

The Harmful Effects of Chronic Stress on the Development of Cancer and The Strategies That Can Be Used to Mitigate It

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ABSTRACT

Stress, a state of worry caused by a difficult situation, is carried out by the parasympathetic nervous system and acute or short-term stress can benefit us in many ways. However, chronic or long-term stress can be extremely harmful and provide detrimental effects to the body by weakening it. Studies have shown a correlation between chronic stress and cancer. One of the mechanisms chronic stress can contribute to cancer is by weakening our immune system. This paper reviews published articles to find connections among the immune, endocrine and nervous systems and how they interact via release of certain cytokines and hormones in response to stressful situations. The impact of enhanced inflammatory processes and cancer progression are discussed. This paper also sheds light into certain mental health issues that cancer patients have faced before or during their cancer diagnosis and treatment. There are certain factors, such as gender, age, genetics, and country or region of residence, which impact stress responses with implications on disease outcome. Cancer patients also experience a lot of changes in the neuronal structure, increase in glucocorticoid signaling, CRH gene expression, and HPA axis as well as DNA damage and p53 protein suppression, when they experience chronic stress. There are also elevated cortisol levels and HPA axis dysregulation which can be combated through anti-inflammatory treatments. The paper concludes by discussing how certain activities, like yoga, tai-chi, and meditation can help alleviate chronic stress. The results are promising as there has been a decrease in self-reported depression and anxiety, and an increase in sleep, relaxation, and cognition.

Introduction

It is a well known fact that chronic stress can negatively impact the growth of cancer by increasing it, and decrease the effects of certain therapies, like chemotherapy, used to treat the disease. One such example of this was found in patients with a type of cancer called non-small-cell lung cancer. Non-small-cell lung cancer is a group of lung cancers with similar characteristics, and its five-year survival rate is about 37%. According to the study, chronic stress had decreased the effects of immune checkpoint inhibitor therapy (Fischer, 2023). Many studies like these have shown what stress does to cancer and to the therapies trying to prevent it. However, there is a very noticeable gap in these studies. There is not enough information on what stress relieving activities can help prevent cancer from worsening, which indicates that longitudinal studies are very much needed. Many cancer patients go through mental stress due to the healthcare system, ongoing treatments, and their life span. Sadly, a lot of them do not get the help that they need due to the stigma of mental health, and because of that, the stress they experience worsens their condition. By addressing this research gap, more effective therapies can be developed, and healthcare providers can have a deeper insight as to how to help the cancer patients, which can help mitigate the harmful effects of cancer

There have been many international studies done that have discovered the effects of stress on cancer.

A case- control study was conducted in Canada, and it was carried out on Canadian men with prostate cancer. This study found a link between workplace stress specifically, and prostate cancer. In 2008, there were a total of 142 studies that occurred across Asia, Australasia, Europe, and America, all of which demonstrated that stress was synonymous with higher occurrences in lung cancer. In 2019, nine observational studies in Europe and North America discovered a correlation between stress and the risk of obtaining lung, esophageal, and colorectal cancers (Stress and Cancer, 2022). In areas in Southeast Asia, cancer is extremely common. One such study found that psychological stress is not known much, which has negative effects since it can cause cancer to worsen, and thus increase. This study found that many patients in that region were under chronic stress due to ongoing treatments (Ostovar et. al, 2022). All in all, these studies prove that chronic stress has negative effects on cancer, and these effects can be extremely dire depending on the region you are located in.

The mental health crisis in the United States has increased drastically due to many factors, including COVID-19. Currently, 1 in 5 adults live with mental illnesses, and about 1 in 5 youth had a mental illness at some point in their life (About Mental Health, 2023). Simultaneously, roughly 2 million people got diagnosed with cancer in the United States in the year 2023 (Cancer Stat Facts: Common Cancer Sites, 2023). These two million people are most likely suffering from mental illnesses due to the rise in them, which can cause dire effects on their cancer growth. The combination of these two factors has created negative consequences as a whole, which is why national attention must be required. In order to fix this, the stigma of mental health must be removed, and mental health services must be integrated into cancer treatments.

