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Perceived cognitive impairment in Chinese patients with breast cancer and its relationship with post-traumatic stress disorder symptoms and fatigue

Jie Li[1], Lixiang Yu[2], Zhouting Long[1], Yang Li[1] and Fenglin Cao[1]*
[1]*Nursing School, Shandong University, 44 Wenhuaxi Road, Jinan, Shandong Province, 250012, China*
[2]*The Second Hospital of Shandong University, Shandong University, 247 Beiyuan Road, Jinan, Shandong Province, 250033, China*

**Correspondence to: Department of Nursing Psychology, Nursing School, Shandong University, 44 Wenhuaxi Road, Jinan, Shandong Province, 250012, China. E-mail: caofenglin2008@126.com*

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Abstract

***Objective*: Clinical reports have shown that adjuvant chemotherapy has a negative impact on perceived cognitive impairment (PCI) of patients with breast cancer; however, evidence concerning the effects of psychological factors such as post-traumatic stress disorder (PTSD) symptoms on PCI is limited, especially in relation to Chinese patients with breast cancer. This research investigated the associations between psychological factors and PCI in Chinese women with breast cancer.**

***Methods*: In total, 204 women with breast cancer were assessed for PCI, PTSD symptoms, fatigue, anxiety, and depression using self-report measures. Hierarchical linear regression was conducted to investigate the associations between the variables of interest and PCI.**

***Results*: Two hundred and two women were included in the final analysis; two of those originally tested were excluded because of missing data. A univariate analysis showed that PCI was significantly related to education, PTSD symptoms (re-experience, avoidance, and hyperarousal), fatigue, depression, anxiety, and undergoing chemotherapy or radiotherapy. Hierarchical linear regression revealed that PTSD symptoms and fatigue ($\Delta R^2 = 0.26$, $P < 0.001$) independently accounted for PCI in Chinese women with breast cancer regardless of age, education level, chemotherapy and radiotherapy. Hyperarousal was the only contributing PTSD symptom to PCI ($B = -1.24$, SE = 0.33, $\beta = -0.39$, $P < 0.001$).**

***Conclusions*: Besides chemotherapy, PTSD symptoms, especially hyperarousal, and fatigue are important risk factors for significant PCI and are therefore worthy of further investigation.**

Introduction

Breast cancer is one of the most prevalent dangers to women's physical and mental health. A growing body of research indicates that female patients with breast cancer experience perceived cognitive impairment (PCI) after treatment [1–4]. As subjective cognitive dysfunctions, PCI seriously impacts quality of life (QOL) and functional abilities of patients nor does objective cognitive impairment (e.g. neuropsychological) [5–7]. Furthermore, PCI is considered as having a better ecological validity than neuropsychological cognition [8]. Chemotherapy was once considered to be the main culprit for these cognitive deficits [1–4,9]; however, results from longitudinal studies have shown that women with breast cancer evidence reduced cognitive performance when compared with healthy controls even before they undergo chemotherapy [10,11]. This finding suggests that other risk factors could be responsible for the cognitive decline witnessed in patients with breast cancer. In addition to chemotherapy, there is some evidence that psychological factors such as anxiety, depression, and fatigue are also related to PCI [7,12]. Nevertheless, the relationships between these need to be investigated further [12].

Post-traumatic stress disorder (PTSD) is classified as a psychiatric disorder that is characterized by symptoms of re-experience, avoidance, and hyperarousal, according to the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition (DSM-IV) [13]. Life-threatening illness, such as cancer, is one of the causes of PTSD listed in the DSM-IV. In women with breast cancer, PTSD incidence ranges from 0 to 32% [14,15]. Previous studies have shown that PTSD is a risk factor for cognitive deficits in older adults [16], patients with schizophrenia [17], and veterans [18]. This suggests that PTSD may also explain the cognitive deficits in women with breast cancer to some extent.

