



Prevalence and Psychobiological Correlates of Depression Among Breast Cancer Patients

Monika Thakur¹ · Roopali Sharma¹ · Anand Kumar Mishra² · Kul Ranjan Singh²

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Abstract

The diagnosis of breast cancer (BC) is associated with psychological stress. Various factors that contribute to psychological reactions are from the diagnosis of cancer to long uncertain treatment. A patient develops many fears in their mind starting after the diagnosis of cancer. Fear of cancer being an incurable disease, changes in body image, fear of death, separation from loved ones, and fear of pain all contribute to psychological disorders and most common disorders in cancer patients are mood, anxiety, depression, and sexual functional disorders. Research studies focus more on cancer. Only a few studies emphasized the coexistence of stress, depression, and the abilities of the individual to cope with such stressors. Depression is a comorbid illness to cancer, and if neglected, it may complicate the treatment of both illnesses, which will result in poor adherence to treatment and less desirable outcome of both the illnesses. Studies from this perspective can have meaningful implications, and can address both areas. Every clinician involved in the care of BC should also plan assessment of stress and depression and arrange medical treatment or coping interventions if symptoms are present. This review article aims to find the prevalence and psychobiological correlates of depressive disorder and its effect on mortality in women diagnosed with BC.

Keywords Breast cancer · Depression · Women

Introduction

BC is the leading cause of death from cancer among women globally. It is the most commonly diagnosed malignancy in Indian women. The incidence rate of the BC is increasing over a period accounting for 1.39 million new cases and 458,400 deaths in 2012. The incidence of BC in Asia is highest at the age of 40 years, while in Europe and USA, it peaks around 60 years. Pre-menopausal patients account for 50% of all cancer in India. More than 1 lakh patients are estimated to be diagnosed in India annually. As per the ICMR-PBCR (Indian Council of Medical Research – Population-Based Cancer Registries), BC was found to be the most common constituting around 30% of all the cases of cancer in urban

registries of Kolkata, Delhi, Ahmedabad, and Trivandrum. The rise in the incidence of 0.5–2% per annum has been seen across all regions of India and in all age groups but more in the younger age group (45 years) [1].

The diagnosis of cancer has a different impact on every individual. It can result in varying grades of stress and psychological and emotional upset. Various factors that can contribute to psychological reactions are from the diagnosis of cancer to long uncertain treatment. A patient develops many fears in their mind starting after the diagnosis of cancer. Fear of cancer being an incurable disease, changes in body image, fear of death, separation from loved ones, and painful procedures all contribute to psychological disorders. Individuals and families facing the diagnosis may develop significant issues in the life of an individual with cancer due to disruption of the life plans, fear of recurrence, fear of death, changes in body image, and self-esteem, which may lead to stress and emotional upset [2].

The self-esteem of the women may be reduced due to loss of symbol of femininity due to surgical interventions and may bring false perception about self, disturbed or negative body image, isolation from friends, family, and society as well [3, 4]. Cancer stigma may also result due to loss

✉ Anand Kumar Mishra
mishra101@gmail.com

¹ AIPS, Amity University Noida, Noida, Uttar Pradesh, India

² Department of Endocrine Surgery, King George's Medical University, Shah Meena Road, Lucknow, Uttar Pradesh 226003, India

of symbols of femininity like hair loss and removal of the breast (partially or complete) as part of the cancer treatment [5]. The physical burden of the illness and associated psychological trauma may lower the patient's opportunity in life and may increase low social acceptance. Thus, their emotional well-being is decreased and results in poor outcomes of the treatment [6]. This review article aims to find the prevalence of depression and psychobiological correlates of depressive disorder and its effect on mortality in women diagnosed with BC.

Methodology

We searched the literature using the key term “Stress, depression, Breast cancer, and biological correlates” from many databases including, PubMed, Research Gate, Google Scholar, and Scopus. The data was scrutinized for published studies in the last 20 years (2001–2020). In the present review, we included the studies published in English literature which used standard tools and were original article, review article, systematic review, and meta-analysis performed on patients with known BC. We excluded all studies which were published in languages other than English, or performed on patients with cancers other than breast cancer, or studies with biasness. There were 150 studies identified but only 41 studies met our inclusion criteria. We excluded five studies which were done on other cancer and had biases. Thirty-six studies were included in this review (Fig. 1).

