

Role of Cortisol Hormone in Disease Progression and Response to Care among Cancer Patients: Systematic Review

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ABSTRACT

Cortisol can increase the complexity of cancer by affecting tumor growth, treatment response, and spread, although the specific mechanisms remain poorly understood. The research aims to understand the role of cortisol in response to cancer. Using the PICOS to conduct a systematic review, the keywords "cortisol, cancer, RCT, and stress" yielded 548 papers from 2019 to 2024 that were found using Scopus (n = 3), ScienceDirect (n = 209), ProQuest (n = 305), and Web of Science (n = 31). Requirements for inclusion: (i) the RCT was authored in English and published in peer-reviewed journals between 2019 and 2024; ii) study participants had a clinical cancer diagnosis; iii) cortisol hormone methods were monitored. Twenty articles fulfilled the requirements for review inclusion. The outcomes of the review of the literature: 1) cortisol's impact on the immune system; 2) its influence on the advancement of cancer; 3) the interaction between therapy and cancer treatment; 4) the use of cortisol levels as a biomarker; 5) the impact on cancer symptoms and quality of life; 6) Cortisol control in cancer patients; 7) the possibility of other medical issues. The study highlights the significance of cortisol in the development of cancer, the effectiveness of treatment, and the quality of life for patients. The fact that excessive cortisol levels can negatively impact the immune system, promote the survival of cancer cells, interfere with medication, and reduce quality of life emphasizes the need for effective cortisol level control in cancer patients.

KEYWORDS: Biomarker; cortisol; cancer; immune system; randomized control trial

INTRODUCTION

Cancer is an illness that significantly affects a person's bodily and emotional suffering¹. Cancer patients not only have to deal with the physical difficulties of a rigorous and sometimes excruciating course of treatment, but they also frequently face severe psychological stress². Globally, 2.3 million cases of breast cancer were diagnosed by 2020, with 685,000 deaths anticipated³. Pregnancy and menstrual age are two variables that have affected the prevalence of breast cancer in the US, but India is also seeing a rise in instances of the disease⁴; this indicates the need for better education programs on breast cancer in the community⁵. Indonesia has the eighth-highest cancer incidence rate (136.2/100,000 people) in Southeast Asia but is ranked 23rd overall⁶. Breast cancer is the most frequent cancer in women, accounting for 42.1 cases per 100,000 people, and it has an average mortality rate of 17 cases per 100,000 people⁶. In Central Java Province, Indonesia, there are 129 suspected breast cancer cases in Puskesmas, and 131 cases referred⁷. Worldwide,

breast cancer is the most prevalent cancer among women. Cortisol can increase the complexity of breast cancer, such as tumor growth, response to treatment, and probability of spread. Thus, cortisol can be a factor that worsens breast cancer conditions^{8,9}.

Age, sex, reproductive variables, radiation exposure, alcohol use, genetics, family history, hormone factors, and lifestyle choices are risk factors for breast cancer. Breast cancer symptoms include discomfort, discharge of milk, skin changes, and a circle or lump¹⁰. In the meantime, the immune system's control and reactions to stress are impacted by cortisol, the stress hormone secreted by the adrenal glands. Thus, cortisol regulates immunity and the body's response to stress in this setting, whereas estrogen influences specific aspects of physical growth¹¹.

There are some obvious benefits to this research. Firstly, novel insights have been discovered that may enhance the prognosis and quality of life for cancer patients. We investigated the relationship between the cortisol hormone and cancer treatment. Through this research, we intend to learn more about the processes behind treatment resistance in breast cancer, which may eventually lead to improved therapeutic outcomes. Additionally, we believe this study will transform how we treat cancer and offer hope to people impacted by it. We also evaluated the predictive biomarker by examining the connection between cortisol levels and treatment results. Our ultimate objective is to improve cancer patients' survival chances and provide better treatment¹².

This study aims to understand the role of cortisol in

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response to cancer and more effective treatment strategies. With a better understanding of these mechanisms, it is expected to improve the prognosis and quality of life of breast cancer patients. Further studies are needed to understand the complex interactions between cortisol and breast cancer, as well as their implications for treatment responses.

