Sleep reactivity predicts insomnia in patients diagnosed with breast cancer

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Abstract

Study objectives: To examine the role of sleep reactivity as a predictor of insomnia in patients diagnosed with breast cancer.

Methods: One hundred and seventy three women with breast cancer participated and were followed up over a period of 9 months. At baseline participants were assigned to a high (n=114) or low (n=59) sleep reactivity group, based on their responses to the Ford Insomnia Response to Stress Test (FIRST). We assessed whether these FIRST groupings (high / low sleep reactivity) predicted changes in insomnia over time using the Insomnia Severity Index (ISI). We also tested if these FIRST groupings predicted insomnia disorder (using ISI index cut-offs) at three different time points (T3, T6 and T9).

Results: Individuals with high sleep reactivity were more likely to experience a worsening of insomnia. Using logistic regression we also found that FIRST grouping predicted insomnia disorder. Results remained significant after controlling for estimated pre-morbid sleep, age and whether someone had chemotherapy.

Conclusions: Our study shows that sleep reactivity may be a robust predictor of insomnia within breast cancer populations. Sleep reactivity should be considered in routine clinical assessments as a reliable way to identify patients at risk of developing insomnia. This would facilitate early sleep intervention for those patients who are considered high risk.

Keywords: Insomnia, Sleep, Breast Cancer, Sleep Reactivity, Ford Insomnia Response to Stress Test, chemotherapy

Brief summary:

Current Knowledge/Study Rationale: There is a need to identify risk factors for insomnia within breast cancer populations. This is the first prospective study to explore whether sleep reactivity predicts insomnia in a female breast cancer population. **Study Impact.** Breast cancer patients who have high baseline levels of sleep reactivity, are more at risk of experiencing sleep deterioration during cancer treatment, an effect that remains persistent and stable following the completion of active treatment. Implementation of sleep reactivity assessment at cancer diagnosis would enable the identification and prioritisation of 'at risk' patients for early insomnia intervention.

Background

Cancer is the second leading cause of death globally and was responsible for 10 million deaths per year [1]. Breast cancer is the most common form of cancer in the UK, accounting for almost a sixth of all cases in males and females [2]. Whilst the incidence of breast cancer has risen by 6% over the last decade, mortality rates have fallen and currently 80% of those living with early stage breast cancer have a projected life expectancy of more than 10 years [2]. Consequently, the number of breast cancer survivors is expected to reach 2 million by 2040. Growing numbers of breast cancer survivors means that a focus upon post-cancer quality of life is increasingly important. Longitudinal research suggests that quality of life in breast cancer survivors 10 years post diagnosis remains significantly lower than in the general population[3-6]. Most commonly, factors such as fatigue, pain and sleep disturbance are reported to hinder cancer-related quality of life [5,7]. In particular, insomnia is amongst the most distressing and debilitating problems experienced by breast cancer survivors, both during and after completion of active cancer treatment [4,8-10].

Insomnia is the most commonly reported sleep disorder worldwide. It is clinically defined as chronic difficulty with sleep initiation, maintenance, consolidation or quality that occurs for more than 3 months despite adequate opportunity for sleep, resulting in daytime impairment [11]. More than a quarter of adults report poor sleep, with an estimated 8-10% meeting diagnostic criteria for insomnia disorder [12,13]. Rates are considerably higher amongst cancer populations, yet despite increasing awareness of the pervasiveness of insomnia, scientific reports of insomnia prevalence within cancer groups remain variable and wide-ranging (30-75%) [14,15]. This is partly due to studies utilizing different insomnia definitions, measurements, timing of assessments, as well as combing different cancer diagnoses together and including different cancer stages and treatments [16]. Patients with breast cancer report particularly high rates of insomnia, with up to 70% reporting symptoms of insomnia [17,18 9].Contrary to earlier findings from population based samples, [19,20], Fleming et al (2019) reported that following completion of active cancer treatment, most patients did not experience a decrease in insomnia symptoms over time. Rather, they reported insomnia as a persistent and unremitting complaint.

