

## Role of Anxiety and Depression in Altering Immune System Associated with Breast Cancer. Systematic Review

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### Abstract

**Background:** Focusing on basic and clinical research, psycho-neuroimmunology researchers are looking at how the factors that cause anxiety and depression and their negative emotions can affect physiological and health conditions. Clinical studies have shown that the central nervous system is associated with endocrine and immune systems.

**Objectives:** To investigate the impact of depression and anxiety on developing breast cancer through immune disturbance pathway

**Methodology:** The present study is a descriptive review of systematic review studies conducted in accordance with the guidelines for preferred cases for reporting systematic and meta-analysis review articles (prisma).

Electronic databases including ISI Web of Knowledge, PubMed, and Scopus, were searched from 2012 to 2020. The search strategy psychological, immune response, anxiety disorder, depression, and psychoneuroimmunology. Additionally, we searched the references of retrieved articles to find additional included a combination of the following Medical Subjects Headings (MeSH) terms: breast cancer, potentially related studies. We have considered herbal therapies, which were applied orally, or topically. The content of all articles was evaluated qualitatively after extracting from the desired databases with PRISMA checklist.

**Results:** the impact of psychological problems on people's illness is very large, when people have a lot of psychological pressure, the incidence will be higher than ordinary people. Health Psychology considers human health to be a complex entity and believes that disease is not caused by a single factor but is the product of biological, psychological, and social factors. Recent research has previously confirmed the effect of psychosocial factors such as stress and how it reacts to the onset and course of the disease. Most of the patients with malignant tumor had negative emotional problems such as anxiety and depression. Depression in cancer is markedly different from depression in healthy individuals, and involves a unique symptomatology and a strong biological etiology.

**Conclusions:** A better understanding of the bidirectional communication between the neuroendocrine and immune systems could contribute to new clinical and treatment strategies.

**Keywords:** Anxiety, Depression, Immune System, Breast Cancer

### Introduction

Cancer is a heterogeneous group of diseases with many causes and the immune system is different in different cancers [1].

The leading cause of death among rural residents is secondary, followed by lung cancer, colorectal cancer, breast, and prostate cancer [2].

Breast cancer accounts for 29% of all cancers in women and 95%

of cancers in women [3] In Iran, breast cancer is one of the most common cancers in women. The prevalence of breast cancer in Iran is in the fourth and fifth decades of life, which is lower than the global prevalence [4].

Etymological studies have shown that genetic, environmental, and socioeconomic factors are only partially responsible for the development and prognosis of cancer [5]. This has encouraged researchers to investigate the effect of psychological factors on the onset

and prognosis of cancer [6]. The association between the psychological and physiological features of cancer risk and progression has been studied through psychoneuroimmunology. Mood disturbance, particularly of depression and anxiety, correlated with psychological stress is common with cancer diagnosis and has been highly. Understanding the trajectory of host factors, particularly immunity, is needed due to their importance in destruction of malignant cells and surveillance against re-emergence of tumors [7,8]. Research suggests a declining pattern of anxiety symptoms from pretreatment to the mid- or end of cancer treatment, with one study demonstrating no change in anxiety at 18 months and again at 8 years [9,10].

Recent research has revealed that in most women with breast cancer, cases of anxiety disorders such as generalized anxiety disorder and post-traumatic stress disorder can be diagnosed clinically [11]. Izci et al. conducted a study in which patients with breast cancer experienced a range of psychiatric problems such as anxiety, depression, adjustment disorders, sexual dysfunction and sleep disorders [12]. Ghezelbash et al. pointed out that most patients with breast cancer have severe depressive disorder, and the prevalence of depression in these women, especially in the first year after diagnosis, is twice that of the general female population. These patients also suffer from anxiety, stress, depression, and fear of relapse or relapse [13]. There are a limited number of epidemiological studies on the psychological consequences of breast cancer in Iran. In this study, the most popular clinical and potential future biochemical screening tools for depression in cancer are briefly discussed.

Given the importance of examining the psychological consequences of breast cancer and its role in the disease process, this study reviews the psychological effects of the disease on the progression of the disease to help improve the mental state of these patients. This short review focuses on the effects of psychological anxiety and depression on breast cancer etiology and progression in relation to immune functions. We believe that this study would provide some insights into the psychoneuroimmunology of breast cancer.

