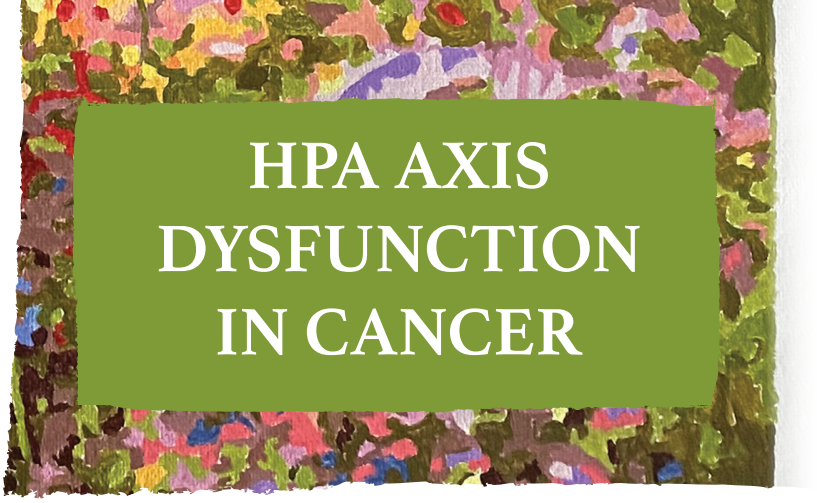
Cleveland's Center for Healing
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Functional Medicine



HPA AXIS DYSFUNCTION IN CANCER

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction occurs when there is a change in the body's stress response over time. Chronic stress, from psychosocial stress, over exercise, emotional disturbance, traumatic life events (such as a cancer diagnosis), or poor diet can initiate dysfunction. When the body experiences chronic stress, the HPA axis releases hormones at an accelerated rate, which can desensitize the glands and cause them to stop responding to signals to stop producing needed hormones. When the stress response is activated, your body initiates a "fight or flight" response to help you respond and manage physical and psychological stress.

In 2018 global cancer statistics published documentation that recurrent cancers worldwide are related to endocrine or hormone alterations, these cancers include breast, uterine, thyroid, prostate, ovarian, and pancreatic[1]. Other cancers are affected as well as stress hormones promote the occurrence and development of cancers through inducing DNA damage, increasing tumor suppressor degradation so more tumors can grow, and stress hormones regulate the tumor microenvironment where the tumor grows. Chronic stress can also activate the inflammatory response and the interaction between inflammatory cells and cancer cells to increase inflammation in the tumor microenvironment, thereby promoting all stages of tumor growth[2].

The Hypothalamic-pituitary-adrenal axis (HPA) is the main stress response system in our bodies. It's made up of three structures: the hypothalamus, pituitary gland, and adrenal glands. These glands are Hormone-secreting glands:

- The Hypothalamus: A small structure in the brain that controls the release of hormones from the pituitary gland
- The Pituitary gland: A pea-sized gland at the base of the brain that releases hormones and controls other endocrine glands
- The Adrenal glands: these two glands located on the kidneys regulate adrenal hormones, especially glucocorticoids, which help restore homeostasis during stress.

The manifestations of stress you notice in your body start with the biological changes associated with activation of the HPA axis. A stressor or stressors first causes a release of Corticotropin Releasing Hormone from the hypothalamus and stimulates the release of Adrenocorticotropic Hormone from the anterior pituitary. This latter hormone then stimulates the release of cortisol, known as the stress hormone, from the adrenal cortex. Cortisol is known for altering many systems in the body in patients with cancer, including the suppression of the immune system and response to healing, decrease in metabolism, inhibition of DNA repair, and effects on apoptotic pathways that affect cell growth[3].

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The main hormone impacting cancer in the HPA axis is cortisol and cortisol is the hormone of focus in this discussion. Cortisol is known as the stress hormone. Its actions make it a key player in the stress response, whether acute or chronic. High cortisol levels in cancer patients have been associated with a worse prognosis and faster cancer progression[4].

