Research Article

Insomnia in Patients with Breast Cancer: Prevalence and Associated Factors

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Abstract

Objective: Insomnia affects around 30% to 60% of cancer patients and is common in most cancers especially in breast cancer. This study aims at evaluating the quality of sleep and determining the predisposing factors of insomnia in breast cancer patients.

Methods: It was a cross sectional study including breast cancer patients consulting at the departments of medical oncology in the university hospitals of Monastir and Sousse in Tunisia. Eligible patients were invited to complete one questionnaire and four scales: the insomnia severity index; the hospital anxiety and depression scale; the brief fatigue inventory and the short form-36 health survey.

Results: Seventy breast cancer patients were included in the study. Forty percent of them had clinically significant insomnia, all of them had mild level of fatigue, 12.9% had depressive symptoms and 21.4% had anxiety symptoms. The alteration of the quality of life was observed in all domains. The physical role functioning was the most affected dimension, whereas social functioning was the least altered dimension.

Insomnia was significantly associated with a longer time since cancer diagnosis (p = 0.01) ; hot flushes (p = 0.015) ; depressive (p < 0.001) and anxiety symptoms (p < 0.001) ; fatigue (p = 0.007) ; poor physical functioning (p < 0.001) ; less ability to function generally (p = 0.015) ; less vitality in daily life (p < 0.001) ; more bodily pain (p = 0.045) ; more mental health issues (p < 0.001) and lower ability to function socially (p = 0.002).

Conclusions: Information concerning the prevalence and predisposing factors of insomnia in breast cancer patients will be of great help in developing future interventions to manage insomnia in this population.

Keywords: Breast; Cancer; Insomnia; Oncology; Quality of Life

Introduction

Cancer incidence is growing in relation with aging of the population and habits modifications in terms of lifestyle and diet. Concurrently, the considerable progresses in diagnosis and treatment of cancer have led to an increase in survival with more long-term survivors, cancer becoming a chronic disease controlled by ongoing therapy. Thanks to these progresses, patients' quality of life (QOL) has become more important and management of symptoms, such as insomnia, is considered to be an important challenge [1].

Insomnia is defined as a predominant complaint of dissatisfaction with sleep quantity or quality during different phases of the sleep cycle and affects around 30% to 60% of cancer patients [2]. It is common in most cancers notably in breast cancer. Women with breast cancer have a higher risk of insomnia for a variety of reasons: hot flashes are more common and more severe in patients treated for breast cancer, depressive and anxiety symptoms are more frequent, and patients may have high levels of fatigue [3].

Given this high rate and negative impact of insomnia in patients with breast cancer, early identification of insomnia symptoms in cancer patients must be a priority. However, in practice, sleep disturbance seems to be under-recognized by clinicians, and research focusing on sleep in breast cancer is relatively rare.

This study aimed to evaluate the quality of sleep and to determine the predisposing factors of insomnia in breast cancer patients.

Materials and Methods
Study design and participants

This was a cross sectional study including breast cancer patients consulting at the departments of medical oncology in the university hospitals of Monastir and Sousse in Tunisia. It has been carried during 6 months (from 15 January 2017 to 15 June 2017).

Inclusion criteria were confirmed diagnosis of cancer and age over 18 years.

Exclusion criteria were: severe cognitive impairments ; severe psychiatric disorder ; having a sleep disorder other than insomnia or taking any medication that could interfere with the quality of sleep ; severe visual, hearing, or language defects impairing the capacity to complete the measures and inability to read or understand the Arabic language.

Data collection

Informed written consent was obtained from all eligible patients. All assessments were performed on a medical consultation using a pre-established questionnaire and scales for the evaluation of insomnia, anxiety and depression symptoms, fatigue and QOL. The questionnaire allowed gathering demographic characteristics and clinical data of patients: age ; marital status ; educational level ; time since cancer diagnosis; cancer stage (according to the seventh edition of American Joint Committee of Cancer Staging System for Breast Cancer) ; treatment modalities (surgery of the primary tumor, radiotherapy, chemotherapy, hormone therapy) and presence of hot flashes, nausea and vomiting.

The scales used were as follow

- **Insomnia severity index (ISI)**

  The ISI [4] is a questionnaire containing 7 items which is conceived to evaluate the severity of insomnia during the previous 2 weeks. The total score ranges from 0 to 28, and the insomnia is considered to be more severe when the total score is higher. The French-Canadian version of the ISI was validated for patients with cancer [5]. Clinical levels of insomnia are considered to be present when the total score reaches 8, a cut-off score that has been associated with a sensitivity of 95% and a specificity of 47% for patients with sleep difficulty [6].