In Georgia, cancer was the second leading cause of death in 2021 and has remained that way ever since (Bayakly, 2023). Given that stress levels increased everywhere after 2020 due to the pandemic, it is likely that chronic stress played a huge role in these deaths. In the United States, the healthcare system is a major source of stress, and Georgia is the worst state in terms of that (Masterson 2023). Given this information, it is imperative that the relationships between stress and cancer be investigated by doing deep research in the healthcare landscape of Georgia. The healthcare system in Georgia is notorious for being expensive, and more than 50% of its residents cannot afford it. To fix this, we must understand the complex relationship between chronic stress, its effects on cancer, and certain stressors as well as implement policies. Carrying these actions out will greatly help the people of Georgia when it comes to healthcare.

All in all, the relationships between stress and cancer must be investigated deeply. Cancer has disastrous effects on people and their families, some worse than others depending on the country or region. Cancer can be negatively affected by chronic stress and can even cause certain treatments to stop working, as proven by many studies. Chronic stress is caused by many problems, and an example of that is the healthcare system. In countries like the United States, the healthcare system is extremely expensive. On top of that, the mental health crisis has been worsening since the COVID Pandemic. Given all of these issues, if cancer patients think about these factors, their cancer will start to worsen, which could eventually kill them. If an investigation is carried out, more efficient treatments can be developed by integrating stress relieving activities into them. By doing this, cancer patients will feel less stressed, which can decrease the negative impacts of chronic stress in cancer.

Methodology

To conduct research on this, groups of people were selected from North America, Europe, Asia, and Australasia. The people were going to be assigned to either an experimental group or a control group. The experimental group was then required to do stress-relieving activities such as yoga, tai-chi, or meditation, while the control group was required to do none. Yoga, tai-chi, and meditation were the chosen activities because many people have reported a level of satisfaction from doing them. The reason stress-relieving activities were utilized is because it is shown that cancer patients experience positive psychological and physical changes (Rush et. al,

2016). Informed consent was then obtained from the participants, as this study would last for one year. Informed consent is required because human participants are involved in this study (2014). Every three months, mental health check ins were then required for submission. These check ins would ask how stressed the patients have been, and the cancer would be tracked to check for any signs of improvements. Additionally, medical information would be taken from each of the patients to investigate any other components that could possibly have an impact on the cancer.

After the one year period is up, the cancer level from the beginning would be compared to their current cancer level for each patient. Then, the patients who are from the same region but different groups would be compared to each other and then all the regions would be compared to each other in the control and experimental groups in terms of their stress and cancer. These comparisons would be made using statistical analysis tools like ANOVA and t-tests. The ANOVA and t-test would have tested for any differences between the means of the experimental and control group after 1 year. They would help determine if there are any significant differences between the groups. There would also be more tests conducted to see if biological sex, race, socioeconomic status, and the region the participants lived in had any effects on stress levels. After all of the research results are gathered, it would be discussed, and new ways to treat cancer would be studied and developed. This is the proposed methodology. A huge limitation in this study were participants leaving in the middle of the study, which affected the results.

