to stress (38, 39).

Beta-blockers

Beta-blockers are a pharmacological class frequently prescribed for hypertension and cardiac ailments, although they might also be efficacious in alleviating stress and anxiety. Beta-blockers function by inhibiting the actions of adrenaline, a hormone that is secreted in reaction to stress and anxiety (40). Beta-blockers can mitigate the impact of adrenaline, facilitating the body's ability to manage stress and induce a state of relaxation. Beta-blockers can provide significant advantages for cancer patients who are encountering physical manifestations of stress, such as an accelerated heart rate or trembling.

Corticosteroids

Corticosteroids are a group of drugs that imitate the actions of

cortisol, a hormone secreted by the adrenal glands in reaction to stress. Corticosteroids have the ability to decrease inflammation and inhibit the immune system, which can be advantageous in controlling stress-induced symptoms in individuals with cancer (41). Nevertheless, corticosteroids can induce notable adverse effects such as weight gain, hypertension, and heightened susceptibility to infections (42). Consequently, they are commonly employed for brief periods to alleviate stress in cancer patients (43).

Conclusion

Stress has been widely acknowledged as a prominent contributor to the growth and spread of cancer, especially in relation to the spread of tumors. The biological mechanisms underlying this association are intricate, but it is hypothesized that stress initiates a series of physiological reactions, including the heightened secretion of stress hormones such as cortisol and adrenaline. These hormonal changes can impair the immune system's capacity to combat cancer cells efficiently and facilitate the metastasis of tumors throughout the body. Persistent stress can also result in inflammation, which offers a favorable environment for the development and spread of tumors. Moreover, stress has been found to impact behaviors such as unhealthy dietary decisions, insufficient physical activity, and inadequate sleep, all of which can additionally contribute to the advancement of cancer. By comprehending the correlation between stress and tumor metastasis, healthcare providers can more effectively customize treatment programs to address patients' emotional well-being in addition to their physical health. ■

References

1. Liu Y, Tian S, Ning B, Huang T, Li Y, Wei Y. Stress and cancer: The mechanisms of immune dysregulation and management. *Front Immunol* 2022; 13:1032294. DOI: <https://doi.org/10.3389/fimmu.2022.1032294>
2. Cui B, Peng F, Lu J, He B, Su Q, Luo H, Deng Z, Jiang T, Su K, Huang Y, Ud Din Z, Lam EW, Kelley KW, Liu Q. Cancer and stress: NextGen strategies. *Brain Behav Immun* 2021; 93:368-383. DOI: <https://doi.org/10.1016/j.bbi.2020.11.005>
3. Obradović MMS, Hamelin B, Manevski N, Couto JP, Sethi A, Coissieux MM, Münst S, Okamoto R, Kohler H, Schmidt A, Bentires-Alj M. Glucocorticoids promote breast cancer metastasis. *Nature* 2019; 567(7749):540-544. DOI: <https://doi.org/10.1038/s41586-019-1019-4>
4. Vignjević Petrinović S, Milošević MS, Marković D, Momčilović S. Interplay between stress and cancer-A focus on inflammation. *Front Physiol* 2023; 14:1119095. DOI: <https://doi.org/10.3389/fphys.2023.1119095>
5. Jenkins FJ, Van Houten B, Bovbjerg DH. Effects on DNA damage and/or repair processes as biological mechanisms linking psychological stress to cancer risk. *J Appl Biobehav Res* 2014; 19(1):3-23. DOI: <https://doi.org/10.1111/jabr.12019>
6. Lempesis IG, Georgakopoulou VE, Papalexis P, Chrousos GP, Spandidos DA. Role of stress in the pathogenesis of cancer (Review). *Int J Oncol* 2023; 63(5):124. DOI: <https://doi.org/10.3892/ijo.2023.5572>
7. Tian W, Liu Y, Cao C, Zeng Y, Pan Y, Liu X, Peng Y, Wu F. Chronic stress: Impacts on tumor microenvironment and implications for anti-cancer treatments. *Front Cell Dev Biol* 2021; 9:777018. DOI: <https://doi.org/10.3389/fcell.2021.777018>. Erratum in: *Front Cell Dev Biol* 2022; 10:865043.
8. Scheau C, Draghici C, Ilie MA, Lupu M, Solomon I, Tampa M, Georgescu SR, Caruntu A, Constantin C, Neagu M, Caruntu C. Neuroendocrine factors in melanoma pathogenesis. *Cancers (Basel)* 2021; 13(9):2277. DOI: <https://doi.org/10.3390/cancers13092277>