The prevalence and chronicity of insomnia in cancer populations is potentially explained by the interaction of biopsychosocial variables that increase insomnia vulnerability (i.e. female gender),

stressors that trigger acute sleep disturbance (i.e. emotional response to diagnosis, direct effects of cancer treatment) and cognitive and behavioural responses to disturbed sleep that modulate chronicity (i.e. sleep-related rumination, increased time spent in bed) [21]. Given this prevalence and chronicity, identifying cancer patients most at risk of developing insomnia is important for early, targeted insomnia intervention. This is also important as chronic insomnia is associated with the development of both anxiety and depression [22,23].

Previous research shows that female gender, younger age, menopausal status and having an anxious or depressive personality type increases insomnia risk in this population [9,24-27]. Research focusing on the early identification of those at high-risk for insomnia prior to cancer treatment has the potential to make an important contribution to insomnia management within cancer care settings.

Sleep reactivity is the tendency to exhibit pronounced sleep disturbance in response to a stressor and is a premorbid vulnerability for insomnia incidence [28]. A valid and reliable measure of sleep system reactivity is the Ford Insomnia Response to Stress Test (FIRST) [29]. Individuals who have highly reactive sleep systems are more vulnerable to experiencing insomnia, even after the initial stressor has dissipated, whereas those with low sleep reactivity experience mild sleep disruptions that return to normal without any serious complications [30]. At least two longitudinal studies have found that the FIRST predicts later insomnia symptoms and persistence of insomnia symptoms over a 3 year period [31] and predicts the development of insomnia disorder in a subset of healthy people without any sleep disturbances [28]. Furthermore, sleep reactivity has a strong genetic component [32,33] and therefore, sleep reactivity may be a predisposing factor for the development of insomnia following breast cancer diagnosis as stressful life events have been found to interact with sleep reactivity [28]. This is important because it would permit early identification of breast cancer patients who may be most at risk for developing chronic insomnia. However, whilst sleep reactivity is a well-established risk factor for future insomnia, it has not yet been investigated in relation to cancer. Therefore, this study seeks to investigate relationships between sleep reactivity and insomnia in women with breast cancer. More specifically, we aim to assess whether FIRST scores predict insomnia severity in women diagnosed with breast cancer. We hypothesize that high baseline FIRST scores will predict higher levels of insomnia at all phases of cancer care than those with low baseline FIRST scores.

Method

Participants and Recruitment Procedure

173 female breast cancer patients (*M*= 58, *SD*= 9.58 years) participated. Inclusion criteria were a confirmed diagnosis of non-metastatic breast cancer, diagnosis < three months and prognosis > six months. Exclusion criteria were (i) untreated/unstable psychiatric illness, diagnosis of another sleep disorder and male gender. We excluded male breast cancer patients because they are few in number and as such, are likely to have different psychological characteristics. To avoid selection bias and priming effects, participants were advised that they were contributing to a study that was monitoring general wellbeing and health-related symptoms. Prior to enrollment, interested patients were assessed for eligibility using the Glasgow Sleep Centre Screening Interview. This comprises assessments of sleep history, current sleep status, and a history of physical and psychological health. Within this interview, we screened for other sleep disorders using a published screening algorithm[34]. Those patients who met inclusion criteria were enrolled onto the study.

Recruitment took place across multiple hospital sites in west central Scotland. Clinical teams identified eligible patients and the project researcher met with them at a scheduled clinic visit to provide further information and complete consent, eligibility and screening procedures. Recruitment was not restricted to individuals who met criteria for insomnia. Rather, we enrolled a cohort, some of whom would develop clinical insomnia or experience exacerbation of pre-existing clinical insomnia since diagnosis, some of whom would display symptoms of insomnia without fulfilling diagnostic criteria for insomnia, and some of whom would continue to sleep well.

Design

We utilised a prospective quantitative approach in which people with newly diagnosed breast cancer were tracked during the course of their cancer care. This prospective method permits clearer identification of personal reactions to both acute and persistent sleep difficulties. Study assessment points are; i) Baseline (following cancer diagnosis; prior to onset of cancer treatment (i.e. surgery/chemotherapy/radiotherapy)), (ii) T3 (3 month follow up – during cancer treatment), (iii) T6 (6

month follow up – completion of cancer treatment) and (iv)T9 (9 month follow up - cancer rehabilitation). In our sample, it was the case that everyone at each timepoint was at the same stage. For example, at T6 everyone in the sample had completed their cancer treatment.