Defining Stress

Stress is a huge and impactful everyday part of life. It is defined as a state of worry caused by difficult situations. Some of these situations can include school, university, jobs, or even personal problems. It is a natural response that is carried out by the parasympathetic nervous system. Acute or short term stress is advantageous to us because it produces alertness, which causes the boosting of performance at school, home, or work, and it can even allow us to recall certain consequences to our actions, so that we do not repeat them. There are multiple types of stress, which can either be caused by psychological issues, the environment, or both. Chronic stress has the opposite effects. Defined as stress for a long period of time, it can cause weakness, insomnia or the inability to focus. In recent years, it has been shown that there is a correlation between chronic stress and cancer (Heid, 2014), which has gained the attention of medical professionals and researchers. The systems that are involved are the endocrine, nervous, and immune systems, and their functions are very complex. Homeostasis is disrupted when chronic stress occurs, causing a cascade of reactions involving the release of hormones such as adrenaline and cortisol by the sympathetic-adreno-medullar systems, the hypothalamic-pituitary-adrenal (HPA) axis, and the release of inflammatory cytokines by the immune system. This paper dives deep into the ways stress leads to immunosuppression, enhanced inflammatory processes, and the progression of cancer. It will also discuss the ways that stress can be managed in healthy ways and review clinical trials and studies that have taken place in this field of medicine.

The Interactions Between Sympathetic-Adreno-Medullar Systems, Hypothalamic-Pituitary-Adrenal (HPA) Axis and the Immune System

When stress occurs, hormones such as adrenaline and cortisol, a type of glucocorticoid, are released by the sympathetic-adreno-medullar systems, the hypothalamic-pituitary-adrenal (HPA) axis that affects physiological systems, and the immune system (Petrinovic et.al, 2023). The sympathetic-adreno-medullar systems and the HPA axis have different functions. While both are activated by stressors, the sympathetic-adreno-medullar system provides a quick and instant response, while the HPA axis is very slow and is activated in extreme

circumstances. The immune system in turn produces inflammatory cytokines, some of which, including interleukin 6 (IL-6) can have direct influence on the nervous system, thus exacerbating the condition (Tanaka et. al, 2014). Due to the information about stressors being processed by the hippocampus, amygdala, and prefrontal cortex, the fight or flight response is activated. The fight or flight response is an automatic reaction carried out by the body during stressful events. The HPA axis and SAM system break down glucose more efficiently, allowing for energy to be redistributed in the body. New data shows that different brain regions control how immune cells respond to stress, affecting how well the immune system functions. If stress occurs before we encounter a threat, our immune system function is enhanced, and if we have prolonged/chronic stress, the function of the immune system is suppressed (Petrinovic et.al, 2023). Chronic stress causes systemic inflammation, thus increasing the risk of chronic diseases through the activation of latent viruses. The frequent activation of latent viruses can cause a decrease in immune function (Morey et. al, 2015).

Interrelationship Between Stress and Cancer

When a patient has cancer, they are more likely to go through chronic stress due to the medical costs of their treatment, given how expensive the treatments are, which can make the condition worse. Another factor in stress is whether they will be able to live or not. One of the effects of cancer is the weakening of the immune system. If one had chronic stress, anxiety, depression, or any mental health disorder prior to cancer diagnosis, there is a high chance that the immune system was already weakened, which leads to higher vulnerability in certain diseases, like cancer (Doolittle, n.d.). Tumor cells secrete immune-suppressive cytokines like TGF- β and IL-10, which allows for the inhibition of antitumor immune cell activity through reducing their proliferation, effector functions, and intratumoral infiltration (Mirlekar, 2022). So, the cancer is weakening an already weakened immune system caused by chronic stress. This isn't particularly helpful when there is a lot of stigma surrounding mental health disorders like depression and anxiety, and when there is a lack of resources around the world. According to the CDC, more than 1 in 5 adults suffer from mental health issues (About Mental Health, n.d.).

These responses can be shaped by biological factors, such as age, gender, and genetics, which can have therapeutic implications. Acute, or short term stress speeds up the response of the immune system by increasing T cell mobilization through a beta-2-adrenergically mediated process, while chronic stress slows it down (Dragos et. al, 2010).The slowing down of the response leads to a decrease in the amount of immune cells, enhanced immunosuppression, and an altered type 1/type 2 cytokine balance, which results in the contribution to cancer growth.