METHODOLOGY

We used systematic review to combine relevant studies on how cortisol affects the response to breast cancer therapy as well as to find new ways to treat breast cancer more effectively. Utilizing the Joanna Briggs Institute Guidelines and the Center for Review and Dissemination, we employed the PRISMA checklist of questions to assess the study's quality. Search strategy and inclusion criteria for systematic reviews

The method for searching for relevant material is to use keywords such as "cortisol," "cancer," "RCT," and "stress," OR Cortisol AND Cancer AND RCT AND Stress. Next, relevant papers from other references are also looked for, and databases such as Scopus, ScienceDirect, ProQuest, and Web of Science are used to find the articles. The PICOS criteria (population, intervention, comparison, outcome, and study design) define the inclusion criteria for journal articles published during the previous five years, from 2019 to 2024 (Table I).

Table I: Description of PICOS systematic review

Criteria	Inclusion	Exclusion
Population	Cancer	Apart from cancer
Intervention	The cortisol hormone	There are no exclusion criteria
Comparisons	NA	There are no exclusion criteria
Outcome	Cortisol hormone in cancer patients	No relevant hormone cortisol in cancer patients
Study type	RCT by looking at cortisol hormone levels	Don't talk about the cortisol hormone
Type of publication	Original studies subjected	Unreviewed research studies
Years	2019 to 2024	Pre-2019
Language	English	Languages besides English

Study selection, data extraction, and management

Research databases Scopus, ScienceDirect, ProQuest, and Web of Science were used for identification. The inclusion requirements for research publications include an English publication year between 2019 and 2024, an RCT study type, and focal subjects, such as the correlation between cortisol and intervention in cancer patients.

The sample population consists of cancer patients, as well as information on analytic techniques, primary findings, and the role of the cortisol hormone in cancer. The procedure is as follows: Make a table with all of the data pulled out of each study, including

pertinent details and conclusions about the subject of the study. Carefully gather data from each chosen research project, ensuring all relevant information is appropriately documented.

After the data have been retrieved, arrange it methodically into tables that are both manageable and accessible. Double-check the retrieved data to ensure the information is accurate and comprehensive. Precisely detect any ambiguities or contradictions in the extracted data. The data are then evaluated and interpreted to draw meaningful conclusions and findings from the examined research. The Cochrane Collaboration's technique, modified from Sterne JAC et al.¹³, was used to assess the risk of bias in each study.

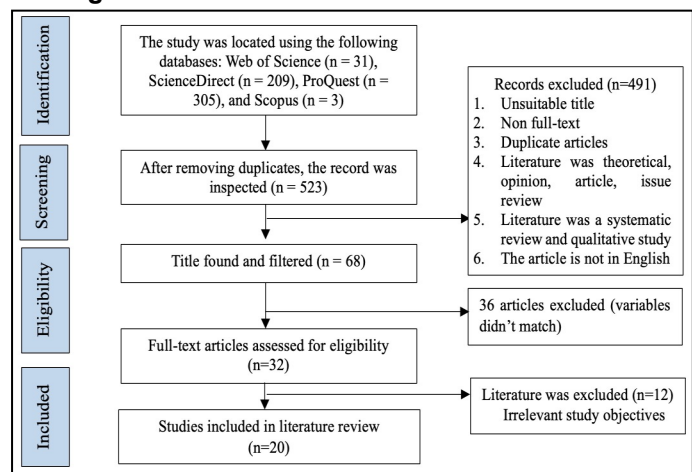
Outcome measures

It is anticipated that more potent treatment plans will be created to enhance patients' quality of life following a deeper comprehension of the function of cortisol.

Study characteristics

Twenty papers satisfy the requirements for review inclusion. RCT studies conducted on cancer patients were used to acquire the articles. A flowchart of the literature selection and search procedure is presented in **Figure I**. By comprehending the correlation between cortisol levels and cancer risk; medical practitioners may create more customized and productive approaches for cancer patients worldwide. (**Figure I**).