Measures

Sleep was assessed using the Insomnia Severity Index (ISI) [35]. The ISI is a seven item measure used to assess insomnia severity based on items related to sleep problems, sleep satisfaction and interference of sleep difficulties with daytime functioning. The ISI is scored as follows: 0-7 = no insomnia, 8-14 = subthreshold insomnia, 15-21= moderate insomnia and 22-28 = severe insomnia. The ISI is a valid diagnostic screening tool for detecting insomnia and can correctly identify people with DSM-5 defined insomnia disorder [36-39]. It has also been validated in cancer populations [40]. As this was a secondary analysis, a priori power analysis was not conducted.

Sleep reactivity was assessed using the Ford Insomnia Response to Stress Test (FIRST) [29]**.** The FIRST is a nine-item scale used to assess an individual's likelihood of experiencing sleep difficulties in response to common stressful situations. Each item is self-rated on a four-point Likert scale and summed to yield a total score (range: 9–36) where higher scores indicate higher levels of sleep reactivity. Participant's completed the FIRST at baseline.

Data analysis

Of the 393 patients approached, 42 were excluded and 178 declined to participate, resulting in a participation rate of 49%. All patients were enrolled following diagnosis but prior to onset of active cancer treatment. To test our hypothesis we divided the sample into a low (≤ 16) or high (>16) FIRST group at baseline based on established criteria. This cut-off was selected as a score of >16 has been shown to predict incident insomnia one year later, over and above parental diagnosis of insomnia and demorgraphic variables [41]. Our hypothesis was tested in two ways. First, we examined the pre-diagnosis phase of cancer care – the period following an abnormal finding, but prior to receiving an official cancer diagnosis (estimated pre-morbid ISI data was collected at Baseline (study entry), which consisted of a retrospective ISI to establish sleep status 3 months prior to diagnosis). To test this we ran a mixed effect

model using the packages lmer and lmerTest [42,43]. Random intercepts were included for participant and specified maximally [44,45]. Our second analysis tested whether FIRST grouping at baseline predicted insomnia status at T3, T6, and T9. Insomnia status was defined as having an ISI score of >14, which is classed as clinical insomnia (moderate severity) based on established ISI cut-offs. Furthermore a score of 14 or more has excellent accuracy in detecting insomnia within cancer populations [40] In all regression models, estimated pre-morbid ISI was entered in the regression models to control for pre-diagnosis levels of sleep. Inspections of QQ plots showed that age and ISI change scores were normally distributed. All data analyses were conducted in R studio.[46] The code is available here https://osf.io/t4d36/ .

Results

Descriptive data for full sample (n=173)

The mean age of the sample was 58 (*SD*=9.58). Further detail on the sample is provided in table 1 and can also be found in Fleming et al., (2019). Correlational analysis between the FIRST and ISI are provided in supplementary info.

[insert table 1 here]

FIRST grouping

Independent sample t-tests showed that the high (*M*=59, SD=9.27) and low (*M*=57, *SD*=10.0) FIRST groups did not differ on age $t(109) = 1.6$, $p= 0.11$ but they did differ on estimated pre-morbid ISI scores (group means were in normal ISI range): low group (*M*=2.16, SD=3.47); high group (*M*= 5.14, *SD*=6.29), $t(170.2)= -4.0$, $p= <0.001$. Chi Square analysis showed no differences at baseline between high and low FIRST groups on employment status *($X^{2,}$* 4, *N*=178) = 7.751, *p=.101*, marital status ($X^{2,}$ 6, *N*=178) = 6.813, p = .338, tumour stage (X^2,3, *N=178) = 0.794, p=.090,* chemotherapy ($X^{2,}$ 1, *N*=178) = 0.008, *p=.927* or radiotherapy ($X^{2,}$ 1, *N=178), 0.002, p=.870.*

Data visualisation

Figure 1 shows the interaction between time and FIRST on ISI scores. The box plots and distributions represent the average ISI scores for each patient. The box plots are showing the median, first and third quartile, and the minimum and maximum ISI scores for low (yellow) and high (green) reactivity. From figure 1, it can be seen that the high sleep reactive group show higher levels of ISI at every time point.