Many cancer patients have demonstrated chronic stress due to the ongoing treatments. In the brain regions of many patients, there have been changes in the neuronal structure such as sustained synaptic plasticity and dendritic alterations in the amygdala and hippocampus. Some other changes include alterations in the CRH gene and protein expression, activation of the HPA axis, glucocorticoid hypersecretion, sensitized stress responses, and alterations in the locus coeruleus-norepinephrine function (Petrinovic et.al, 2023). During chronic stress, both the HPA and SAM systems are activated, which allows for high levels of stress hormones to be released. Due to their release, DNA damage is induced, and the function of the p53 protein is suppressed, which promotes tumorigenesis (Ozaki et. al, 2011). The activation of the HPA system leads to the production of steroid hormones called glucocorticoids, in response to stress. During inflammation, glucocorticoids increase the development of cancerous tumors, and if prolonged, can cause a feedforward loop of the release of damage-associated molecular patterns (DAMPs) (Khadka et. al, 2023). They also stimulate cell proliferation by activating certain pathways and influence the tumor microenvironment. Chronic stress also allows for the accumulation of immune cells with immunosuppressive effects, the production of proinflammatory cytokines, and the reprogramming of myeloid cells into hyperinflammatory ones. Inflammation is a huge feature of cancer because

cancer itself can cause neuroinflammation, which alters circadian rhythm dysfunction, sleep disturbances, aberrant glucocorticoid production, and dysregulation of neural network activity. In cancer patients, pro-inflammatory cytokines, which are produced in the blood-brain barrier, allow for stress responses to be impaired and more inflammatory mediators to be produced. Also, oncological treatments such as radiation and chemotherapy can play a huge role in this and can appear as a side effect of the treatments or short-term (Francesco et. al, 2021). Glucocorticoid treatment is used as a supportive therapy, and it has led to HPA dysfunction for many patients.

Clinical data has shown that there are elevated levels of cortisol and dysregulation of the HPA axis in cancer patients, especially those with high tumor grade and advanced cancer, due to cancer treatments and chronic stress. For example, patients with advanced breast cancer showed flattened circadian rhythms and erratic fluctuations compared to human beings with normal functioning, thanks to elevated circadian cortisol levels (Sephton et. al, 2000). This has led to immunosuppression. Chronic stress creates pro-inflammatory factors, such as cytokines and catecholamines, which are located in peripheral tissues and the brain. The pathways involved, such as NF-kB and STAT 3, are activated, resulting in the production of proinflammatory cytokines, thus promoting tumor growth through cell proliferation (Zhang et. al, 2021).

Chronic stress also causes the activation of microglia in certain brain regions, allowing for the production of proinflammatory cytokines. Therefore, stress-related neurocircuitry is reinforced through chronic stress and cancer activated microglia (Petrinovic et.al, 2023). The inflammation that occurs due to stress is controlled by the positive feedback of certain pathways. So, researchers are developing new treatments that can prevent them from occurring. One of them is being developed to block IL-1 β , a stress induced cytokine. This has been tested in cardiovascular disease, and it led to lower incidence of lung cancer. Another cytokine being targeted is known as the macrophage migration inhibitory factor (MIF), which is known for causing a dysregulated immune response. Lastly, Il-6 signaling is being looked at as well because it is one of the most frequently dysregulated pathways. In fact, it is characterized by increased levels of cortisol which plays a role in depression and anxiety, seen in many cancer patients. However, clinical trials have been carried out against this pathway and have shown a poor response to it. All in all, anti-inflammatory therapy has a strong potential, but there are some clinical trials that are ongoing as of today.

All in all, the activation of the HPA axis during chronic stress results in the release of hormones like cortisol. Due to this, the immune system is deeply weakened since cortisol levels diminish the activity and function of immune cells. Chronic stress also leads to the suppression of the tumor suppressor protein p53, which results in NF-kB and STAT 3 transcription factors being activated. This ends up causing the increased production of cytokines like IL-1 β and Il-6, which are involved in the inflammation of cancer.