- **Hospital anxiety and depression scale (HADS)** [7]:

  The HADS was used to measure anxiety and depression. It is a 14-item, self-administered rating scale with two subscales, each containing seven items and measuring anxiety or depression. Each item is rated on a four-point scale, from 0 to 3, resulting in maximum subscale scores of 21 and an overall score ranging from 0 to 42, with higher scores indicating greater levels of distress. The reliability and validity of the HADS has been established in a variety of clinical populations, including cancer patients. Scores of 11 or more on either subscale are considered to be a significant 'case' of psychological morbidity (abnormal), while scores of 8 -10 represent 'borderline' cases and scores of 0 -7 'normal' cases.

- **Brief fatigue inventory (BFI)**

  The BFI consists in a one-page fatigue assessment tool that contains nine items, each rating the severity of fatigue on a 0 to 10 scale (0 means no fatigue while 10 represents the worst fatigue the patient can imagine) [8]. The first three items assess current level of fatigue, usual level of fatigue, and worst fatigue in the past 24 hours. The next six items assess the extent to which fatigue interferes with different aspects of life, such as work or social relations, during the preceding 24 hours [9]. To define the levels of fatigue, the following ranges have been considered: 0 - 3 indicating mild levels of fatigue, 4 - 6 indicating moderate fatigue and scores above 7 indicating severe fatigue [10]. This tool has been successfully used in previous studies with both breast cancer survivors [11] and healthy persons [12].

- **Short Form-36 health survey (SF-36)** [13]

   The SF-36 is 36-item survey designed to measure health related QOL. Domains reflected by the SF-36 factor scores are as follow: physical functioning and pain ; role limitations due to physical health problems on the one hand and to personal or emotional problems on the other hand ; mental health ; social functioning and the perception of general health. Each item is weighted to obtain a score between 0 (worst quality) and 100 (best quality) for each of the 8 dimensions. The scores of the questions dealing with each specific area of the functional health status are calculated on the average to get a final score in each of the 8 dimensions measured.

Statistical analyses

Statistical analyses were performed using SPSS 24.0 statistical software package. Conventional formulae were used to calculate the mean and standard deviation. The tests were selected based on nature of the variables to be compared. We used t student tests to analyse the relationship between qualitative and quantitative variables and the Chi square tests to analyze the relationship between qualitative variables. For multivariate analysis, the variables that were statistically associated with a level of less than or equal to 0.2 were introduced in the logistic regression model. Significance levels for all comparisons were set at $p < 0.05$.

Results

Descriptive results

Seventy breast cancer patients were included in the study. As shown in table 1, the mean age of patients at the time of diagnosis was 43 ± 2 years [29], ninety percent of patients were married and 48.6% had a primary educational level. The mean time since cancer diagnosis was 30 ± 3 months. Twenty-seven percent of the patients were classified as having stage II cancer and 24% were classified as having stage IV cancer. Eighty eight percent of patients had a surgery of the primary tumor, 75.7% had radiotherapy, 94.3% had chemotherapy, 70% had a hormone therapy, and 15.7% had a targeted therapy.

The mean ISI score was 8.07 ± 0.86 [0 - 22]. Forty percent of patients have clinically-significant insomnia based on ISI score. The mean BFI score was 1.75 ± 0.11 [0 - 3]. All patients have mild level of fatigue based on BFI score. The mean score of depressive symptoms was 6.24 ± 0.46 [0 - 17] and the mean score of anxiety symptoms was 6.91 ± 0.56 [0 - 20]. 12.9% had depressive symptoms and 21.4% had anxiety symptoms based on the HADS score. The QOL of patients was altered and that this alteration affected all domains. The physical role functioning with a mean score of 25.71 ± 5 [0 -100] was the most affected dimension, whereas social functioning was the lowest altered dimension with a mean score of 67.64 ± 4.17 [0-100] (Table 2).

Characteristics of the population	value
Age: years (Mean ± SD)	43.19 ± 2.13
Marital Status: n (%)	
Single	5 (7)
Married	63 (90)
Divorced	2 (3)
Level of Education: n (%)	
Illiterate	8 (11.4)
Primary school	34 (48.6)
Secondary school	22 (31.4)
Universitary	6 (8.6)
Time since cancer diagnosis: months (Mean ± SD)	30.74 ± 3.4
Stage: n (%)	
Stage I	17 (24.3)
Stage II	19 (27.1)
Stage III	17 (24.3)
Stage IV	17 (24.3)
Surgery of the primary tumor: n (%)	
Yes	62 (88.6)
No	8 (11.4)
Radiotherapy: n (%)	
Yes	53 (75.7)
No	17 (24.3)
Chemotherapy: n (%)	
Yes	66 (94.3)
No	4 (5.7)
Hormone therapy: n (%)	
Yes	49 (70)
No	21 (30)

Table 1: Characteristics of the study population (N=70).