There are two theories that have linked PTSD with cognitive impairment. One is the theory of self-regulation, which posits that the resources used for cognitive tasks are limited because the stress from the cancer diagnosis is using up all that are available [19]. The other is the idea that stress exposure activates the hypothalamic–pituitary–adrenal (HPA) axis for adaption, which may induce the hypoactivation of the HPA axis and impair the hippocampal structure [20], which is associated with important cognitive functions such as memory [21] and executive function [22]. Most likely, PCI of patients with breast cancer can be explained under

the first theory. Although evidence has indicated that PTSD might impair cognitive function in women with breast cancer, studies examining PTSD as one of the risk factors for PCI in this population are few. Reid-Arndt *et al.* reported that self-related stress was correlated with neuropsychological cognitive deficits (such as memory, attention, and verbal fluency difficulties) [23]. PTSD was not discussed directly but rather in terms of the perception of stress presented in that study, and its relationship with subjective cognitive impairment/PCI was not evaluated. For this reason, our efforts are focused on evaluating PCI's association with PTSD, in addition to fatigue, anxiety, and depression.

Compared with Western countries, the incidence of breast cancer in China has traditionally been low; however, it has grown rapidly in recent years [24]. Recent data have shown that the prevalence of breast cancer for Chinese women is 129.3/100,000 [25], which indicates that there are a large number of women with breast cancer for the huge population base of China. Because this is such a widespread issue, it is clear that more attention should be paid to the cognitive disturbances experienced by these women; however, research into the PCI of Chinese patients with breast cancer is scant. Compared with Western countries (e.g. America), there are some specificities of Chinese breast cancer patients: (1) younger age at onset of breast cancer, (2) shorter lifetime duration of breastfeeding resulting from the unique one-child policy, (3) lower screening rates and longer delays in breast cancer diagnosis, and (4) lower frequency of breast-conserving surgery [26]. Therefore, it is very necessary to evaluate PCI and its related factors in Chinese women with breast cancer.

In this study, we investigated the extent to which chemotherapy and psychological factors (PTSD, fatigue, anxiety, and depression) were related to PCI in Chinese patients with breast cancer. We hypothesized that (1) chemotherapy was associated with PCI after controlling for related characteristic variables and (2) PTSD and other psychological factors were associated with PCI over and above chemotherapy and related characteristic variables.

Methods

This cross-sectional, observational study was conducted at Shandong University's Qilu Hospital and was approved by the Research Ethics Committee of the Nursing School, Shandong University.

Participants

Patients with breast cancer were recruited for this study if they were at least 1 week post-surgery following the removal of a cancerous breast mass, whether they had received chemotherapy or were planning to have chemotherapy. The patients were recruited at the hospital when they went to receive the first cycle of chemotherapy after surgery or for the second or later cycles of chemotherapy. The inclusion criteria were (1) female, (2) a breast cancer diagnosis made by an oncologist, followed by breast surgery, (3) aged 20–60, and (4) ability to read and understand Chinese. The exclusion criteria were (1) brain metastasis, (2) history of mental illnesses (e.g. schizophrenia, dementia), and (3) unable to provide informed consent. All participants were aware of their breast cancer diagnosis at the time of recruitment.

Measures

PCI was measured by the 20-item PCI subscale of the Chinese version of the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) Version 3, which was used to measure participants' subjective cognitive function over the past week [27,28]. The Chinese version was translated according to rigorous guidelines and was tested to ensure sound concurrent and convergent validity, internal consistency (Cronbach's $\alpha = 0.707–0.854$), and test–retest reliability (intraclass correlation coefficient = 0.693–0.793) [28]. A higher score for each domain indicated better functioning. The Cronbach's α of FACT-Cog was 0.874–0.959 in our sample.

The PTSD Checklist-Specific Stressor Version (PCL-S) [29], a 17-item self-rating questionnaire using a five-point Likert scale (from 1 'not at all' to 5 'extremely'), was used to assess PTSD symptoms (re-experiencing, avoidance, and hyperarousal) in women with breast cancer. Both the original and Chinese versions of the PCL had sound psychometric properties for use in various traumatic populations (Cronbach's $\alpha = 0.77–0.82$ for the Chinese version) [30,31]. In this study, participants were instructed to complete the PCL in reference to the 'breast cancer', and the Cronbach's α for the PCL was 0.945.

