


## VIEWPOINT

### Cancer Focus

# Hormonal basis of brain fog in cancer treatment

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**The cognitive side effects of cancer treatment are common, but no targeted therapy exists yet to treat or prevent such neurological sequelae. We explore the role of hormones as mediators between cancer therapy and cognitive impairment, discussing potential future directions.**

## Cancer treatment induces cognitive impairments

Thanks to advances in cancer treatment, the survival of cancer patients has increased significantly. According to the American Cancer Society, in 2022, ~47% of cancer patients have lived more than 10 years since diagnosis, and there will be 22.5 million cancer survivors in the U.S. by 2032 ([American Cancer Society, 2022](#)). As the overall cancer survival rate increases, more cancer survivors are battling the long-term adverse side effects of cancer treatment including those in the central nervous system (CNS). For instance, many breast cancer patients experience cognitive deficits including worsened memory or concentration even after treatment cessation, and these adverse neurological sequelae can last for years ([Schagen et al., 1999](#)). As the population of cancer survivors continues to grow, understanding the cognitive impairments associated with cancer treatment is critical to improving the quality of life for cancer patients. Despite the increased research efforts into cancer therapy-induced cognitive impairment, there is currently no FDA-approved therapy for preventing or treating these neurological sequelae.

All forms of cancer treatment carry the potential to impact CNS function. High-dose cranial radiation and the administration of chemotherapy agents are associated with worse cognitive function. Additionally, the

increasing use of immunotherapy is also associated with cognitive impairment and immune-related adverse events in the neurological system ([Schagen et al., 2022](#)). Several cellular mechanisms have been proposed to explain cancer treatment-induced cognitive impairments. Cancer treatment can directly impair neuronal function by reducing neurotransmitter release or altering synaptic structure. Various agents in cancer therapy block cell division, affecting the proliferating neural stem cells (NSCs) and neuroglial progenitor cells, thereby compromising neurogenesis and gliogenesis after treatment. Glial cells play crucial roles in neurodevelopment and plasticity. For example, microglia are professional scavengers that prune synapses during neurodevelopment and adulthood. Astrocytes form tripartite synapses with neurons to support synaptogenesis and modulate synaptic activity. Oligodendrocytes dynamically myelinate neuronal axons to modulate their conduction speed. Recent findings revealed that microglia, astrocytes, and oligodendrocytes are all affected by chemotherapy, leading to neuroinflammation and inhibited adaptive myelination that are responsible for the associated cognitive impairments ([Geraghty et al., 2019](#); [Gibson et al., 2019](#)). Molecularly, preclinical studies demonstrated that cancer therapy-induced cognitive deficits involve

proinflammatory cytokines (e.g., TNF $\alpha$  and IL-6), oxidative stress (e.g., increased production of reactive oxygen species), damaged mitochondria, reduced neurotrophic factor (e.g., brain-derived neurotrophic factor) release, and disrupted lipid metabolism ([Gibson and Monje, 2019](#)). A mystery surrounding the explanation of chemotherapy-induced cognitive impairments lies in the fact that numerous cancer therapeutic agents do not cross the blood-brain barrier (BBB). Consequently, the mechanism by which these agents induce changes in the above-mentioned cellular and molecular modulators, affecting brain function, remains unclear. Our hypothesis posits that systemic cancer therapies may have a profound impact on the endocrine system, thereby influencing brain function.

## The endocrine-brain axis is vulnerable to cancer treatment

It is well established that cancer treatments can induce long-term endocrine dysregulation by affecting the function of major hormone-producing organs such as the hypothalamus, pituitary gland, thyroid, parathyroid, adrenal glands, and reproductive organs ([Gebauer et al., 2019](#)). All common cancer treatment modalities, such as surgery, radiation, chemotherapy, and immunotherapy, have the potential to cause endocrine disorders. For example, cranial radiotherapy,

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which treats brain tumors or prevents brain metastasis, can cause hormone deficiency due to damage to the hypothalamus and pituitary gland (Constine et al., 1993). Deficiencies in hormones are frequently observed following cranial radiation. Given the central role of the hypothalamic-pituitary axis in modulating endocrine function, radiation-induced effects can extend to many types of hormones and endocrine functions. Likewise, chemotherapy and immunotherapy agents can also damage the endocrine system, although the effects of individual agents vary (Byun et al., 2017; Gebauer et al., 2019).

Numerous hormones play important roles in neurodevelopment, neuroplasticity, and neurodegeneration. For example, thyroid hormones modulate neurogenesis, synaptogenesis, and gliogenesis; insufficient thyroid hormone production can cause neurological deficits (Bernal, 2000). Similar to thyroid hormones, various other hormones influence different aspects of neuronal function. In addition, stress is an inevitable aspect associated with cancer and cancer therapy, and hormones associated with chronic stress are known to affect cognition (de Souza-Talarico et al., 2011), potentially imposing challenges in the daily lives of cancer patients.

