

# Depression, quality of life and breast cancer: a review of the literature

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**Abstract** Depression is misdiagnosed and undertreated among breast cancer population. Risk factors for depression in the 5 years after diagnosis are related more to the patient rather than to the disease or its treatment. The breast cancer stage (early and advanced) is not statistically significant in terms of rates of psychosocial distress except for recurrence. Risk factors of depression might impair quality of life such as fatigue, past history or recent episode of depression after the onset of cancer, cognitive attitudes of helplessness/hopelessness, resignation. Body image impairment from mastectomy and sexuality aftermath generates higher rates of mood disorders. The link between increased risk of breast cancer and depression is controversial among the literature. Some studies suggest a protective factor, others find a relation between stress, immunity and cancer occurrence or even mortality. Breast cancer survivors report a higher prevalence of mild to moderate depression with a lower quality of life in all areas except for family functioning. Treatment of depression in breast cancer women improves their quality of life and may increase longevity. Antidepressant medications remain the

cornerstone of depression treatment. The hypothetical link between their prescription and increased breast cancer risk is not supported by literature's data.

**Keywords** Breast cancer · Depression · Mood disorders · Quality of life

## Introduction

Breast cancer is one of the most important cancer in Occidental countries in terms of incidence and mortality rates. In Europe, breast cancer incidence is about 28.9% of all cancer cases and responsible of 7.8% of all death in 2006 [1]. Nowadays, its treatment is offering to the patients high rates of survival. These survivors will be at high risk of developing psychological distress and therefore potential mood disorders [2, 3].

Psychological discomfort among breast cancer patients is related with depression and depressive disorders, anxiety and anxiety disorders, anger and low self-esteem and low emotional support [4].

Importance of fears and concerns regarding death and disease recurrence, impairment of body image, alteration of femininity, sexuality and attractiveness are factors that can precipitate psychological distress [5] even years after diagnosis and treatment [6].

## Prevalence of mood disorders in breast cancer

The spectrum of psychiatric disorders and psychological distress in cancer has been assessed for many years and among several studies [7–10]. One of the most classical studies was done by Derogatis et al. [7]. They collected

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data from three cancer centers with a pool of 215 patients. They looked at the prevalence of psychiatric disorders and reported that 50% of patients will have a normal response to cancer in terms of day to day stress or response to crisis. The fifty other percentages will present adjustment disorders with depressed or anxious symptoms and among these 50, 20% of patient will have major depressive episode. For Harter et al. [8], through a cross-sectional design, among 517 patients (75% female patients) recruited from two acute inpatient care clinics, two rehabilitation clinics and nine specialized practices for oncology, the prevalence rates of mental disorders was estimated to 56.5% for the lifetime periods. Interestingly, they found that the current rates of affective and anxiety disorders were approximately 25–33% higher than prevalence rates found in general population. The most prevalent current disorders were affective (9.5%), and anxiety disorders (13%) especially among the female population [8].

Prevalence of depression among early breast cancer women is twice as many than seen in the general female population, especially during the first year after diagnosis [11].

First breast cancer recurrence is an extreme difficult time and is often associated with psychological distress which include higher rates of anxiety and depressive disorders (>40%) [12]. The highest rates of prevalence for depression are classically found among the following localization: head and neck, lung and pancreas. Nevertheless, prevalence of depression in breast cancer is estimated around 52.65% by Zabora et al. [9] in a large sample of cancer patients ( $n = 4,496$ ).

In 227 advanced breast cancer, Grabsch et al. [10] found a 42% rate of psychiatric disorders and 35.7% of these had depression or anxiety or both. Minor depression was found in 25.6%, major depression in 7% and anxiety disorder in 6.2%.

Around a quarter of all breast cancer patients have comorbid depression: estimation between 20 and 30% in earlier breast cancer [13] with increased rates during advanced and palliative stage (more than 50%) [14]. Table 1 summarizes the main studies assessing the prevalence of depressive disorders among early and late breast cancer stage.