Strategies to Minimize/Mitigate Stress

Many activities, such as yoga, meditation, and tai-chi have been used to moderate chronic stress effectively. Many studies have shown that patients who have done yoga have had a reduction in self-reported depression and anxiety. Meditation allows you to focus on one thing and get rid of all of your other thoughts, thus relieving stress (Meditation: A Simple, Fast Way To Reduce Stress, n.d.). Yoga and tai-chi allow you to stretch and take deep breaths as you are doing those exercises, which have been found as stress-relieving. For yoga, fatigue was only an outcome, but it helped improve sleep and cognition conditions in cancer patients. Pranyama, a type of breathing exercise, and many other relaxation techniques have been associated with the decrease in anxiety, while hyperventilation techniques such as Bhastrika, Kapalabhati, and Ujjayi pranayama have been associated with antidepressant effects (Rao et. al,2017). In 2017, there were several studies analyzing the effects of yoga on breast cancer, and they suggested that yoga helps alleviate anxiety, depression, sleep, and tiredness. Meditation has also been proved to show the same effects as yoga, and when used alongside medical treatment, it can lower blood pressure, as stated by the National Institute of Health (“Take a Moment With Meditation”, 2020). Lastly,

a study involving 22 randomly controlled trials and 1,410 cancer survivors showed that people who practice tai chi three to five times a week have lower cancer-related fatigue and cortisol levels (Gubili et.al, 2023).

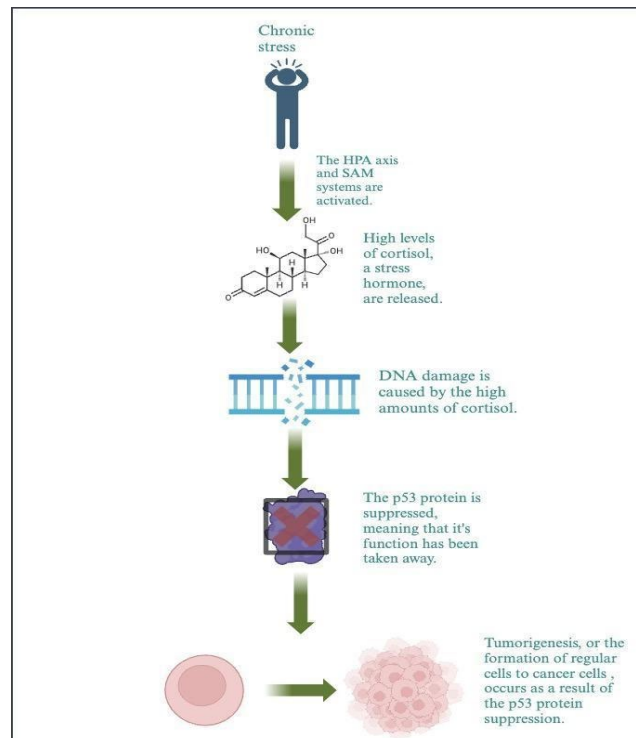


Figure 1. Relationship Between HPA Axis and SAM Systems. In this figure, it is shown that the HPA axis and SAM systems are activated due to chronic stress. Due to this activation, high levels of cortisol are released, which causes damage to the double helix structure of the DNA. The p53 protein is then suppressed due to the damage, causing tumorigenesis, or the formation of cancer cells from body cells. The suppression of the p53 protein can also cause the activation of the NF-kB and STAT-3 transcription factors, causing the production of certain cytokines and thus, causing cancer inflammation (Created in BioRender.com by Manasa Shankar).