[enter figure 1 here]

Insomnia Changes over time (Mixed Effect Model)

To test our hypothesis, a hierarchical mixed model regression analysis was conducted with ISI scores as the dependent variable. Time was entered in the stage one; age was entered in the stage two; chemotherapy was entered in the stage three; and FIRST at stage four. This approach allowed the incremental variance in poor sleep at later points in disease course to be examined in relation to FIRST scores. The final stage showed that FIRST and the interaction between FIRST and time added 11% in the explained variance on ISI scores. In other words, taking the estimated pre-morbid ISI scores as the reference category, patients in the high FIRST grouping reported higher scores on ISI at every timepoint when compared to patients in the low FIRST grouping. Table 2 summarizes our hierarchical mixed model regression analysis.

(Insert table 2)

Sleep Reactivity as a predictor of Insomnia Disorder(Logistic Regressions)

Next we used ISI cut offs to establish whether FIRST grouping would predict insomnia status at 3 timepoints during the course of the study. Scores of >14 on the ISI indicate clinical insomnia, and this threshold was chosen as it is more conservative and will allow us to pick up insomnia cases that are clinically relevant. The sample was split into an 'insomnia disorder' group or 'no insomnia' group based on whether they had scores of > 14 at baseline, T3 , T6 and T9. Table 2 shows the number of cases of insomnia disorder at each of these time points based on their FIRST grouping.

[Insert Table 3 here]

Logistic regression models (T3, T6. T9)

In our logistic regression models, FIRST grouping, estimated pre-morbid ISI scores (to account for differences in sleep before study entry), age and chemotherapy were all included as predictors of insomnia status. At every timepoint, FIRST grouping and estimated pre-morbid ISI scores were significant predictors of insomnia status. Furthermore, at T6 and T9 chemotherapy was also a significant predictor of insomnia status. Table 4 displays a summary of all the models.

[Insert Table 4 here]

Discussion

Approximately 50% of breast cancer patients experience poor sleep at all phases of their cancer care, including the months following completion of their cancer treatment. Previous research has shown that once insomnia symptoms develop, they tend to remain persistent (Fleming et al., 2019). The aim of this study was to investigate whether sleep reactivity, which is an individual's predisposition to experience sleep disruption in response to stress, predicts insomnia during the course of cancer treatment and follow-up. Early identification of patients who are most at risk for developing insomnia is vital, and to our knowledge, this study was the first to assess sleep reactivity in patients diagnosed with breast cancer. Our key finding is that sleep reactivity is an important predictor of insomnia at all phases of cancer care when controlling for estimated pre-morbid-sleep status, chemotherapy and age.

Our analysis investigated whether participants in the High FIRST group experienced greater changes in sleep from pre to post diagnosis. Both high and low sleep reactivity groups showed sleep deterioration following cancer diagnosis. This was expected given the stress associated with receiving a diagnosis of cancer and apprehension about upcoming treatments[47]. However, we found that worsening of sleep was considerably greater in the high sleep reactivity group than in the low reactivity group indicating that the high reactivity group were more vulnerable to experiencing significant sleep disruption.

Importantly, our analysis took into account individual differences in estimated pre-morbid insomnia scores suggesting that FIRST grouping is a meaningful and important predictor variable.