Results

The prevalence of depressive disorder among BC patients ranged from 1 to 49% [7–19] except in few studies where prevalence of depression was more than 50% [13, 20, 21]. Severity of depression varied among different studies. Most commonly mild depression was prevalent (Table 1). However, in one study, it was stated that 69.4% of participants had serious levels of depression [7–23]. The prevalence of the depression among BC patients also varies among countries and continents. The age of women with breast cancer in selected studies ranged from 43.81 to 60.55 years. The sample size range in these studies was 60 to 270 in original research studies. Duration of BC in most studies was about 1–2 years. Depression among women with BC was assessed using BDI = Beck Depression Inventory, PHQ = Public Health Questionnaire, ZDS = Zung Depression Scale, HADS = Hospital Anxiety and depression Rating Scale, DASS = Depression, Anxiety, and Stress Scales, SCLR = Symptomatic Checklist (revised), HAM-D = Hamilton Depression Rating Scale, and DSM = Diagnostic and Statistical Manual.

Depression and BC: Psychological Basis

The various factors responsible for psychological basis of depression in BC found were adjustment to diagnosis, concern of loss of their femininity, or their damaged body, self-image, sexuality, complications of the disease, fears and worries

Fig. 1 Data extraction flow chart

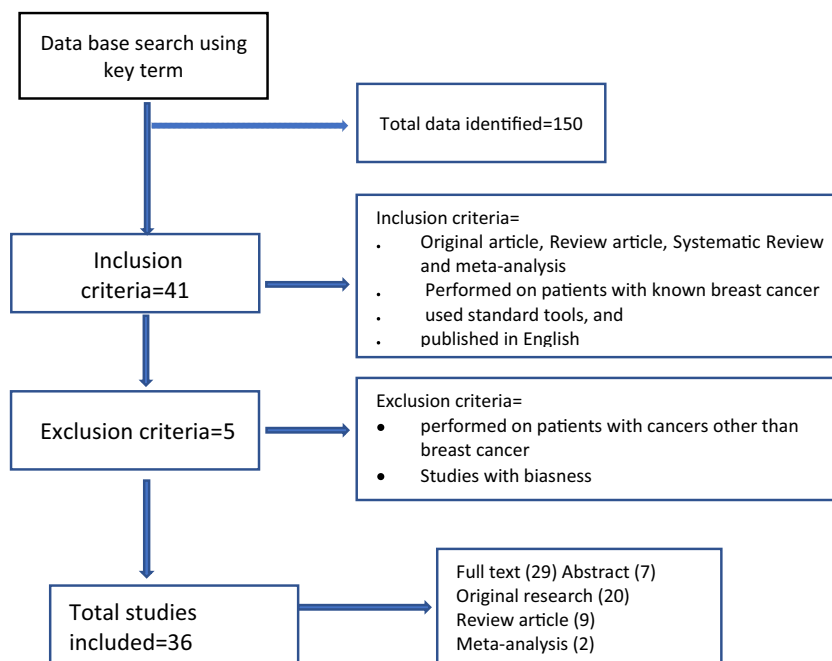


Table 1 Prevalence of depression in BC patients

S.No	Author (year)	Study design	Sample size (n)	Mean age of participants	Tools	Results
1.	Pilevarzadeh et al. [10]	Meta-analysis	72 studies	–	HAM-D BDI DASS ZDS	Prevalence of depression: 32%
2.	Tahan et al. [11]	Systemic review	46 (2960) studies	–	DASS-21 BDI GDS	Prevalence of depression: 34%
3.	Thakur et al. [12]	Cross-sectional	104	43.34±8.62	HAM-D	Depression prevalence: 47.5% Mild: 54.1%; moderate: 33.3%; severe 10%
4.	Musarzaie and Naji-Esfahani [13]	Retrospective-prospective study	194 patients with BC	60.48±12.97	ZDS	Depression was prevalent in 67.05% while 32.5% do not exhibit any symptoms of depression.
5.	Jafari et al. [14]	Systematic review	160, studies	43.81 (SD=47.12) to 55.91 (SD=14.55)	HAM-D BDI DASS ZDS	Most studies show mild depression.
6.	Tsaras et al. [15]	Descriptive cross-sectional	152 BC patients	53.25±12.10	PHQ-2	38.2% were suffering from depression.
7.	Dujmović et al. [16]	Prospective	100 patients undergoing BC surgery	60.26 years	(BDI)-21	Pre-surgery—moderate depression (10.12) Post-surgery—minimal depression (8.61)
8.	Purkayastha et al. [17]	Cross-sectional	270	53.56 years	PHQ-9	Depression prevalence: 21.5%
9.	Srivastava et al. [18]	Prospective study	200	49.65±13.51	HADS	Prevalence of depression was 28%. Normal: 48.8%