### Diagnosis of depression among breast cancer

In order to make a diagnosis of depression among this specific population, several parameters have to be taken into account such as the diagnosis system used which mean what kind of criteria might be the more relevant regarding the nosography used: DSM, CIM 10 [15] and the time of evaluation which is an important factor since psychological disturbance changes in the course of time [16, 17].

Moreover, incidence of depression, appears to be dependent of the following parameters: disease severity, level of patient disability and physical impairment, performance status and past history of depression [18–20].

Paradoxically, major depression and depressive symptoms are underrated and undertreated in women with breast cancer [21].

One explanation could be that women with breast cancer are generally reluctant to disclose their affective concern [22]. Another reason could be that oncologists are not so familiar with depressive symptoms screening [23]. Diagnosis failure of mood disorders can be problematic because depression and its associated symptoms diminish quality of life, affect compliance with medical therapies and might reduce survival [21]. Besides clinical classical symptomatology of depression such as sadness, anhedonia, guilt, helplessness, hopelessness, suicidal ideation's, the following risk factors of depression among breast cancer patients must be looked for:

- past history of psychiatric illness [24],
- the nature and more than four cancer-related concerns (e.g., pain) [25],
- a lack of confiding relationship [26],
- a personality characterizes by neuroticism [27],
- a minority status from a racial and ethnic point of view [27].

### Relation between depression and breast cancer

When we consider an hypothetical relation between breast cancer and depression, several questions might be raised:

- Is depression a risk factor for breast cancer?
- Is depression a prognostic factor for breast cancer mortality?
- Is there a correlation between depression and disease severity (breast cancer advanced stage)?
- Is depression a protective factor for breast cancer?
- Is breast cancer a risk factor for depression?
- What is the impact of depression on quality of life among breast cancer patients?

### Depression as a risk factor for breast cancer

Considering women with a depressive state at high risk of developing breast cancer is not a fanciful question. In the Geek Antiquity, Galien had already noticed that women with melancholy mood due to “an increase rate of black bile” were prone to develop breast cancer [28]. Several metaanalysis tried to find a link between mood disorders

**Table 1** Prevalence of depressive disorders and breast cancer

Authors	Tumoral site breast	DSM	Mood disorders (%)	Major depression (%)	Minor depression (%)
Grabsch et al. [10]	227 BC (AS)	DSM-IV	35.7	7	25.6
Hegel et al. [94]	236 BC (ES)	DSM-IV	60	11	Not mentioned
Mehnert et al. [95]	127 BC (ES)	DSM-IV	16	4.7	3.1
Burgess et al. [11]	222 BC (ES)	SCID	50	40	20
Okamura et al. [57]	50 BC (AS) (recurrence)	DSM-IV	22	2	20
Ell et al. [34]	250 BC (stage 0-III)	PHQ-9	30.4	38	65
Kissane et al. [58]	503 BC	DSM-IV	ES: 36.7	ES: 9.6	ES: 27.1
	303 ES		AS: 31	AS: 6.5	AS: 24.5
	200 AS				
Okamura et al. [12]	55AS (recurrence)	DSM-III-R	AS: 42	AS: 7	AS: 35
Kissane et al. [96]	303 ES	DSM-IV	ES: 42	ES: 9.6	ES: 27.1

BC breast cancer, ES early stage, AS advanced stage

and breast cancer. One of them has been done by McKenna et al. [29]. These authors have assessed 46 studies with the following criteria:

- anxiety/depression, childhood family environment, conflict-avoiding personality, denial/repression coping, anger expression, extraversion–introversion, stressful life events, separation/loss,
- significant effect sizes for denial/repression coping, separation/loss experiences and stressful life events.

Their results overall support a modest association between specific psychosocial factors and breast cancer occurrence, specially when considering denial/repression coping and separation and loss experiences [29].

Since years, female patients had the fantasy that stress and special life events could be linked with the development of breast cancer. Studies examining the relationship between stressful life events and breast cancer risk have produced conflicting results.