Characteristics	Value
Presence of clinical levels of insomnia: n (%)	
Yes	28 (40)
No	42 (60)
Levels of fatigue: n (%)	
mild levels of fatigue	70 (100)
Moderate levels of fatigue	0 (0)
severe levels of fatigue	0 (0)
Levels of depressive symptoms: n (%)	
Normal	51 (72.9)
Borderline	10 (14.2)
abnormal	9 (12.9)
Levels of anxiety symptoms: n (%)	
Normal	49 (70)
Borderline	6 (8.6)
Abnormal	15 (21.4)
Score of SF36 : Mean ± standard deviation	
Physical functioning	61.83 ± 26.57
Physical role functioning	25.71 ± 41.91
Emotional role functioning	51.42 ± 50.34
Vitality: **Energy / fatigue**	48,14 ± 27.21
Social role functioning	67.64 ± 34.96
Mental health	59.3 ± 23.98
Bodily pain	57.53 ± 26.03
General health perceptions	54.29 ± 25.8

Table 2: Assessment of the presence of insomnia; the levels of fatigue, anxiety and depression; and the quality of life (N=70).

Factors associated with insomnia among patients with breast cancer

Time since cancer diagnosis (p = 0.01) and hot flushes (p = 0.015) were associated with increased risk for clinical insomnia, while no other demographic, clinical or treatment variable was related to clinical insomnia after univariate analysis (Table 3). Insomnia was significantly associated with depressive symptoms (p < 0.001), anxiety symptoms (p < 0.001) and fatigue (p = 0.007). Univariate tests were performed on each of the eight dimensions of the SF-36 using sleep disturbance as a grouping variable. Patients with clinical insomnia had lower ability to function because of poor physical functioning (p < 0.001) ; less ability to function generally (p = 0.015) ; less vitality or energy in daily life (p < 0.001) ; more bodily pain (p = 0.045) and more problems with mental health (p < 0.001). Patients with clinical insomnia also reported lower ability to function socially (p = 0.002) (Table 4). For multivariate analy-

sis, variables entered were: hormone therapy, hot flushes during last month, depression score, anxiety score, fatigue score, physical functioning score, role limitation due to emotional problems score, energy/fatigue score, emotional well-being score, social functioning score, bodily pain score, and general health score. Only the physical functioning score was significantly associated with clinical insomnia after the multivariate analysis (p = 0.035).

	Presence of clinical Insomnia, n (%)	Absence of clinical Insomnia, n (%)	p value
Marital Status			
Single or divorced	3 (10)	4 (9.7)	1
Married.	25 (90)	38 (90.3)	
Stage			
Stage I and II	16 (57.1)	20 (47.6)	0.43
Stage III and IV	12 (42.9)	22 (52.4)	
Time since cancer diagnosis			
≤24 months	7 (25)	24 (57.2)	0.01*
>24 months	21 (75)	18 (42.8)	
Surgery of the primary tumor			
Yes	23 (82.1)	39 (92.9)	0.25
No	5 (17.9)	3 (7.1)	
Radiotherapy			
Yes	21 (75)	32 (76.2)	0.9
No	7 (25)	10 (23.8)	
Chemotherapy			
Yes	25 (89.3)	41 (97.6)	0.29
No	3 (10.7)	1 (2.4)	
Hormone therapy			
Yes	22 (78.6)	27 (64.3)	0.2
No	6 (21.4)	15 (35.7)	
Hot flushes			
Yes	19 (67.9)	16 (38.1)	0.015*
No	9 (32.1)	26 (61.9)	
Nausea and vomiting last month			
Yes	6 (21.4)	7 (16.7)	0.61
No	22 (78.6)	35 (83.3)	

Table 3: Association between demographic, clinical and treatment variables and insomnia* p < 0.05.