10.	Maharani et al. [19]	Descriptive-analytic	260 patients with BC	55.91±14.55 years	(DASS)-42	Mild depression: 13.1% Moderate depression: 10.7% Severe depression: 11.9% Very severe depression: 15.50% No depression: 4.1% Low depression: 8.1% Moderate depression: 18.4% Serious depression: 69.4%
11.	Shakeri et al. [20]	Descriptive	98 women with BC	47.60±14.05 years	(BDI)-21	Symptoms of mild-to-severe depression: 50% of patients Approximately 26% of participants had mild-to-severe depression and 13% fulfilled the criteria of clinical depression at 18 months post-diagnosis. Depression prevalence was >50%.
12.	Ardebil et al. [21]	Cross-sectional	60 Iranian BC patients	43.81±47.12 years	(BDI)-21 items	
13.	Chen et al. [22]	Cohort study	222 women diagnosed with BC	48.4±7.8 years	ESDS-18 items DSM-3	
14.	Burgess et al. [23]	Cohort study	–	–	HADS BDI	Prevalence ranges from 1.5 to 46%.
15.	Massie [7]	Systematic review	–	–	–	–

Abbreviations: BDI = Beck Depression Inventory, PHQ = Public Health Questionnaire, ZDS = Zung Depression Scale, HADS = Hospital Anxiety and Depression Rating Scale, DASS = Depression, Anxiety, and Stress Scales, SCLR = Symptomatic Checklist (revised), HAM-D = Hamilton Depression Rating Scale, DSM = Diagnostic and Statistical Manual

about death and recurrence of the disease, mental impairment, financial concerns, and family problems (4, 5,7,15,20,22).

Most patients of BC may experience the symptoms of depression at a varied frequency of time. Sadness was reported as a common finding and was essential to differentiate between normal sadness or blue mood and depressive disorder [7]. Adjustment to diagnosis may vary among individuals; few may find it difficult while others may respond normally. Women may perceive the grief or loss of their femininity, or their damaged body, self-image, and sexuality. Various psychological factors determine the association of depression with BC patients and its severity at different stages of illness [4, 5, 22], such as denial and anger at the initial stage, and anxiety and depression at the later stage. Fears and worries about death and recurrence of the disease, financial concerns, and family problems lead to emergence and increase of severity of depression (Fig. 2).

Research conducted by Chen et al. [22] suggested that lower income factor is positively correlated with depression and severity. Living alone or separated status are other factors which can contribute to depression [22]. Family support is an important factor in BC patients, and research studies showed that higher family support was associated with lower risk for depression [4]. Most studies stress on assessing the severity of depression so that intervention can be tailored according to patient's need, ranging from small counselling sessions to medication or psychotherapies. Various studies have concluded that therapies such as counselling and relaxation