## Objectives

The main purpose of the present study was to examine the psychological consequences of immune response, breast cancer in women based on past studies

## Regulatory Pathway

Interactions between the limbic-hypothalamic-pituitary-adrenal (HPA) axis and inflammatory reactions mediated by the immune system have been greatly expanded, with many studies showing that mental health can regulate different parts of the cellular immune response [1]. The connection between the CNS and the immune system is made through chemical messengers secreted by nerve cells, endocrine organs, or immune and stressful cells [14].

Activation of these pathways leads to elevated levels of certain hormones, such as cortisol and catecholamine's (epinephrine and nor epinephrine) in the blood. The amount of these hormones in the blood affects the functioning of the immune system. High levels of cortisol and epinephrine lead to a decrease in the number of white blood cells in the blood. In addition, as cortisol and epi-

nephrine increase, the rate of lymphocyte proliferation and natural killer cells (NK cells) decreases [15].

Straub and Yan, Psychological factors (stress, anxiety, and depression) affect the tumor microenvironment (peripheral immune cells and inflammatory processes) via the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system, and non-adrenal stress hormones, which may alter disease prognosis [9,16].

Moreover, tumor growth, progression, and metastasis have also been correlated with anxiety, depression, and numerous other psychological and behavioral abnormalities [17]. Stress-induced changes in the sympathetic nervous system (SNS) led to significant immune and prolonged anxiety-like behavior changes [1,18]. Distress or depression can lead to a poor repair of damaged DNA, an abnormal chromatic exchange, and reduced apoptotic activity [19].

Concentrations of proinflammatory cytokines in patients with major depression correlate with disease severity and HPA activity [20]. The effects of personality traits and depression on cancer risk and survival appear to be extremely as small as the data obtained from prospective cohort studies in population-based and clinical databases [21]. Many randomized controlled trials have examined the relationship between psychological factors and the immune system in cancer [22,23].

Recent studies show that the immune effect of Psychological intervention (PI) may be related to the neuroendocrine changes caused by cognitive changes and improvement in the patient's psychological state [10,24]. Subjects who are immunosuppressed either through pharmacological means or via immunodeficiency diseases have an increased risk of cancer [25].

## Immune Modulation

The immune system is a system of molecules, cells, and tissues that, in fact, provide a security barrier to the invasion of microorganisms. The system consists of two main components: the innate immune system or nonspecific against a variety of microorganisms similar acts adaptive immune system or have the ability to accurately detect pathogens different from each other and according to the type of immune response, various components of the Secure system may be enabled [15,25].

Studies involving both animals and humans suggest that natural killer (NK) cells are particularly important in the elimination of metastatic tumor cells [26].

Depression in otherwise healthy adults reduces the number of circulating natural killer (NK) cells, which normally have a tumor surveillance role, and the same is predicted to apply in cancer patients [27].

In addition, higher levels of social support were associated with heightened NK cell responses to cytokines, independent of the level of depression [28].

Most organ related carcinomas are associated with high concentrations of TNF which inhibits the activity of tyrosine phosphatase,

which in turn results in diminished expression of the Class-I MHC antigen on the cell surface, thus permitting malignant cells to escape immune surveillance. Therefore, stress and depression can foster tumor progression by inhibition of the expression of class-I and class-II MHC molecules and by reducing NK activity [14,29].

## Methods of Study Search Strategy

The present study is a descriptive review of systematic review studies conducted in accordance with the guidelines for preferred cases for reporting systematic and meta-analysis review articles (prisma).

Electronic databases including ISI Web of Knowledge, PubMed, and Scopus, were searched from 2012 to 2020. The search strategy psychological, immune response, anxiety disorder and depression and psychoneuroimmunology. Additionally, we searched the references of retrieved articles to find additional included a combination of the following Medical Subjects Headings (MeSH) terms: breast cancer, potentially related studies. We have considered herbal therapies which were applied orally or topically. The content of all articles was evaluated qualitatively after extracting from the desired databases with PRISMA checklist.

## Inclusion and Exclusion Criteria

The criteria for entering the study were: Persian and English language articles published in scientific-research journals inside and outside the country, the full text of which was available; Research articles on systematic, observational, descriptive and qualitative review; Articles that report the psychological consequences of breast cancer and the role of immune system responses. Withdrawal criteria included articles that did not have full text; Studies that did not contain sufficient information, studies that did not have the necessary adequacy, or PRISMA attention to the checklist had methodological weaknesses.