A metaanalysis done by Duijts et al. [30] have assessed several studies between 1966 and 2002. They evaluated the relationship between stressful life events and breast cancer risk with the following criteria:

- stressful life events such as death of spouse, death of relative or friend, personal and non personal health difficulties, change in marital, financial and environmental status.

They found a statistically significant effect for stressful life events especially for death of spouse, death of relative or friend. The conclusion of their work does not support an overall association between stressful life events and breast cancer risk. Regarding all the parameters studied, only a modest association could be identified between death of spouse and breast cancer risk [30].

A biological hypothesis through disturbances of various areas of the immune systems predisposing to cancer could be an explanation of this association [31].

Moreover, there is no evidence that severely stressful life experiences occurring 5 years before breast cancer diagnosis negatively affect survival among women with non metastatic breast cancer [32] or increase the risk of recurrence [33].

### Depression and risk factors in breast cancer

Among a breast cancer population, depressive disorder can be correlated with the following factors: ethnic minority women (e.g. Southern California), low-income women, pain, anxiety and health related quality of life [34]. Poor social and cultural environment among these disadvantaged sections of the population can be a cause of depression. Being depressed, these patients are not prone to seek earlier consultation for screening when a breast lump appears.

But still, cancer stage and treatment status are not correlated with depression [34].

Other factors can be related with increased depression and anxiety during breast cancer disclosure: speaking about life expectancy and survival speaking about disease aftermath's and treatment outcomes on quality of life, speaking about importance of being involved in cancer treatment decision process, using the word cancer which remains for the majority of patients synonym of inescapable death [35].

In a study done by Gallo et al. [36] among 2,017 persons with 203 new cases of cancer, the aims was to demonstrate a relationship between major depression and new onset of cancer at thirteen year follow-up. If mainly for all type of cancer, no overall association of depression (RR = 1, 95%

CI) or dysphoric episode (RR = 1.3, 95% CI) was found with increased risk of cancer at follow-up, except an increased risk of breast cancer among women with major depression (adjusted RR = 3.8, 95% CI).

Jacobs et al. [37] studied among 1,273 women with 29 breast cancer hospitalized psychosocial variables that predicted increased risk of breast cancer with an occurrence 20 years prior to breast cancer diagnosis.

Although the number of breast cancer patients is small regarding the population studied, they found that maternal death in childhood (OR = 2.56,  $P < 0.001$ ) and chronic depression with severe episodes in adulthood (OR = 14.0,  $P < 0.001$ ) could be considered as psychosocial variables that would predict increased risk of breast cancer [37].

Neither relatively recent life events nor other recent depressive and anxiety disorders were associated with increased risk of breast cancer.

Other prospective studies are needed to confidently establish these variables as risk factors.

In another study done by Lokugamage et al. [38], among 2,253 women with 83 breast cancer hospitalized, the same psychosocial variable were studied by Cox proportional hazards models: parental death or parental divorce in childhood before age 16 and psychiatric disorders between 15 and 32 years.

Interaction between these psychosocial variables was non-significant ( $P = 0.1$ ) even if both of these events had an increased breast cancer risk compared with those who experienced neither (Hazard Ratio = 2.64, 95% Confidence interval).

This study does not provide strong support for the hypothesis that early loss or adult psychiatric disorders are associated with breast cancer risk.

In an other control and randomized study, Montazeri et al. [39] comparing breast cancer ( $N = 243$ ) versus benign tumor ( $N = 486$ ), suggested that depression ( $P < 0.0001$ ) and related symptoms such as hopelessness ( $P < 0.001$ ), loss of interest and pleasures ( $P < 0.001$ ) could be considered as a factor for breast cancer risk.

Regarding recent metaanalysis, depression cannot be considered as a risk factor for breast cancer although depression may predispose individuals to behavioural risk factors (alcohol consumption, smoking) [40] and delay for screening mammography when confronted to a breast lump [41] that would lead them at higher breast cancer risk.