9. Cahn BR, Goodman MS, Peterson CT, Maturi R, Mills PJ. Yoga, Meditation and mind-body health: Increased BDNF, cortisol awakening response, and altered inflammatory marker expression after a 3-month yoga and meditation retreat. *Front Hum Neurosci* 2017; 11:315. DOI: <https://doi.org/10.3389/fnhum.2017.00315>. Erratum in: *Front Hum Neurosci* 2022; 16:868021. Erratum in: *Front Hum Neurosci* 2023; 17:1278043.
10. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. *J Sport Health Sci* 2019; 8(3):201-217. DOI: <https://doi.org/10.1016/j.jshs.2018.09.009>
11. Hong H, Ji M, Lai D. Chronic stress effects on tumor: Pathway and mechanism. *Front Oncol* 2021; 11:738252. DOI: <https://doi.org/10.3389/fonc.2021.738252>
12. Caiazza F, Ryan EJ, Doherty G, Winter DC, Sheahan K. Estrogen receptors and their implications in colorectal carcinogenesis. *Front Oncol* 2015; 5:19. DOI: <https://doi.org/10.3389/fonc.2015.00019>
13. Popoli M, Yan Z, McEwen BS, Sanacora G. The stressed synapse: The impact of stress and glucocorticoids on glutamate transmission. *Nat Rev Neurosci* 2011; 13(1):22-37. DOI: <https://doi.org/10.1038/nrn3138>
14. Schneiderman N, Ironson G, Siegel SD. Stress and health: Psychological, behavioral, and biological determinants. *Annu Rev Clin Psychol* 2005; 1:607-628. DOI: <https://doi.org/10.1146/annurev.clinpsy.1.102803.144141>
15. Powell ND, Tarr AJ, Sheridan JF. Psychosocial stress and inflammation in cancer. *Brain Behav Immun* 2013; 30 Suppl:S41-S47. DOI: <https://doi.org/10.1016/j.bbi.2012.06.015>
16. Grajek M, Krupa-Kotara K, Białek-Dratwa A, Sobczyk K, Grot M, Kowalski O, Staśkiewicz W. Nutrition and mental health: A review of current knowledge about the impact of diet on mental health. *Front Nutr* 2022; 9:943998. DOI: <https://doi.org/10.3389/fnut.2022.943998>
17. Cook JL, Russell K, Long A, Phipps S. Centrality of the childhood cancer experience and its relation to post-traumatic stress and growth. *Psychooncology* 2021; 30(4):564-570. DOI: <https://doi.org/10.1002/pon.5603>
18. Chiriac VF, Baban A, Dumitrascu DL. Psychological stress and breast cancer incidence: A systematic review. *Clujul Med* 2018; 91(1):18-26. DOI: <https://doi.org/10.15386/cjmed-924>
19. Dai S, Mo Y, Wang Y, Xiang B, Liao Q, Zhou M, Li X, Li Y, Xiong W, Li G, Guo C, Zeng Z. Chronic stress promotes cancer development. *Front Oncol* 2020; 10:1492. DOI: <https://doi.org/10.3389/fonc.2020.01492>
20. Herrera-Martínez AD, Román ÁR, Corrales EP, Idrobo C, Ramírez PP, Rojas PM, Lázaro CR, Araujo-Castro M. Adrenal incidentalomas, cortisol secretion and cancer: is there a real crosstalk? *Front Endocrinol (Lausanne)* 2024; 14:1335202. DOI: <https://doi.org/10.3389/fendo.2023.1335202>
21. Antonova L, Aronson K, Mueller CR. Stress and breast cancer: From epidemiology to molecular biology. *Breast Cancer Res* 2011; 13(2):208. DOI: <https://doi.org/10.1186/bcr2836>
22. Beurel E. Stress in the microbiome-immune crosstalk. *Gut Microbes* 2024; 16(1):2327409. DOI: <https://doi.org/10.1080/19490976.2024.2327409>
23. Chen M, Singh AK, Repasky EA. Highlighting the potential for chronic stress to minimize therapeutic responses to radiotherapy through increased immunosuppression and radiation resistance. *Cancers (Basel)* 2020; 12(12):3853. DOI: <https://doi.org/10.3390/cancers12123853>
24. Chen Y, Tan F, Wei L, Li X, Lyu Z, Feng X, Wen Y, Guo L, He J, Dai M, Li N. Sleep duration and the risk of cancer: A systematic review and meta-analysis including dose-response relationship. *BMC Cancer* 2018; 18(1):1149. DOI: <https://doi.org/10.1186/s12885-018-5025-y>
25. Collatuzzo G, Pelucchi C, Negri E, Kogevinas M, Huerta JM, Vioque J, de la Hera MG, Tsugane S, Shigueaki Hamada G, Hidaka A, Zhang ZF, Camargo MC, Curado MP, Lunet N, La Vecchia C, Boffetta P. Sleep duration and stress level in the risk of gastric cancer: A pooled analysis of case-control studies in the stomach cancer pooling (StoP) project. *Cancers (Basel)* 2023; 15(17):4319. DOI: <https://doi.org/10.3390/cancers15174319>
26. Lin C, Tian H, Chen L, Yang Q, Wu J, Ji Z, Zheng D, Li Z, Xie Y. The efficacy of cognitive behavioral therapy for cancer: A scientometric analysis. *Front Psychiatry* 2022; 13:1030630. DOI: <https://doi.org/10.3389/fpsy.2022.1030630>
27. Rush SE, Sharma M. Mindfulness-based stress reduction as a stress management intervention for cancer care: A systematic review. *J Evid Based Complementary Altern Med* 2017; 22(2):348-360. DOI: <https://doi.org/10.1177/2156587216661467>
28. Weis J. Support groups for cancer patients. *Support Care Cancer* 2003; 11(12):763-768. DOI: <https://doi.org/10.1007/s00520-003-0536-7>
29. de Witte M, Orkibi H, Zarate R, Karkou V, Sajjani N, Malhotra B, Ho RTH, Kaimal G, Baker FA, Koch SC. From therapeutic factors to mechanisms of change in the creative arts therapies: A scoping review. *Front Psychol* 2021; 12:678397. DOI: <https://doi.org/10.3389/fpsyg.2021.678397>
30. Choi JW, Hua TNM. Impact of lifestyle behaviors on cancer risk and prevention. *J Lifestyle Med* 2021; 11(1):1-7. DOI: <https://doi.org/10.15280/jlm.2021.11.1.1>
31. Kim K, Yoon H. Health-related quality of life among cancer survivors depending on the occupational status. *Int J Environ Res Public Health* 2021; 18(7):3803. DOI: <https://doi.org/10.3390/ijerph18073803>
32. Jang A, Brown C, Lamoury G, Morgia M, Boyle F, Marr I, Clarke S, Back M, Oh B. The effects of acupuncture on cancer-related fatigue: Updated systematic review and meta-analysis. *Integr Cancer Ther* 2020; 19:1534735420949679. DOI: <https://doi.org/10.1177/1534735420949679>
33. Romero SAD, Emard N, Baser RE, Panageas K,