Cancer patients are often prescribed prednisone during cancer treatments, because of its anti-inflammatory properties and its action reduces side effects of chemotherapy. Prednisone is a corticosteroid (cortisone-like medicine or steroid). It works on the immune system. Patients are typically prescribed prednisone for colon, kidney, bladder, prostate, cervical, ovarian, and pancreatic cancers treatment. The roles of prednisone and other synthetic glucocorticoids have been controversial as these treatments can also induce resistance to chemotherapy[5]. Cortisone is not the same hormone as cortisol, the stress hormone.

Changes in the cancer patient's HPA axis are common. Not only because of stress but also from the different antitumor therapies used, which can lead to hormones producing side effects. Chronic stress affects specific hormones that regulate targets through the HPA axis and sympathetic nervous system, inducing events critical for the initiation and progression of cancers[6]. Tumor induced inflammation can increase cortisol levels. And cortisol released under stress can impair antitumor immunity and negatively impact cancer progression. Cortisol has been known to suppress the immune system's ability to detect and destroy cancer cells. This increases the chances for early-stage cancers to escape the immune system and develop further mutations[7].

Stress can and does promote the occurrence and development of tumors. Once we are exposed to excessive stress and long-term chronic stress, anxiety develops and damage to our health occurs. In cancer patients, both the sympathetic nervous system (part of our fight or flight response for an emergency) and the HPA axis are abnormally activated. Neurotransmitters and hormones are secreted into the vicinity of the tumor or in the systemic circulation. With the increase in cortisol, tumor progression is promoted by molecules regulating cancer cell growth, survival, blood vessel formation, and immune responses[8].

Elevated Cortisol has the effect of causing weight gain in many patients. Cortisol can have a hyperglycemic effect elevating blood sugars possibly leading to diabetes and have an impact on obesity, which can increase the risk of malignancies.

For every cancer root, we discuss the effects of that cancer root on mitochondria. Mitochondria are implicated in all cancer processes, from the cell's change from a normal cell to a cancer cell, metastasis to other sites and resistance to therapy. The harsh tumor environment constantly exposes cancer cells to toxic cell stressors, such as decreased nutrients, low oxygen, and oxidative stress. Excessive or prolonged exposure to these stressors can cause irreversible mitochondrial damage, leading to cell death. Normal cells will not survive irreversible mitochondrial damage. On the other hand, to survive hostile microenvironments, cancer cells activate their own stress response to maintain mitochondrial integrity for the cancer cells. This adaptive mechanism, which is closely linked to mitochondrial function, enables rapid adjustment and survival in harsh environmental conditions encountered during tumor distribution, thereby promoting cancer progression. The mitochondrial stress response empowers rapid adjustment to the adverse environmental conditions encountered during tumor cell distribution and offers a survival advantage of the cancer cell leading to tumor growth, metastasis, and drug resistance[9]. At high concentrations and/or for prolonged periods of time, exposure to corticosteroids/cortisol causes a decrease in mitochondrial activity and decreases ATP production for energy. There is an increase in reactive oxygen species causing cellular damage[10]. Damage to DNA and to cellular RNA and proteins occurs and may cause cell death. In a study by Flaherty et al, it has been demonstrated that acute exposure to cortisol increase DNA damage and cell repair is reduced[11].

It's important for cancer patients who are healing to identify their level of stress, possibly levels of cortisol via testing, and to find stress reduction techniques to lead to a decreased level of cortisol.

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Understand what Symptoms of Elevated Cortisol are:

1. Elevated cortisol can cause rapid weight gain in the belly, but also in the face and chest. Cortisol affects levels of ghrelin and leptin. Ghrelin is referred to as the "hunger hormone" as it induces hunger. Leptin, on the other hand, will cause you to feel full or satiated. Cortisol lowers leptin while increasing ghrelin, leading to weight gain, especially in the abdominal area
2. Easy bruising and slow healing are also signs of elevated cortisol. Elevated cortisol affects the immune system.
3. Muscle weakness can occur and be noticed in the upper arms and thighs.
4. Chronic fatigue is a common symptom of elevated cortisol.
5. Cortisol has effects on the gastrointestinal system because it slows movement through the stomach and leads to bloating and indigestion. It can also lead to diarrhea. It negatively impacts the G.I. microbiome.
6. Increase in blood pressure can occur.
7. Bone loss can lead to Osteoporosis, increasing your risk of fractures.
8. Mood changes such as depression and anxiety, mood swings and sadness also tend to occur more frequently.
9. Cortisol influences our circadian rhythm, not just as a player in the stress response. Cortisol is released in large amounts in the morning but levels at night will be the lowest. The duration of stress can increase cortisol chronically and this can affect the circadian rhythm leading to fatigue, sleep difficulties and more. Chronic insomnia or frequent nighttime waking is a symptom.
10. Other biological changes can include elevated blood sugars, muscle pain, or muscle tension.