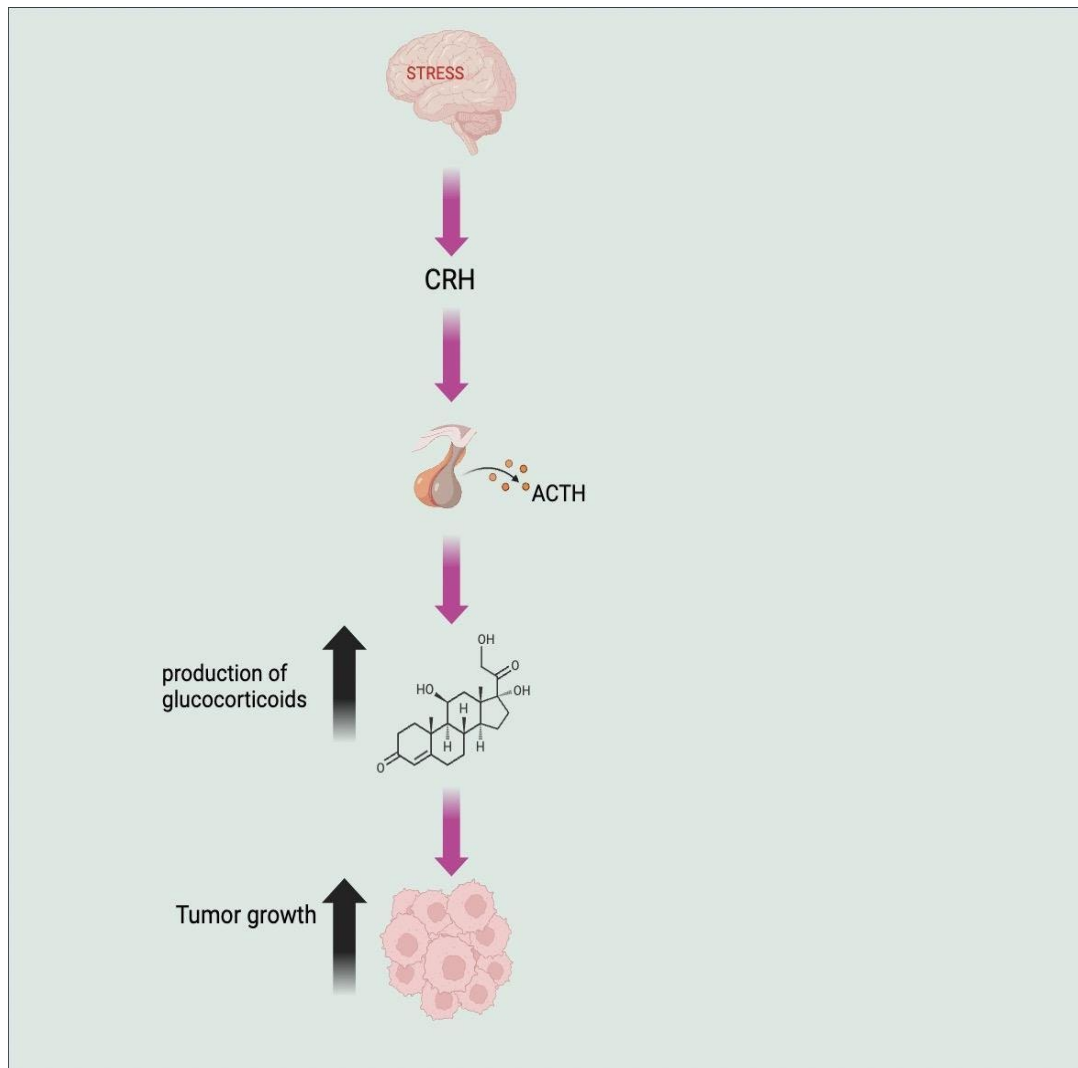


Figure 2. Stress Causing Increased Tumor Growth. Increased amounts of stress as well as tissue damage, causes the hypothalamus to release increased amounts of the corticotropin-releasing hormone, commonly known as CRH. This in turn causes the adrenocorticotropic hormone (ACTH) to be released by the pituitary gland. After that, the production of glucocorticoids is increased, allowing for the increased growth of cancerous tumors, which causes cancer to spread throughout the body (Created in BioRender.com by Manasa Shankar).