	Presence of clinical insomnia (mean ± SD)	Absence of clinical insomnia (mean ± SD)	p value
Depression score	8.17 ± 4.1	4.95 ± 3.1	<0.001**
Anxiety score	9.39 ± 4.9	5.26 ± 3.7	<0.001**
Fatigue score	2.14 ± 0.9	1.50 ± 0.9	0.007**
SF36 physical functioning	46.60 ± 21.90	71.98 ± 24.6	<0.001**
SF36 Role limitation, physical health	18.75 ± 37.6	30.35 ± 44.3	0.24
SF36 Role limitation, emotional problems	32.14 ± 47.5	64.28 ± 48.4	0.008**
SF36 Energy/Fatigue	33.15 ± 22	58.13 ± 25	<0.001**
SF36 Emotional well being	46.89 ± 24	67.57 ± 19	<0.001**
SF36 Social functioning	51.87 ± 32	78.15 ± 32	0.002**
SF36 Bodily pain	49.91 ± 22	62.61 ± 25	0.045*
SF36 General health	45.17 ± 27	60.37 ± 23	0.015*

Table 4: Association between distress symptoms, fatigue, quality of life and insomnia SD: standard deviation ; * p < 0.05 ; * p<0.01.

Discussion

The present study set the aim of estimating the quality of sleep and identifying the risk factors for insomnia among patients with breast cancer. Forty percent of patients had clinically-significant insomnia based on ISI scores. Insomnia was significantly associated with time since cancer diagnosis, hot flushes, distress symptoms, fatigue and QOL. These findings contribute to the current understanding of insomnia symptoms as experienced by breast cancer patients and highlight the need for effective treatments to manage insomnia in this population. In general, the prevalence of insomnia among breast cancer patients ranges from 30% to 60% [1] and is higher than those found in non-cancer patients. The results of this study fall into this range showing that 40% of breast cancer patients have subjective sleep problems, which is besides in total accordance with Malone's study [14] findings indicating that 40% of cancer survivors reported sleep difficulties, and with Taylor's findings [15] reporting that 43% of study participants had clinically significant problems with sleep.

Except time since breast cancer diagnosis and hot flashes, no other demographic, clinical, or treatment variables were associated with insomnia in this population. These results seem to be consistent with those of Bardwell., *et al.* who showed that demographic, health behaviour, and other patient variables were not significant risk factors for sleep problems while vasomotor symptoms were significant predictors of insomnia [16]. In the present study, 68% of patients with clinically-significant insomnia reported hot flashes. These findings are consistent with those of Couzi., *et al.* who showed a positive correlation between hot flashes and the prevalence of insomnia in breast cancer patients [17] and with

those of Savard., *et al.* who suggest through polysomnographic data, that hot flashes, were significantly associated with a higher percentage of wake time, a lower percentage of stage 2 sleep, and a longer REM (Rapid Eye Movement) latency [18]. In accordance with the present results, previous studies [1,19] have demonstrated that patients who had been diagnosed with breast cancer more than two years ago were significantly more likely to report insomnia than those diagnosed less than two years back.

This study did not find that chemotherapy had a deleterious effect on sleep, while this has previously been reported by some studies, and this might be due to the fact that these studies used different methods. In fact, these studies [20,21] indicate that the effect of chemotherapy on insomnia levels could be mediated by their side effects, such as headache, nausea, digestive and urinary symptoms, and night sweats. The effect of chemotherapy was also explained by some other mechanisms such as psychological reactions and disruption of circadian rhythms [6]. Radiotherapy was not found to be associated with significantly increased sleep disruptions. However these findings do not support the studies of Donovan [22] and Trudel-Fitzgerald [23] in which headache, fatigue, dyspnea, night sweats, and nausea were significant predictor factors of insomnia within the context of radiotherapy. In this study, there was no significant association between hormone therapy and insomnia symptoms exacerbation, but the hormone therapy effect was significantly mediated by hot flashes. This also seems in accordance with other observations [1,17] suggesting that aromatase inhibitors have been associated with increased vasomotor symptoms like hot flashes and arthralgia, which have been linked to difficulty falling or remaining asleep [1]. All these findings provide further

support for the hypothesis that there is an increase in the severity of insomnia by adjuvant treatments for cancer, and this increase should encourage appropriate management of the side effects of these treatments [6].

Findings from this study also confirm that anxiety and depressive symptoms are associated with insomnia which is consistent with the results of other studies [1,24]. It has in fact been reported that anxiety activates the subcortical regions and frequently can cause arousal of the autonomic nervous system which can cause difficulty falling asleep [25]. In addition, anxiety is related to reduced levels of the GABAergic neurotransmitter in the parafacial zone neurons which can potently trigger deep sleep [26]. This significant association between these psychological distress symptoms and sleep problems suggest that treatment of depression and anxiety may help improving sleep problems.