Figure I: Included are the studies' PRISMA flow diagrams



The search result obtained 548 articles, with three from Scopus, 209 from Science Direct, 305 from ProQuest, and 31 from Web of Science. Of the 32 articles surveyed, 12 did not meet the criteria because they contained theoretical reviews or opinions or were irrelevant to the purposes of the research. Therefore, only 20 articles match the research questions and meet the inclusion criteria chosen to be included in this study.

The title and abstract manuscripts were evaluated for topic relevance based on the following inclusion

criteria: (i) RCT published in English-language peer-reviewed journals between 2019 and 2024; (ii) study participants with a clinical diagnosis of cancer; and (iii) measurement of the cortisol hormone approach. In cases when the initial examination failed to provide apparent indications of relevance, the complete article was examined to ascertain its inclusion status. The entire text was reviewed once the first cohort of articles was gathered to guarantee its ultimate inclusion in the review. Twenty articles fit the inclusion criteria in this instance.

RESULTS & DISCUSSION

Respondent characteristics

Aged 18 to 65, all responders were cancer patients who had nursing interventions, had their cortisol levels checked before and after treatments, and had samples of their saliva, hair, urine, and blood drawn to test for the cortisol hormone. Patients with prostate, colorectal, and breast cancers comprised the respondents.

Table II: Characteristic of studies

Years	Country	Age range in years	Respondents	Sampling of cortisol
2022 ¹⁴	Portugal	18-65	Breast, prostate and colorectal cancer	Saliva
2020 ¹⁵	Yunani	52,8	Breast cancer	Hair
2023 ¹⁶	Czech	≥ 18	Breast cancer	Blood
2023 ¹⁷	Iran	20-63	Cancer	Blood
2020 ¹⁸	Iran	44-45	Breast cancer	Blood
2022 ¹⁹	USA	14-29	Cancer	Hair
2023 ²⁰	USA	Mean 59.5	Breast cancer	Saliva
2021 ²¹	China	25-62	Breast cancer	Blood
2022 ²²	China	15-39	Cancer	Saliva
2019 ²³	USA	47-81	Cancer	Saliva
2023 ²⁴	Germany	56.5-59.9	Breast cancer	Saliva
2021 ²⁵	USA	Mean 50	Prostate cancer	Saliva
2023 ²⁶	China	18-74	Cancer	Saliva
2022 ²⁷	Norway	>18	Breast cancer	Blood
2022 ²⁸	Denmark	>18	Prostate cancer	Blood, saliva
2024 ²⁹	USA	Mean 50	Colorectal cancer	Hair
2019 ³⁰	USA	Mean 56.6	Breast cancer	Blood, saliva, urine
2023 ³¹	Iran	44.00-42.62	Breast cancer	Saliva
2020 ³²	Canada	Mean 58.1	Cancer	Saliva
2022 ³³	Spain	Mean 57	Breast cancer	Saliva

The role of cortisol in response to cancer

From the 20 articles obtained, the researchers then reviewed each article using the Scispace AI application by inserting 20 articles that matched the inclusion criteria. Then, they read every article and asked, "What is the role of cortisol in cancer disease and treatment strategies?" Each answer is made in

table form, then grouped, and the results are themed (**Table II**).

The results of this study show that the role of the cortisol hormone in breast cancer dynamics includes 1) the effects of cortisol on the immune system, 2) the effects on cancer progression, 3) therapeutic interaction with cancer treatment, 4) the use of cortisol levels as a biomarker; 5) effects on the quality of life and cancer symptoms; 6) the management of cortisol in cancer patients; 7) the risk of other health complications.

The effect of cortisol on the immune system

The adrenal glands generate the steroid cortisol hormone, which controls the body's immunological response, metabolism, and stress response. However, cortisol has many significant benefits; too high or too low can cause health problems. Unequal cortisol levels can occur as a result of adrenal disorders or chronic stress. They can lead to various health problems, including sleep disturbances, weight loss, fatigue, and immune system disorders³⁴.