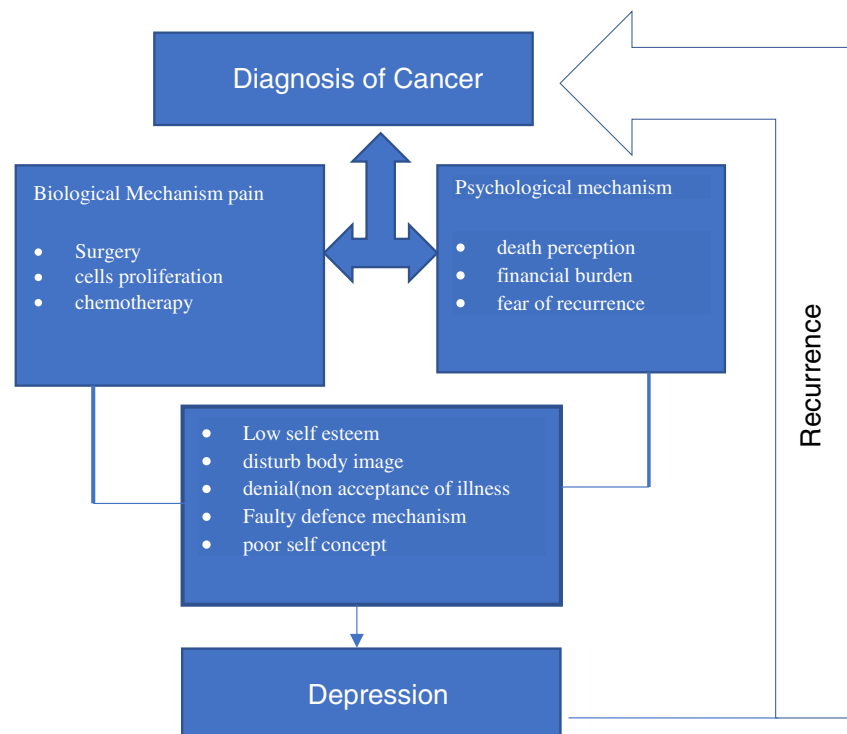
techniques improve psychological well-being in women with a new diagnosis with gynaecological cancer also [8–10].

Depression and BC: Biological Basis

Literature supports that inflammation and depression are associated bidirectionally. Cytokines like interleukin (IL)-1 β , IL-6, and tumour necrosis factor- α which induced sickness behaviour are associated with depression. There is suggestion that proinflammation causes activation of various inflammatory processes like activation of platelet activation factors and oxidative and neuro-oxidative stress, which might damage mitochondria. Symptoms of depression are associated with chronic inflammatory response in individuals suffering from cancer [24]. Poorly tolerated therapeutic modalities that are part of cancer treatment are associated with inflammatory reactions. The above hypothesis is supported by the evidence that depression in cancer can be effectively treated with newer drugs having anti-inflammatory properties [25, 26].

IL-6 and TNF- α perform the function of neurogenesis, and support neuronal plasticity, However, the hyperactive immune pathway dysregulates these processes. This leads to the increase release of glutamate and oxidation and slows down neuronal growth [27, 28]. All these processes lead to excitotoxicity which impairs the plasticity of the neurons [28]. There is reduced expression of dopamine antagonist. In non-human primate studies, INF- α has been observed to decrease

Fig. 2 Psychobiological sequence of depression among breast cancer patients



the expression of dopamine agonist (DA)-2 receptors and reduce striatal DA release, leading to feelings of anhedonia (inability to feel pleasure). INF- α also found to be associated with decreased conversion of phenylalanine to tyrosine, which in turn lead to low production of DA in brain and, potentially, depressive symptoms. Although the clear mechanisms behind this are still unravelling [25].

Hypothalamus-pituitary-adrenal (HPA) axis theory is also responsible and relevant for depression caused by cancer. It suggests that various stressors cause coordinated response from nervous, endocrine, and immune system, primarily hypothalamus, pituitary, and adrenal system [29]. Chronic activation of this network is believed to be associated with stress and negative consequences for the body. Hyperactivity of the HPA axis is reported as a major sign among major depressive disorder [30, 31].

Depression and BC: Recurrence and Mortality

Depression as comorbidity significantly increases distress and dysfunction for patients diagnosed with BC [6]. Chen et al. [22] conducted a study BC with depression and without depression to see the association between depression and BC recurrence from Taiwan National Health Insurance Research Database. Depression cohort had a higher rate of recurrence when compared with matched non-depression cohort (17.1% vs. 12.5%; $P < .001$). Also, they had a higher risk of 5-year cumulative overall mortality although it was not statistically significant (10.2% vs. 8.5%) [32]. HPA axis dysregulation worsens the cortisol dysregulation in depression patients and this is responsible for poor survival [31].