Cancer-related fatigue is generally considered to be highly prevalent (70 - 80%) [27]. Defined as chronic tiredness, lack of energy, and weakness, it differs from the temporary feelings of fatigue experienced by a healthy person, is not related to one's degree of activity, and is not alleviated by rest or sleep [28]. We found that fatigue among breast cancer patients is significantly associated with clinically-significant insomnia. Similar results were reported by other studies [27,29] in which both cancer and cancer treatment-related fatigue were significantly associated with both subjective and objective disturbance of sleep. Previous studies [27,30] also showed that fatigue was experienced by patients before chemotherapy, and worsened during treatment. Some possible explanations for this might be direct effects of the tumor, anemia, fever, pain, weight loss, hormonal changes, hot flashes, loss of muscle mass and infection [27]. Other explanations for this could be depression, chronic inflammatory state, low physical activity and inadequate nutrition [31]. On the biological level, fatigue and sleep disturbances were significantly associated with changes of circulating levels of IL-6, IL-1RA and CRP [27], which suggests that fatigue and poor sleep quality may share some common causing features, such as inflammation in cancer patients.

In accordance with the present results, a previous study [13] has provided preliminary evidence that sleep problems can be considered as predictors of impairment in the QOL of patients with breast cancer which affects their ability to be efficient in work and daily activities because of physical problems and less ability to function generally. Breast cancer patients with poor sleep also reported less vitality or energy in daily life for daily activities, which

is consistent with research indicating that cancer patients having insomnia or poor sleep will have more sleepiness and fatigue during the day [32].

Finally and taking all of this into account, it seems that insomnia is a major health problem in breast cancer and patients should have an effective treatment for their insomnia symptoms, a treatment that can be pharmacotherapeutic and/or psychotherapeutic. Pharmacotherapy is the most used for cancer patients with insomnia and it usually consists in hypnotic drugs [2]. The studies on these drugs among non-cancer patients show that benzodiazepines [33] and benzodiazepine receptor agonists [34] are effective in increasing total sleep time and ameliorating sleep continuity, but to our knowledge there have been no studies evaluating the effect of pharmacotherapy on insomnia in breast cancer patients. In addition, there are disadvantages to the use of these drugs, such as possible addiction and possible interactions with the cancer treatment drugs [2]. The psychotherapeutic methods used in general for insomnia are cognitive behavioral therapy for insomnia (CBT-I), mindfulness and relaxation. CBT-I uses, in addition to implementing sleep hygiene, a behavioural approach and cognitive restructuring techniques. Regarding breast cancer patients, CBT-I was significantly associated with an improvement affecting both subjective and objective measures of sleep [35]. CBT-I has also been reported to be effective in reducing fatigue, pain and menopausal symptoms, such as hot flushes and night sweats and in improving mood, QOL and immunological function [35]. In fact, Savard., *et al.* [36] showed that treatment with CBT-I led to significant changes in white blood cells and lymphocytes and to higher secretion of interferon gamma and interleukin-1b, suggesting a relationship between insomnia and immune regulation in the sense that improvement of insomnia symptoms might have positive effects on the immune system [2]. Some studies comparing pharmacotherapy to CBT-I, found that pharmacotherapy had faster effect in reducing sleep latency [37], and that CBT-I started having effects by the second week but maintained its effects longer, whereas patients taking only pharmacotherapy tended to relapse after discontinuation [38]. Effectiveness of CBT-I was also superior to pharmacological treatment in terms of reduction in sleep latency, increase of sleep efficiency, and obtaining more normal sleepers [38]. Psychological treatment for insomnia also includes mindfulness and relaxation. Carlson., *et al.* [39] reported that mindfulness may help improve sleep in breast and prostate cancer. Muscle relaxation training was found to reduce the latency of sleep onset in cancer patients with insomnia, and the improvement was maintained after three months [40].

As study limitations, we mention the cross sectional nature of study, making it impossible to identify the chronology of the symptoms occurrence, and the absence of a control group.

Implications for psychosocial oncology

- This study emphasizes the high prevalence of insomnia, fatigue, anxiety and depression in patients with breast cancer, which should lead to clinicians to more screening, deeper investigation and active management of these aspects.

- All domains of quality of life in patients with breast cancer are altered, and this alteration should be more frequently assessed and targeted by specific interventions.

- Factors that are associated with insomnia in patients with breast cancer give an idea about possible predisposing factors for this disturbance and highlight its impact on different aspects of patients' lives.

- Pharmacological and psychological interventions must be used to alleviate insomnia in patients with breast cancer, but these interventions need to be tested in this particular context.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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