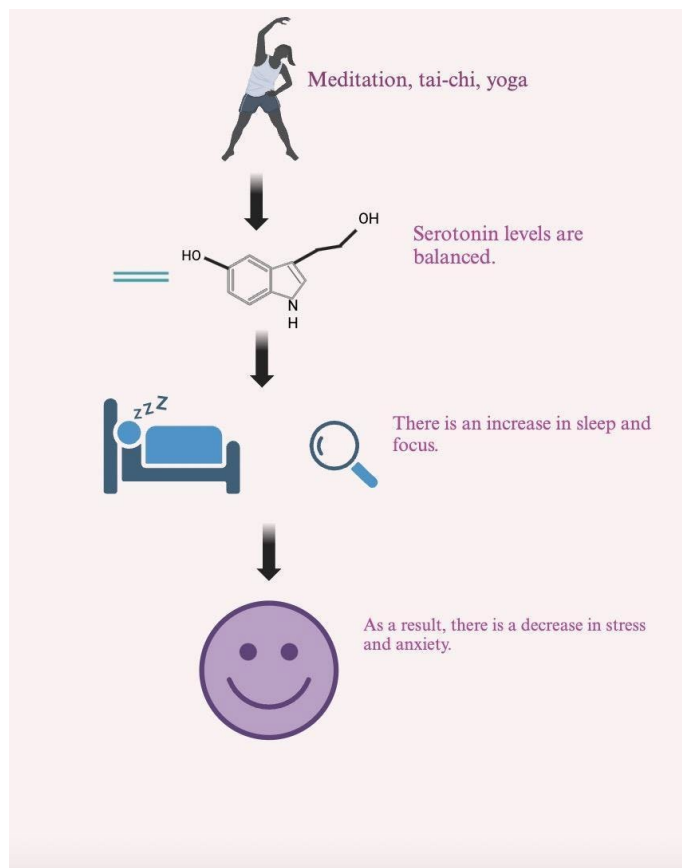


Figure 3. Physical Activities that Help Minimize Stress. This figure shows how relaxing activities such as meditation, tai-chi, and yoga allow for a huge decrease in anxiety and depression. One of the factors causing the two mental health issues is the imbalance of serotonin, a monoamine neurotransmitter that regulates sleep and mood. Some who experience depression or anxiety usually have very high or low levels of serotonin, which is what causes an imbalance in it. By doing meditation, tai-chi, and yoga, your serotonin levels start to balance out. This balance causes an increase in sleep and focus. As a result, there is a decrease in stress and anxiety, thus decreasing the harmful effects of cancer (Created in BioRender.com by Manasa Shankar).

Conclusion

In conclusion, the relationship between chronic stress and cancer has been identified. The relationships and interplay between the SAM systems, HPA axis, and the immune system causes inflammation and immunosuppression. The consequences of chronic stress are very dire, especially when one is in the horrid situation of cancer. An example of this is stopping the inhibition of tumor growth. Alterations in neuronal structure, hormonal dysregulation, and many other changes caused by chronic stress have had a huge impact on the progression of cancer. There are many ways to combat this huge and important problem. First, spreading awareness of mental health issues around the world through tools like social media, may aid in greatly decreasing mental health issues regarding depression and anxiety, which are deeply rooted in chronic stress. By decreasing them, less people will have chronic stress and a weakened immune system. Second, longitudinal studies, or studies that last for a long period of time, can be carried out on many different types of patients, allowing researchers to identify any patterns in terms of chronic stress, which is now made easier given the recent technology such as Artificial Intelligence. for example. By identifying certain patterns, researchers can come up with efficient

treatment plans to help people. Lastly, recommending activities such as yoga, tai-chi, and meditation can help reduce chronic stress, thus improving the mental and physical health of cancer patients.

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