Liang et al. [33] in a prospective observational study done on 3095 BC patients concluded depression responsible for higher mortality. They concluded that depression diagnosed before BC had a modest but significantly increased risk of death from any cause and this is more associated with advanced-stage disease. The prevalence of depression at baseline was 11.5% and women with depression were more likely to be younger, have higher BMI, be physically inactive, be current smokers, have a history of postmenopausal hormone therapy, and have more comorbid conditions (all p 's < 0.05). Hjerl et al. [34] concluded increased mortality for late-stage breast cancer survivors, but not for early-stage breast cancer survivors in Denmark patients. Kanani et al. [35] found worse overall survival in English BC patients. Goodwin et al. [36] found worse survival and in US patients of BC having depression. The other research studies suggested the association of psychological triggers as a marker of increased risk of mortality among breast cancer patients [37]. There are various mechanisms given poorer survival associated with BC are central nervous system dysregulation, survivors being less capable of functioning successfully in modern society, and survivors

faced with adherence difficulties to chemotherapy and other complementary treatment which can lead to faster cancer progression.

Discussion

BC cancer can be an important cause of depression. Prevalence of depression varies among different communities. Research studies have demonstrated various grades of depression with mild form as the most common but few studies have reported moderate and severe depression also [12, 20].

The prevalence of depression with BC varies among different countries. The prevalence of depression with BC in Asian countries like China were (26%) [22], India (21.5–47.55%) [12, 17, 18], and Thailand 16.7% [38]. Turkish women diagnosed with BC showed 27.7% moderate depression and 19.5% severe depression [39]. Among European countries, depression with BC prevalence in Greece was 54.4%, and in Germany, moderate 11% and severe 12% [40, 41]. Similarly, a study in Italy has reported a prevalence of depression with BC 18% [42]. A 5-year cohort study conducted in UK showed 50% of prevalence with BC during first year of cancer diagnosis which tend to decrease with time [23]. Studies conducted in USA showed the prevalence of depression with BC 46–56% [43–45].

This wide variation in prevalence may be because of variation in methodology, demography or related to culture and ethnicity or stage of cancer, duration of cancer, and number of treatment sessions [3, 6, 10, 23]. Marital status may or may not contribute to depression [3, 22, 23]. Prevalence of depression was also associated with type of intervention like chemotherapy or radiation therapy [3, 16, 23]. Income status correlated with severity of depression. Longer periods after cancer diagnosis were negatively related to depressive symptoms, which suggest severity of depression decrease as the duration of the diagnosis proceeds [3, 22, 23]. Use of varied coping strategies and cultural diversities may affect the prevalence of depression and other psychological morbidities [4, 5, 22]. Different assessment tools for evaluating depression may cater different results.

Assessing the link between depression and BC, it is also identified as a causative agent of depression. Studies suggested depression and mood disorders could increase the risk of breast recurrence and mortality, and different biological predictors were found to be correlating with depression such as pro-inflammatory cytokines, HPA axis, and neuro-oxidative stress [24–26]. Menopausal status of the women was found to be associated with depression; however, in one study, no significant difference was found in the prevalence of depression by menopausal status [10]. Few studies could not find association of clinical factor with depression [12, 22, 23].

Depression itself can reduce the willingness of a female to undergo screening tests and counselling which is important for early identification and diagnosis of BC. So, females with depression are less likely to think about their health and neglect screening tests for early diagnosis, treatment, and better prognosis.

Conclusion

Advancement in the treatment of cancer has led to an increase in survival among cancer patients. But psychiatric illness like depression is either not recognized or neglected. Depression may result in poor outcome to the treatment of both the conditions due to non-compliance to treatment. It is associated with higher recurrences and mortality in BC patients.

The above article depicts the importance of early recognition of depression in patients suffering from BC. Holistic care of the patient it is very essential for cure and therefore it is important to address the comorbidity of depression and other psychological distress, as part of routine assessment either through a psychooncologist or through consultation-liaison psychiatry.

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