In our analysis of insomnia disorder, results indicated that elevated sleep reactivity increases the likelihood of having insomnia disorder at 3, 6 and 9 months post-cancer diagnosis. Importantly, regression models controlled for levels of estimated pre-morbid insomnia, chemotherapy and age, which are important predictors of disrupted sleep within cancer populations [9]. Furthermore, it is also important to note that while baseline levels of sleep reactivity predicted insomnia at later time-points, average ISI scores were within normal limits (<7) prior to diagnosis, even in those with elevated sleep reactivity scores. This suggests that even normal sleepers (i.e. low ISI scores), can experience a large decline in their sleep across the phases of cancer diagnosis and treatment, and measures of sleep reactivity (FIRST) can identify these high-risk individuals prior to insomnia onset. Another key finding from the regression analyses was the comparable predictive value of chemotherapy and sleep reactivity. Previous research has shown chemotherapy to be a predictor of persistent insomnia in this population [9], and our study suggests that sleep reactivity may be as strong a predictor as chemotherapy.

The finding that sleep disruption is a persistent and troubling problem in this population is consistent with a number of previous studies[9,17]. Indeed, a recent qualitative study in 27 cancer survivors reported that poor sleep was a long-term problem that impacted negatively on quality of life including sociability, physical activity and psychological well-being [48]. Chroinic insomnia is associated with risk of exacerbated morbidity and mortality in cancer patients [49]. Indeed, there has been a shift from viewing sleep as an inevitable symptom of cancer to being regarded as an independent risk factor for the development of physical and mental ill health [13] and one where preventative strategies may play a critical role. Importantly, insomnia has been associated with a twofold increase in the risk of depression[50], with strong and consistent evidence that insomnia increases the risk of incident depression [51]. Furthermore, insomnia may be linked to poorer cancer outcomes by adversely impacting immunity and influencing tumour growth and progression[51,52].

Our study suggests that when identifying individuals who may be at risk for developing insomnia during their cancer care, sleep reactivity is an important factor to consider. This is especially important because individuals who have highly reactive sleep systems are not necessarily poor sleepers at T0 and therefore

may not be picked up if screening is based on presenting complaints. Despite the emerging evidence that insomnia is prevalent and persistent, insomnia assessment and treatment is rarely offered in cancer care [9,53]. This is despite current DSM 5 guidelines indicating that sleep problems should be treated irrespective of other health or psychiatric complaints [11].The gold-standard treatment for insomnia disorder is cognitive behavioural therapy (CBT-i), which has considerable efficacy within breast cancer populations [54]. Our study shows that the FIRST is a reliable and accurate screening tool to identify newly diagnosed breast cancer patients most at risk for experiencing sleep disturbance. Once identified, we recommend that these individuals are offered support for their sleep at the earliest available time, to mitigate and lower the risk of chronic insomnia and its associated cancer-related morbidity. Studies have shown that mild symptoms of insomnia can be treated effectively with CBT-I and can improve symptoms of anxiety and depression [55,56].

There are a few limitations in our study design. First, we recruited only females with breast cancer, so our results cannot be generalised to male breast cancer patients or other cancer diagnoses. Secondly, it was out of the scope of the current study to validate the FIRST in this cancer population. Thirdly, further replication of this work is needed to confirm effectiveness of using the FIRST to identify patients at risk for insomnia. Finally, recruitment was conducted within one health board in Scotland, potentially limiting the representativeness of the study sample. However, a key strength of this study is the utilisation of a prospective design, which allowed us to monitor changes of insomnia symptoms over time.

In conclusion, our study demonstrates that sleep reactivity, assessed by the FIRST, is a useful predictor of insomnia in breast cancer patients, which also predicts clinical levels of insomnia during the cancer treatment and rehabilitation pathway. We call for routine assessment of sleep reactivity in newly diagnosed breast cancer patients to help identify those most at risk for developing insomnia disorder during cancer care.

Abbreviations:

CBT-i : Cognitive Behavioural Therapy for Insomnia

FIRST: Ford Insomnia Response to Stress Test

ISI: Insomnia Severity Index

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Figure 1: The interaction effect between time and reactivity on ISI scores.