Cortisol levels in breast cancer patients are positively correlated with stress responses, inflammation, and disease progression³⁵. In breast cancer, metabolic adaptation allows tumors to grow and develop resistance to therapy. Cortisol, the stress hormone, affects the dynamics of breast cancer. Research shows a relationship between rates, disease progression, response to treatment, and the effects of psychosocial interventions that can lower cortisol levels. In contrast, cortisol can affect immune responses and inflammation, potentially influencing cancer development indirectly³⁵. According to recent research, women who have high amounts of cortisol in their bodies are more likely to develop breast cancer, especially over the long term. Cortisol can also affect how breast cancer cells grow and spread through the signal pathway inside cells³⁶.

Cortisol, on the other hand, plays a distinct role in breast cancer. Cortisol affects the progression of breast cancer and how the body reacts to treatment. Due to its immunosuppressive properties, cortisol can inhibit immune system function; this can be problematic for cancer patients since the body's ability to combat cancer cells depends on a robust immune system. Prolonged increases in cortisol levels have been demonstrated to impair the immune system's ability to fight infections. They may also reduce the effectiveness of several cancer therapies that depend on the immune system. Excessive stress can cause the body to produce more cortisol, disrupting the HPA axis' normal function¹⁹.

Glucocorticoids are a class of steroid hormones produced by the adrenal glands. The human body's most prevalent glucocorticoid hormone, cortisol, is essential for controlling immunity, metabolism, stress reactions, and other bodily processes. The effect of the glucocorticoid hormone on breast cancer depends heavily on the specific situation or context; this implies that the effect may differ based on certain elements

Table III: Theme

Effects of cortisol on the immune system	Effects on cancer progression	Interaction therapy with cancer treatment	Use of cortisol levels as a biomarker	Effects on quality of life and cancer symptoms	Management of cortisol in cancer patients	Risk of other health complications
<p>* Cortisol, the stress hormone, plays an important role in stress response and immune regulation.</p> <p>* Hair cortisol has recently been a reliable stress marker and can indicate an ongoing stressor.</p> <p>* Analysis of the cortisol levels in saliva in breast cancer patients can provide insight into strategies that may be used to regulate the response of the cortisol hormone to cancer patients.</p>	<p>* Cortisol, the stress hormone, is important in the body's response to stress and affects various physiological processes, including inflammation.</p> <p>* High levels of cortisol are often associated with stress and anxiety, which are common in cancer patients.</p> <p>* Depositing cortisol in the hair over time can provide insight into the stress level experienced by participants during the study period. Chronic increases in cortisol can have destructive effects, affecting the risk and progression of cancer.</p>	<p>* Cortisol, the stress hormone, affects the progression of cancer and the outcome of treatment.</p> <p>* By reducing the concentration of cortisol, the treatment response is potentially enhanced.</p> <p>* Additional treatment strategies for cancer patients can help them manage stress and anxiety, as well as have the potential to affect levels of the cortisol hormone.</p>	<p>* The level of salivary cortisol as a stress biomarker.</p>	<p>* Increased cortisol levels have been linked to increased stress, which can negatively affect the quality of life of cancer patients.</p> <p>* Stress has been associated with a variety of negative behaviors and symptoms in cancer patients, such as decreased physical activity, increased drug use, and the worsening of post-treatment symptoms such as pain and fatigue.</p> <p>* In cancer patients, imbalances in cortisol levels, flat curves of cortisol release, and decreased sensitivity to glucocorticoid hormones have been associated with symptoms of fatigue, sleep disorders, and cognitive dysfunction.</p> <p>* In cancer patients, excessive activity on the hypothalamic-hipofyse-adrenal axis (HPA), along with inflammatory mediators and immune factors, can play a role in triggering or aggravating anxiety and depression.</p>	<p>* Various types of interventions, such as mindfulness (MBCT), psychoeducation, music therapy, exercise, an attention-based stress reduction program (MBSR), and others, have been shown to effectively lower cortisol levels and improve stress management in cancer patients.</p> <p>* Chronic stress affects the long-term survival of breast cancer patients.</p>	<p>* Chronic stress can lead to increased cortisol levels and cortisol curves, with negative health outcomes such as cardiovascular problems and diabetes.</p>

involved in the development of breast cancer. The significance of assessing glucocorticoid receptors in breast cancer treatment customized to individual circumstances (personalization) was emphasized. In other words, it is essential to understand how these hormones interact with breast cancer cells to design therapies that are more effective and tailored to patient-specific needs³⁷.