Hormone therapies are frequently used to treat certain types of neoplasm and have been successful in increasing the survival of cancer patients. In certain prostate cancers, the hyperactivity of androgen receptor (AR) induces tumor growth. Therefore, hormone therapy is used to lower the level of androgens (e.g., testosterone) or inhibit AR activity. Similarly, hormone therapy is one of the major treatment strategies for estrogen receptor-positive breast cancers. As sex hormones can protect the nervous system, such hormone therapies that reduce the level of sex hormones or block the activity of hormonal receptors can adversely influence cognition. Patients who receive hormone therapy for cancer often report experiencing brain fog, such as worsened memory and attention (Lange et al., 2019; Haggstrom et al., 2022). In addition to hormone therapy, some cancer therapies (e.g., chemotherapy) induce menopause and affect sex hormone release, which could indirectly affect cognition.

Given the connections between cancer treatment, hormonal dysregulation, and

the impact of hormones on cognition, it is highly likely that dysregulated hormones are critical mediators for long-term cognitive defects associated with cancer treatment. However, the extent and mechanism by which cancer treatment-induced endocrine dysregulation directly leads to the long-term cognitive deficits observed in cancer survivors remain unclear.

### Key knowledge gaps in the endocrine–brain axis in cancer, research considerations, and future directions

Many hormone-induced neurological effects are reversible if the excess hormones are suppressed, or hormonal insufficiency is overcome. Timely intervention will be important to avoid the long-lingering neurological side effects associated with cancer treatment. We postulate that hormonal dysregulation is one of the key factors leading to cancer therapy-associated cognitive impairment, which potentially can be reversed by hormonal modulation. One might consider hormone therapies that modulate hormone production for a particular combination of cancer and cancer treatment. However, before implementing such strategies, research efforts to better understand the underlying mechanisms and the potential effects of hormones on cancer progression and treatment efficacy are essential. Moreover, cancer treatment-induced cognitive impairments often result from the combined effects of multiple dysregulated systems. The quantification of changes in hormonal levels within the CNS (e.g., in the cerebrospinal fluid) before and after cancer treatment in patients can offer valuable insights into critical hormones that connect cancer treatment to the associated cognitive deficits. It is also critical to determine CNS hormonal changes shortly and long after cancer treatment to gain information on both short-term and long-term effects.

Various other factors may also influence endocrine and cognitive function during cancer treatment. Many medicines that are given to cancer patients, either during or after treatment, can alter CNS function. For example, patients with a history of chemotherapy may exhibit a higher sensitivity to general anesthetics. The impact of anesthetic agents on chemotherapy-induced cognitive impairment depends on factors such as the type and dosage of the agents

(Guran et al., 2022). Additionally, some agents, like steroids and benzodiazepine (a  $\gamma$ -aminobutyric acid receptor agonist), are co-administered during cancer treatment, potentially affecting the endocrine system and cognition. Future research is essential to investigate the combined effects of other medicines alongside cancer treatment.

Age and sex are important factors for understanding the impact of cancer treatment on endocrine and cognitive deficits. Previous studies primarily used adult animals, thus focusing on modeling adult cancer patients. New models are needed to understand the distinct scenarios faced by children, young adults, and seniors. In 2020, there were approximately half a million people who survived childhood and adolescent cancer (National Cancer Institute, 2023), with more than 50% of childhood cancer survivors living with long-lasting endocrine side effects due to cancer therapy-induced hormonal dysregulation (Brignardello et al., 2013). Pediatric cancer patients, having received treatment during neurodevelopment, exhibit cognitive issues affecting their daily life, such as academic performance (Pierson et al., 2016). Future studies should delve into the diverse impacts of different cancer treatments on the endocrine system and neurodevelopment, and explore the intricate interactions between these two systems. Similarly, in seniors, where age is a major risk factor for neurodegeneration, investigating how cancer treatment influences the onset and types of neurodegenerative conditions would significantly benefit from examining the potential link between age and hormonal function. Beyond age considerations, mouse cognitive behavioral tests frequently reveal sex-dependent phenotypes, as brain cells from different sexes may respond differently to hormones. For instance, microglia express estrogen receptors, contributing to sex-dimorphic functions. It is imperative to assess potential sex differences thoroughly in upcoming clinical and pre-clinical studies.

One notable caveat in cancer treatment studies is the reliance on *in vitro* assessments of the impact of cancer therapy agents (e.g., chemotherapy) on cultured brain cells, especially NSCs. However, a large number of cancer therapy agents do not cross the BBB and the doses used in the *in vitro* studies may not represent

concentrations in the CNS. Additionally, some cancer or cancer therapy agents can alter BBB integrity, a possibility that also deserves careful evaluation. If an agent induces cognitive deficits without entering the CNS and directly altering brain cell function, systematic inflammation or endocrine dysfunction may be the underlying factors that induce the neurological sequelae. Another consideration is that most *in vivo* pre-clinical studies of cancer treatment-induced endocrine/cognitive impairment were carried out by administering single or multiple cancer treatment agents (e.g., radiation, chemotherapy, or immune checkpoint inhibitors) to cancer-free rodents. However, the presence of cancer itself can influence endocrine and CNS functions. When modeling cancer treatment in animals, it is crucial to consider the direct effects induced by cancer cells on cognition. CNS

issues may arise not only from tumors within the brain but also from neoplasms outside of the CNS via inflammation or the gut-brain axis (Borniger et al., 2018). While it is essential to study the cognitive impact independently of cancer or cancer treatment alone, it is also important for future studies to establish experimental models that evaluate the combined endocrine and cognitive effects of both cancer cells and their corresponding therapy agents.

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