Another explanation for a possible link between depression and breast cancer risk could be the psychoneuroimmunology pathway.

Nunes et al. [42] have found that immune and hormonal measurements differed significantly between a depressed group ( $N = 40$ ) versus a non-depressed group ( $N = 34$ ). In the depressed group control, they found a significant lower proliferation of lymphocyte in response to a mitogen and a

significant decreased production of cytokines, which normally activate the immune system and specially Natural Killer cells.

Specific neuroimmunology pathway might link depression and breast cancer-related morbidity and mortality due to dysregulation of cortisol secretion (reduced diurnal variability) and lower lymphocyte proliferation and decreased production of cytokines and therefore natural killer cell activity [43].

Metastatic breast cancer that exhibited a reduced diurnal variability in cortisol secretion had diminished NK cell function and earlier mortality [43].

At this point, we still agree with the conclusion of Bernard Fox almost twenty years ago in his editorial published in JAMA in 1989 [44], looking at the association between depression and cancer morbidity and mortality: “Nevertheless, the combined evidence is... not consistent with a strong relationship between depressive symptoms and cancer among major segments of the population” [44].

### Depression as a prognostic factor for breast cancer mortality

Could depression be a risk factor for breast cancer evolution? Regarding the literature, there are some positive arguments supporting this assertion.

First, major depression decreases motivation and reduces compliance with treatment such as chemotherapy [45].

Secondly, major depression could be an important predictor of late-stage breast cancer diagnosis because patients when confronted to a lump will delay seeking for medical consultation [46].

Thirdly, considering the two previous points, major depression might have a detrimental effect on outcome in breast cancer patient [47].

Can depression being considered as a possible prognostic factor for breast cancer mortality?

The answer to that question remains unclear.

Some studies suggest a link between depression and breast cancer mortality [35, 47, 48].

Watson et al. [47] in a prospective study among 578 early breast cancer found that depressive symptoms and hopelessness are linked with a significantly reduced chance of survival at 5 years follow-up (HR = 3.59, CI 95%).

Hjerl et al. [48] made an analysis of data from breast cancer central registers in a retrospective cohort Danish study comparing early stage ( $N = 10,382$ ) and late stage ( $N = 10,211$ ). In this study, they found that breast cancer with depression had a modestly but significantly higher risk of mortality, depending on stage of cancer and time of depression.

When women are confronted to advance and even to palliative or terminal stage, they can have suicidal ideation or even suicide attempts that can hasten death [49, 50].

Depression can also affect compliance with medical cancer therapies (chemotherapy, surgery and radiotherapy) and give the possibility to the cancer to run by itself [21].

### Depression and disease severity

Is there a correlation between depression and breast cancer advanced stage?

Here also, it is very difficult to give a clear answer.

They might be an unclear support for such a correlation due to multiple bias [51].

Side effect of treatment (chemotherapy or radiotherapy) such as nausea, fatigue and pain are often associated with depressive symptoms [52, 53] but are not necessarily induced by depression and low self esteem and loss of autonomy are commonly seen in advanced breast cancer.

Depressive symptoms among young women with breast cancer are not predictors of disease severity [51].

Regarding literature, studies remain contradictory to find a link between depression and breast cancer recurrence or depression and breast cancer advanced stage.

### Depression as a protective factor for breast cancer?

Two prospective studies one Dutch and the other one Finnish conclude that women with depressive symptoms might have a lower risk of developing further breast cancer. In the Dutch study [54], a cohort of 5,191 women was followed during 5 years. Depression screening was made by Edinburgh Depression Scale. Two years after the questionnaire screening, 1.1% (58 women) developed breast cancer. Women with depressive symptoms had a lower risk for breast cancer (OR = 0.29, 95% CI = 0.09–0.92,  $P = 0.04$ ). In the Finnish study [55], a cohort of 10,892 women were followed during 6–9 years with a breast cancer incidence estimated 1.15 times the average in age group 50–59.