- MacLeod J, Walker D, Barton-Burke M, Liou K, Deng G, Farrar J, Xiao H, Mao JJ, Epstein A. Acupuncture versus massage for pain in patients living with advanced cancer: A protocol for the IMPACT randomised clinical trial. *BMJ Open* 2022; 12(9):e058281. DOI: <https://doi.org/10.1136/bmjopen-2021-058281>
34. Martino J, Pegg J, Frates EP. The connection prescription: Using the power of social interactions and the deep desire for connectedness to empower health and wellness. *Am J Lifestyle Med* 2015; 11(6):466-475. DOI: <https://doi.org/10.1177/1559827615608788>
35. Triozzi PL, Goldstein D, Laszlo J. Contributions of benzodiazepines to cancer therapy. *Cancer Invest* 1988; 6(1):103-111. DOI: <https://doi.org/10.3109/07357908809077033>
36. Vinkers CH, Olivier B. Mechanisms underlying tolerance after long-term benzodiazepine use: A future for subtype-selective GABA(A) receptor modulators? *Adv Pharmacol Sci* 2012; 2012:416864. DOI: <https://doi.org/10.1155/2012/416864>
37. Gosmann NP, Costa MA, Jaeger MB, Motta LS, Frozi J, Spanemberg L, Manfro GG, Cuijpers P, Pine DS, Salum GA. Selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors for anxiety, obsessive-compulsive, and stress disorders: A 3-level network meta-analysis. *PLoS Med* 2021; 18(6):e1003664. DOI: <https://doi.org/10.1371/journal.pmed.1003664>
38. Williams S, Dale J. The effectiveness of treatment for depression/depressive symptoms in adults with cancer: A systematic review. *Br J Cancer* 2006; 94(3):372-390. DOI: <https://doi.org/10.1038/sj.bjc.6602949>
39. Smith HR. Depression in cancer patients: Pathogenesis, implications and treatment (Review). *Oncol Lett* 2015; 9(4):1509-1514. DOI: <https://doi.org/10.3892/ol.2015.2944>
40. Farzam K, Jan A. Beta Blockers. [Updated 2023 Aug 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK532906/>
41. Dietrich J, Rao K, Pastorino S, Kesari S. Corticosteroids in brain cancer patients: Benefits and pitfalls. *Expert Rev Clin Pharmacol* 2011; 4(2):233-242. DOI: <https://doi.org/10.1586/ecp.11.1>
42. Yasir M, Goyal A, Sonthalia S. Corticosteroid Adverse Effects. [Updated 2023 Jul 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK531462/>
43. Haywood A, Good P, Khan S, Leupp A, Jenkins-Marsh S, Rickett K, Hardy JR. Corticosteroids for the management of cancer-related pain in adults. *Cochrane Database Syst Rev* 2015; 2015(4):CD010756. DOI: <https://doi.org/10.1002/14651858.CD010756.pub2>

Received: February 09, 2024 | Revised: March 03, 2024 | Accepted: March 10, 2024