Ways you can balance your cortisol levels in addition to continuing your oncology treatments

1. What you eat can not only impact your cancer, but also your cortisol levels, eating foods such as processed meats, high sugar foods, caffeine and alcohol, which provide little nutritional value, have been associated with more psychiatric symptoms and can increase cortisol levels. MD Anderson Center lists foods, like cookies, cakes, sugary drinks, white bread, and pasta as foods to avoid, they cause blood sugar levels to rise rapidly. The body then produces insulin to bring blood sugar levels back down, which can lead to a crashing period that affects other hormones, including cortisol[12]. The resulting chronic elevation in insulin, known as hyperinsulinemia, over time, also drives cancer growth and metastasis.
2. Caffeine is known to increase cortisol, limiting caffeine intake is recommended to reduce elevated cortisol levels.
3. Relaxation techniques, like deep breathing exercises, yoga, mindful meditation, and prayer all will help reduce cortisol levels. In functional medicine we typically recommend regular meditation twice a day for 20 minutes. Reducing stress levels will help suppress the release of cortisol. Getting into a daily habit using these tools can help bring cortisol levels down.
4. Getting enough sleep is critical, sleep is the time for cellular healing in the body. Many times, elevated cortisol disrupts sleep. Typically, you find you wake up at 3 o'clock in the morning and can't go back to sleep. This is a sign of elevated cortisol as cortisol starts to rise early in the morning to get us ready for the day. It's already elevated, its effects are compounded. There are supplements that can assist patients in bringing their elevated cortisol levels down at night in addition to relaxation techniques. Adaptogenic herbs such as Ashwaganda and Rhodiola, Adaptogen's help the body adapt to stress. Holy basil tea is another action. Magnesium can also help patients relax.
5. In the warmer weather, spend as much time outside as possible: get your bare feet on the ground and practice grounding/earthing, here's a link to learn more about its effects on inflammation and healing:

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Oschman JL, Chevalier G, Brown R. The effects of grounding (earthing) on inflammation, the immune response, wound healing, and prevention and treatment of chronic inflammatory and autoimmune diseases. J Inflamm Res. 2015 Mar 24;8:83-96. doi: 10.2147/JIR.S69656. PMID: 25848315; PMCID: PMC4378297.

6. The Grounded Documentary (Steven Kroschel)--free on Youtube. He is a filmmaker for National Geographic and runs a wildlife rescue in Haines, Alaska. He tested it on his whole town. --Heal For Free.
7. Websites: http://earthinginstitute.net. Under the research tab you will find placebo-controlled studies on the benefits of grounding/earthing. You can also look under the FAQ tab at the about where to buy earthing products. It will send you to a different website from which you can order products.
8. http://www.intuition-physician.com. This is the website for Laura Koniver MD. She is an integrative physician and earthing expert and does web-based classes. She reviews articles for tvarious topics regarding the benefits of ground/earthing. She also sells grounding products. She is featured in the two documentaries above.
9. People: James Oschman PhD (cell biologist, and pioneer scientist in the field of energy medicine. Did some of the original research on the benefits of grounding. Also wrote the book: energy medicine: the scientific basis). Clint Ober--Brought a lot of momentum to considering the benefits of earthing. Co-wrote the book Earthing: The Most Important Health Discovery Ever? With Stephen Sinatra MD (integrative cardiologist and also expert on grounding) and Martin Zucker.
10. Joseph Mercola also talks about earthing

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12 - https://www.mdanderson.org/cancerwise/8-foods-that-impact-stress