Table 1: Descriptive details for the sample

		% of participants	Count
Employment status at recruitment	Employed	19.7%	34
	Unemployed	5.8%	10
	Sick leave	36.4%	63
	Retired	35.8%	62
	Missing	2.3%	4
Marital Status	Married	53.2%	92
	Single	13.3%	23
	Divorced	11.0%	19
	Widowed	12.1%	21
	Living with partner	4.6%	8
	Separated	2.3%	4
	Missing	3.5%	6
Tumour Stage	T1	48.6%	84
	T2	36.4%	63
	T3	3.5%	6
	T4	.6%	1
	DCIS	10.4%	18
	Missing	.6%	1
Surgery Type	Wide Local Excision	8.8%	7
	Mastectomy	25%	20
	Quadrantectomy	0%	0

	No surgery	0%	0
	Lumpectomy	62.5%	50
	Other	3.8%	3
Chemotherapy	Yes	46.2%	80
	No	53.8%	93
Radiotherapy	Yes	93.6%	162
	No	6.4%	11
Menopause status	Pre	23.8%	19
	Pre	3.8%	3
	Post	53.8%	43
	Missing	18.8%	15

Table 2: Stepwise regression: insomnia changes over time

	Model 1	Model 2	Model 3	Model 4
(Intercept)	4.13 ***	13.23 ***	8.91 **	7.86 **
	(0.50)	(2.51)	(2.79)	(2.54)
Time (Study entry vs. Pre-morbid ISI)	4.78 ***	4.78 ***	4.78 ***	5.67 ***
	(0.42)	(0.42)	(0.42)	(0.51)
Time(T3 vs. Pre-morbid ISI)	4.57 ***	4.57 ***	4.57 ***	5.42 ***
	(0.42)	(0.42)	(0.42)	(0.51)
Time(T6 vs. Pre-morbid ISI)	4.42 ***	4.42 ***	4.42 ***	5.13 ***
	(0.42)	(0.42)	(0.42)	(0.51)
Time (T9 vs. Pre-morbid ISI)	4.20 ***	4.20 ***	4.20 ***	4.95 ***
	(0.42)	(0.42)	(0.42)	(0.51)
Age		-0.16 ***	-0.10 *	-0.07
		(0.04)	(0.04)	(0.04)
Chemotherapy			2.70 **	2.91 ***
			(0.85)	(0.78)
FIRST (sleep reactivity)				-2.78 **
				(0.94)
Time(Study entry vs. Pre- morbid ISI) * FIRST (sleep reactivity)				-2.60 **
				(0.88)
Time (T3 vs. Pre-morbid ISI)* FIRST (sleep reactivity)				-2.51 **
				(0.88)
Time (T6 vs. Pre-morbid ISI)* FIRST (sleep reactivity)				-2.10 *
				(0.88)
Time (T9 vs. Pre-morbid ISI)* FIRST (sleep reactivity)				-2.20 *
				(0.88)
R2 (fixed)	0.07	0.12	0.15	0.26
R2 (total)	0.67	0.67	0.67	0.68

*** p < 0.001; ** p < 0.01; * p < 0.05.

Table 3: Insomnia status by FIRST grouping at each study assessment point .

Baseline	***Insomnia Disorder***	***No Insomnia***
High	*32*	*82*
Low	*3*	*56*
T6		
High	*31*	*83*
Low	*5*	*54*
T9		
High	*31*	*83*
Low	*2*	*57*

FIRST= Ford Insomnia Response to Stress Test,

Table 4: Logistic regression: Predicting Insomnia Status

		Standardized estimate	Wald	p-value
Timepoint 3	(Intercept)	-1.78	-6.68	< 0.001
	FIRST(sleep reactivity)	-0.80	-2.60	0.009
	Pre-Morbid ISI	0.56	2.92	0.003
	Age	-0.28	-1.20	0.231
	Chemotherapy	0.40	1.74	0.08
Timepoint 6	(Intercept)	-1.81	-6.77	< 0.001
	FIRST(sleep reactivity)	-0.56	-2.13	0.033
	Pre-Morbid ISI	0.57	2.75	0.006
	Age	-0.13	-0.57	0.567
	Chemotherapy	0.97	3.81	< 0.001
Timepoint 9	(Intercept)	-1.99	-6.48	< 0.001
	FIRST (sleep reactivity)	-1.01	-2.74	0.006
	Pre-Morbid ISI	0.53	2.69	0.007
	Age	-0.24	-0.97	0.330
	Chemotherapy	0.54	2.24	0.024