## Study selection and data extraction

In this study, out of 463 articles, 256 articles that were not in line with the title of the research were screened in the study (after the initial screening, 207 studies were entered in the second stage of

screening. Screening criteria in the second stage were unrelated articles). In terms of abstract, duplicate articles in terms of title and low quality were based on the Prisma checklist. At this stage, 24 articles were inconsistent in terms of abstract with the subject under study, 29 articles in terms of duplicate research title and 78 studies due to lack of minimum quality criteria. Based on the Prisma checklist, out of the study and finally 76 qualitative articles were entered into the systematic review study (figure1)

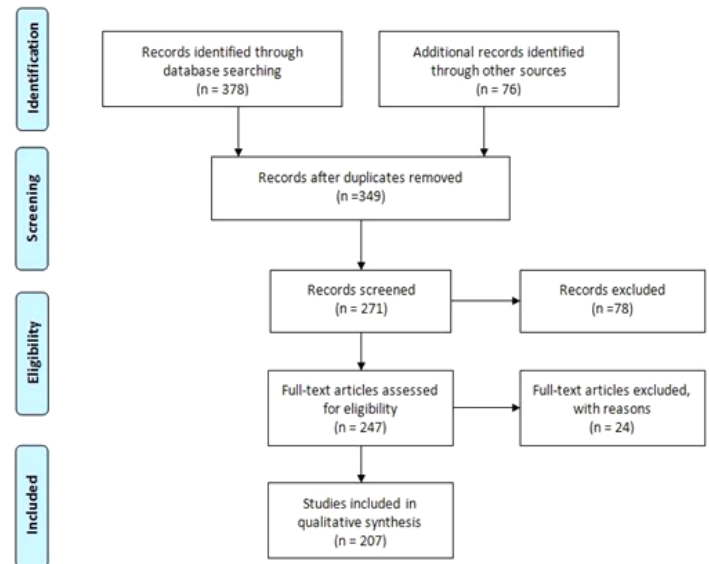


Figure 1: Flow chart of the study selection process.

The influence of psychological intervention on (PI) immune cells in breast cancer patients

Since many of the included studies focused on the effect of PI in breast cancer patients, we conducted a subgroup analysis for breast cancer patients. The CD3+ cell count, CD4+/CD8+ ratio, and NK cell count in breast cancer patients were significant higher in the PI group than in the control group ( $P > .05$ ), but there were no differences in the CD4+ cell and CD8+ cell count between the two groups (TABLE1)

Outcome	control group sample	experiment group sample,	Mean difference.	P value	number of studies
CD4	186	192	-0.01	0.28	8
CD8	175	196	0.01	0.36	8
CD3	200	200	0.07	0.001	8
CD4/CD8 ratio	73	86	0.21	<.001	2
NK cell	235	263	0.03	<.001	7

## Discussion and Conclusion

According to the relevant literature at home and abroad, and related research, the impact of psychological problems on people's illness is very large, when people have a lot of psychological pressure, the incidence will be higher than ordinary people.

the product of biological, psychological, and social factors. Recent research has previously confirmed the effect of psychosocial factors such as stress and how it reacts to the onset and course of the disease [30].

Health Psychology considers human health to be a complex entity and believes that disease is not caused by a single factor but is

Most of the patients with malignant tumor had negative emotional problems such as anxiety and depression [31].

Depression in cancer is markedly different from depression in healthy individuals, and involves a unique symptomatology and a strong biological etiology [32]. The main purpose of the present study was to examine the psychological consequences of immune response and breast cancer in women based on past studies. The nature of breast cancer is such that the patient has many ambiguities due to the difficult conditions of the disease and even the difficult conditions of treatment and its side effects, and does not know whether the disease will respond to treatment or not only will not improve, but also to It spreads to other parts of the body. The existence of such ambiguities and the reaction that the person shows to it can lead to a high level of intolerance in these patients and keep the negative and anxious moods in the defective cognitive cycle active. Studies indicate that PI can result in changes in the levels of some immune indicators in cancer patients during different treatment periods [33,34].

PI may promote the activity of these cells, and a general meta-analysis showed that the activity of NK cells is increased. NK cells, which are members of the family of innate immune cells, assume that the function of cancer cells kills' immune control, is the first line of defense against tumors and infections [12].

### Conclusions

A better understanding of the bidirectional communication between the neuroendocrine and immune systems could contribute to new clinical and treatment strategies.

Further investigations are necessary to determine the mechanism and stability of the immune effect of PI.

### Limitations

One of the limitations of the study was the lack of segregation of the stage of the disease in breast cancer in the research conducted there. Furthermore, the plausible ability of cancer cells evading detection by the immune system makes it difficult to conclusively define the benefits of PI on an individual's immune response

**Conflict of interests:** The authors declared that there are no conflicts of interests

**Ethical Issues:** Ethical standards has been adhered to during all stages of the study

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