There was no evidence of depression being significant predictor of increasing breast cancer incidence.

### Breast cancer as a risk factor for depression

Could breast cancer be considered as a risk factor for depression? In other words, are women with breast cancer more at risk to develop depression than healthy women?

Morasso et al. [56] tried to detect depression among 132 breast cancer patients with several stage of disease (stage I–

III). Using screening tools for detecting mood disorders such as Psychological Distress Inventory, HADS and DSM-III-R criteria, they found a prevalence of psychiatric disorders near 38% with a classical rate of depression (major episode, adjustment disorder) near 25.9.8% had Major Depressive Disorder during the follow-up, 10.6% had adjustment disorders with depressed mood, 4.5% had adjustment disorders with mixed anxiety and depressed mood.

Increased age among breast cancer population was predictive of mood disorders during follow-up but not the type of surgery (mastectomy/conservative surgery). One could expect that women treated with mastectomy would develop more depression than women treated by lumpectomy (conservative surgery).

### Depression, quality of life and breast cancer

Risks factors of depression might impair quality of life such as fatigue, past history or recent episode of depression after the onset of breast cancer, cognitive attitudes of helplessness/hopelessness and resignation [57, 58].

Considering the problematic of quality of life and its measurement, the following parameters need to be taken into account: attractiveness, body image impact, sexuality, importance of menopausal symptoms such as hot flashes burden and presence of lymphedema [10].

During breast cancer disclosure, quality of information delivered by doctors and communication about disease concerns and feelings are two important parameters to preserve quality of life [59].

Depression can have a detrimental impact on quality of life in breast cancer patient. Many studies have clearly demonstrated that depression and its associated symptoms such as dysphoria diminish quality of life, affect compliance with medical therapies and reduce survival. This is due to the fact that depression affects interpersonal relationships, occupational performance, stress and perceptions of health and physical symptoms. Therefore, it impacts patients' overall quality of life [3, 21, 60, 61].

Two studies [62, 63] found that depression is correlated with lower quality of life.

Weitzner et al. [62] studied 60 long-term stage I-III breast cancer survivors (disease-free for 5 years) versus 93 low risk breast cancer screening patients. Depression was assessed by the Beck Depression Inventory Scale. Among breast cancer survivors and low risk breast cancer patients, respectively, 29 and 15% had depression. In both groups, increased depression is correlated with lower quality of life functioning except for family functioning.

Breast cancer survivors report a higher prevalence of mild to moderate depression with a lower quality of life in all areas (e.g. sexual activity) [64] except family functioning [65].

Quality of life among breast cancer population needs assessment and treatment of mood disorders.

In a population of 691 old women (>65-years old) with breast cancer, Ganz et al. [63] assessed psychosocial adjustment at 15 months after surgery. They showed a decline in mental health scores at the MHI-5 (Mental-Health-Inventory) and noticed that physical, emotional and social dimensions impact their quality of life but cancer specific psychosocial quality of life improved over time (15 months).

Another point is that depressed breast cancer patients are frequently more interested and users of alternative medicine [66]. Even if for some patients, complementary medicine could alleviate side effects of classical breast cancer treatment and so increases their quality of life, it might also be the sign of depressed and hopelessness behavior. The thoughts of these patients can be deciphered as “regular medicine cannot save me anymore, so let us turn to unproved medicine”.

Quality of life can be impaired by the number of stressful life events, body image problem, sexual intercourse, financial problems, anxious preoccupations and of course depression [67]. Depression burden which has a negative impact, influences severity and number of side effects from medical treatment (surgery, chemotherapy, radiotherapy, hormonotherapy) by increasing digestive inconvenient (nausea), sense of fatigue and decreasing cognitive function (difficulty concentrating) [5, 68] which can lower quality of life.

But medical variables such as tumor stage or sociodemographic data (education, marital status) except younger age do not have an adverse impact on quality of life [69].