Effects on cancer progression

Additionally, cortisol can influence the internal signaling mechanism, allowing breast cancer cells to proliferate and disseminate. According to research, high cortisol levels and ongoing stress may accelerate the development of cancer. Cortisol may encourage the growth of cancer cells and their metastasis or the spread of cancer to other body areas³⁸.

Interaction therapy with cancer treatment

There are two ways that glucocorticoids (GCs) influence how quickly breast cancer progresses. First, GCs may have a beneficial or detrimental impact on the development of breast malignancies. Second, GC may be used in a treatment plan to treat breast cancer in addition to other therapies, as it may be utilized as a supplement in the anticancer treatment for breast cancer (BC)³⁹. Dexamethasone stops the growth of estrogen-induced breast cancer cells in hormone-sensitive cancers. However, in cancers that are not sensitive to the hormone, dexamethasone can make

them more challenging to treat with chemotherapy and raises the possibility that it may spread to other bodily areas⁴⁰.

One indication or indicator that the prognosis for breast cancer is getting worse is the glucocorticoid receptor (GR); this indicates that the likelihood of a poor result is raised by the presence of GR in breast cancer. Thus, an effort is underway to create a medication known as a GR antagonist that would be more effective in treating triple-negative breast cancer (TNBC). Improving treatment efficacy entails searching for medications blocking or lowering GR activity in TNBC breast cancer³⁷. High cortisol levels may reduce the effectiveness of chemotherapy in breast cancer patients, which might affect the course of treatment.

Chronic stress can lead to high cortisol levels, which can increase cancer patients' tiredness, anxiety, and depression and lower their quality of life. Persistent stress can also make physical symptoms like pain, nausea, and sleep disturbances worse, which can hinder healing and treatment responses^{41,42}.

Use of cortisol levels as a biomarker

It is possible to forecast the chance of breast cancer recurrence by measuring the amount of cortisol, the stress hormone. More precisely, there is a greater chance of recurrence in those with low baseline cortisol levels. Thus, cortisol and cortisone (the

metabolite of cortisol) can be used as biomarkers, i.e., potential biological indicators or markers, to assess the risk of relapse at an individual level⁴³. Understanding the impact of cortisol on breast cancer dynamics is crucial to developing targeted interventions and improving patient outcomes.

Cortisol levels are indicators that may be used to gauge how well a treatment is working and estimate the chance of a breast cancer recurrence. An increased risk of recurring breast cancer has been associated with a lower baseline cortisol level before medication. Therefore, cortisol and cortisone, the active forms of cortisol, can both function as potential biomarkers to assess the risk of breast cancer recurrence on an individual basis; this means that they can offer essential hints for figuring out each person's risk of developing breast cancer again⁴³.

Effects on quality of life and cancer symptoms

Higher cortisol levels have been associated with more stress and poorer health outcomes for those with breast cancer. Long-term stress can change immune system cells, raising the risk of cancer. High cortisol levels can reduce the number of lymphocytes, indicating the negative influence of stress hormones on cancer development⁴⁴⁻⁴⁶.

The effects of feeling tired and stressed on cortisol levels are not interdependent. Both stress and fatigue affect the regulation of the hypothalamus-pituitary-adrenal. Stress impacts the decrease in cortisol levels after the stress situation ends (decompression), and high-stress levels can also lead to a decline in growth. Chronic stress and fatigue are associated with increased cortisol levels, a potential stress biomarker. Additionally, cortisol levels have been linked to depression disorders, worse memory function, and cognitive decline, particularly in people with specific genetic predispositions⁴⁷.

Individual characteristics linked to stress and exhaustion were observed in studies conducted in Kenya, although there were no significant predictors for cortisol levels. A study in Kenya found that while personal traits, including life performance satisfaction and job drive, were associated with stress and fatigue, cortisol levels were not significantly predicted by any of these traits⁴⁸. Throughout their survival periods, women with cancer require ongoing psychological care to help them cope with stress and worry.