Breast cancer treatment can be traumatic for women who can develop afterwards different patterns of depression that might worsen quality of life [3]. Deshields et al. [3] among 84 women assessed depression 3 and 6 months after completion of treatment for breast cancer. Depression and quality of life were measured, respectively by two scales CES-D (center for epidemiological studies-depression scale) and FACT-B (functional assessment of cancer therapy breast). The following results showed:

- never depressed: 51 (61%): better quality of life
- become depressed: 3 (4%): poorer quality of life
- recover: 8 (9%): better quality of life
- stay depressed: 10 (12%): poorer quality of life
- vacillate (variable patterns): 12 (14%): worse quality of life.

### Antidepressant medications and Breast Cancer risk

Treatment of depression in breast cancer women improves their quality of life and may increase longevity [21].

Antidepressant medications remain the cornerstone of mood disorders treatment.

The possible link between the prescription of antidepressant medications and the later development of breast cancer remain controversial. Is there a risk using psychotropic medications such as antidepressant and breast cancer occurrence? This is an important issue for the medical community who is used to give frequently to depressed patients these types of drugs. So far, epidemiological data have shown conflicting and inconsistent results for any association between antidepressant use and breast cancer [70]. There is controversial hypothesis due to methodological limitation bias case control studies, lack of accounting for potential confounding factors and multiple statistical comparisons [71].

Some studies suggested the possible implication of antidepressant such as sertraline [72], paroxetine [73] and tricyclics if used greater than two years' duration [73, 74] and breast cancer risk occurrence by an increased rate of prolactin [75]. In a recent paper [76], a large population-based case-control study among women enrolled in Group Health Cooperative was done between 1990 and 2001 with 2904 primary breast cancer diagnosed and five controls were selected for each case ( $N = 14,396$ ). Women of 34% had used antidepressants up to one year, 20% had filled two prescriptions for tricyclic antidepressants (TCAs) and 6% for selective serotonin reuptake inhibitors (SSRIs) or atypical antidepressants. No patterns of increased risk were seen since first use or time since last use of these several antidepressants. This result was confirmed in others studies [77–79].

Studies do not support a specific link between antidepressant medications and increased breast cancer risk regardless of duration of use, daily dose, specific drug used (SSRIs, TCAs) [77–82].

The possibility of an association has not been excluded, although further studies are needed before the body of scientific evidence can be definitively conclusive [82].

In order to take care of breast cancer patients with depressive disorders, pharmacological treatment must be combined with psychosocial interventions. Psychosocial interventions improves the well-being of cancer patients by decreasing emotional distress and depression in women diagnosed with breast cancer but not necessarily survival [83–86]. In a recent randomized controlled trial among 485 women with advanced breast cancer, Kissane et al. [87] have compared the impact of supportive-expressive group therapy (SEGT) versus relaxation therapy on survival. These authors did not find a significant prolong survival from these therapies (median survival 24 months in SEGT and 18.3 in controls) [87]. But SEGT improved quality of life and treatment and protection against depression.

Many psychotherapeutic interventions for this particular population can be implemented such as individual psychosocial support [88], adjuvant psychological therapy [89], cancer support group [90], online support for adjuvant psychological treatment [91], cognitive-behavioral stress management intervention [92].

All these psychosocial interventions can be used to treat depression and will also improve the range of coping strategies and therefore quality of life [93].

## Conclusion

Comorbid depression significantly increases the burden of distress and dysfunction for patients with breast cancer.

Diagnosis, surgery and recurrence of breast cancer are important period for clinical psychological distress and depression screening in order to manage them appropriately and to prevent recurrence of psychiatric disorders [57].

Unidentified and untreated depression among breast cancer patients significantly compromises women's quality of life [51]. A psycho-oncologist is required to treat these mood disorders and to deal with psychological aspects such as representation of femininity, sexuality and risk of sterility.

As treatment of depression remain paramount for improving their quality of life [20], there is no need to support a change in the current use of antidepressant medications in the management of depression among breast cancer patient [77, 82].

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