Prolonged stress and a lack of social connections can affect how breast cancer develops. Support from the people around us can also affect how the immune system works. Efforts to manage stress and using certain drugs, such as melatonin and beta-blockers, can help reduce the risk of developing cancer. Glucocorticoids, a specific type of hormone, can make tumor cells grow faster, thus making them difficult to treat. Prolonged stress can activate specific nervous systems in the body, affecting how the tumor grows and spreads to other body parts (metastasis). The system that regulates the relationship between nerves and hormones in the body also plays a vital role⁴⁹.

While elevated cortisol levels reinforce the link between exhaustion and poor sleep quality, they can also reduce depression and poor sleep quality. Generally speaking, more research is needed to thoroughly understand the various ways that fatigue and stress affect cortisol levels. Stress is caused by demanding jobs, lengthy commutes, security concerns, and moral dilemmas. It's not clear whether the symptoms of depression are always associated with the levels of cortisol in the hair. Research reveals conflicting findings and a non-trivial correlation between young people's cortisol levels and depressive symptoms. In academic settings, a Chinese study discovered a correlation between young individuals' greater hair cortisol levels and fewer symptoms of stress and despair⁵⁰.

Research on the types of cells found in breast cancer and how genes are activated can provide important information. This information could help develop new ways to prevent breast cancer and provide better treatment. More investigation is required to confirm preliminary results and identify more precise biological markers to aid in the treatment of patients with breast cancer.

Management of cortisol in cancer patients

Regular exercise can help control the levels of cortisol in the body. Research suggests that routine physical exercise can reduce cortisol levels, which helps manage stress and improve overall well-being. Following a breast cancer diagnosis, exercise can also aid with weight loss, which lowers the chance of dying. Therefore, leading an active lifestyle with routine exercise can be an essential strategy for dealing with breast cancer⁵¹.

Exercise, a healthy diet, and weight modifications can all significantly influence the onset of breast cancer. Following a cancer diagnosis, being overweight may raise one's mortality risk. Engaging in physical activity can lower the risk. Lifestyle adjustments such as maintaining a healthy weight may enhance general health. Reduced physical activity and high fat intake are additional factors associated with cancer risk. Targeted actions and preventive efforts, such as hormone replacement therapy, reduced alcohol consumption, and weight control, can help reduce the risk of breast cancer. But it's crucial to weigh the advantages and any potential drawbacks carefully^{52,53}.

Risk of other health complications

Chronically high cortisol exposure can have negative health implications, such as an elevated risk of cardiovascular disease^{54,55}, a weakened immune system, decreased bone mass, mental health conditions like anxiety and depression, and metabolic abnormalities like obesity⁵⁶ and insulin resistance⁵⁷. The long-term effects of low cortisol levels include excessive exhaustion, mood and cognitive disorders, weight loss, and low blood pressure⁵⁸⁻⁶⁰.

CONCLUSION

This work provides essential information on how the

cortisol hormone functions in cancer. The results showed that elevated cortisol levels often reduced the body's response to treatment, indicating that cortisol played a significant role in the effectiveness of cancer therapy. Nurses who are more aware of these connections might provide patients with better treatment; this includes monitoring patients' cortisol levels to see how their body reacts to medication and educating them about living a healthy lifestyle that affects cortisol levels. The study's findings have spurred the development of more effective treatment programs that prioritize cortisol management and stress reduction, both proven to enhance treatment outcomes and the quality of life for cancer patients.

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AUTHOR CONTRIBUTION

Retnaningsih D. contributed as the lead author in designing the concept of the systematic review, developing the research framework, and conducting the relevant literature analysis.

Nursalam N. provided comprehensive methodological guidance and assisted in validating the analysis results.

Nihayati HE. played a role in writing, editing, and ensuring the overall narrative has scientific coherence and meets publication standards. Sh S. contributed to the selection of relevant articles and references, as well as supporting the strengthening of theoretical arguments based on recent studies.

All authors worked collaboratively to finalize the draft, with joint responsibility for the entire contents of the manuscript.

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