Fatigue was measured by the Chinese version of the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F), Version 4. This scale demonstrated good construct validity and internal consistency (Cronbach's $\alpha = 0.93$) [32]. Summing up each item score yielded a total score. The higher the total score, the better the functioning. In this study, Cronbach's α of the FACIT-Fatigue scale was 0.910.

The Chinese version of the Hospital Anxiety and Depression Scale (HADS) was used to measure depression and anxiety [33,34]. This is a 14-item self-report scale, with seven items assessing depression symptoms (HADS-D) and the others assessing anxiety symptoms (HADS-A) that had been experienced in the past week. The Chinese version of the HADS has demonstrated good concurrent validity and internal consistency (Cronbach's $\alpha = 0.76–0.81$). In our study, the Cronbach's α of HADS-D was 0.811, and the same measure for the HADS-A scale was 0.836.

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Statistical methods

Univariate relationships among study variables were analyzed with Spearman correlation analysis and nonparametric tests (Mann–Whitney U tests). Spearman correlation analysis was used to analyze the associations between continuous variables and ordinal categorical variables. The relationship between dichotomy variables (e.g. presence or absence of chemotherapy treatment) and PCI was analyzed with Mann–Whitney U tests. Given that demographic and other clinical factors might contribute to the relationship between chemotherapy, psychological factors, and PCI, we performed hierarchical linear regression with the PCI score of FACT-Cog as the dependent variable. Age, education [35], and demographic variables that were statistically significant ($P < 0.1$, two tailed) in the univariate analysis were included in the regression model in block 1 as control variables, and significant ($P < 0.1$, two tailed) clinical variables in the univariate analysis were included in block 2. This method was used in the case of detraction from the statistical power. All psychological factors were inputted in block 3. An alpha level of $P < 0.05$ (two tailed) was used to establish statistical significance.

Results

Participants' characteristics

After taking the inclusion and exclusion criteria into consideration, 221 women were eligible to participate, but 17 refused. Two subjects were excluded because of missing PCL-S and HADS values; thus, we had a total sample of 202 subjects from which we could receive data to be used for the statistical analyses. Those who refused to participate in the study did not differ significantly on age in comparison to those who completed the study (45.8 ± 6.9 vs 45.2 ± 8.0, $P = 0.771$).

As shown in Table 1, the majority of participants were Han (98%) and married (99%). Almost three fourths (71.8%; $n = 145$) of them had completed senior high school or higher. Over 80% (88.7%; $n = 181$) of the patients were in stage 0–III at the time of diagnosis. Fifty percent of the patients ($n = 101$) were receiving chemotherapy at the time of recruitment, and most of them (80.2%) had received 6 or fewer cycles. Nine (4.5%) patients received radiotherapy, and 11 (5.4%) received hormone therapy. The descriptions of PCI, PTSD symptoms, fatigue, anxiety, and depression are presented in Table 2.

Table 1. Demographic and clinical characteristics of the patients ($n = 202$)

	n	valid %	*M* ± *SD*
Age (years)			45.2 ± 8.0
Education			
Junior high or lower	57	28.2	
Senior high/intermediate general	70	34.7	
Higher general	38	18.8	
Graduate/postgraduate	37	18.3	
Race			
Han	198	98.0	
Hui	4	2.0	
Marital status			
Single	2	1.0	
Married	200	99.0	
Cancer stage[a]			
0	11	5.4	
I	47	23.3	
II	80	39.6	
III	41	20.3	
IV	23	11.4	
Postmenopausal	55	27.2	
Hemoglobin level (g/ml)			122.2 ± 13.9
BMI			24.5 ± 3.7
Receipt of chemotherapy			
Yes	101	50.0	
No	101	50.0	
Number of cycles of chemotherapy			
1–3 cycles	36	17.8	
4–6 cycles	45	22.3	
>6 cycles	20	9.9	
Receipt of radiotherapy	9	4.5	
Receipt of hormone therapy	11	5.4	

SD, standard deviation
[a]using AJCC/UICC TNM Classification.

Table 2. Descriptive data for the study variables

	25th quartiles	75th quartiles	Obtained range	Possible range
PCI	53	70	18 ~ 72	0 ~ 72
PTSD symptoms	21	36	17 ~ 81	17 ~ 85
Re-experience	6	11	5 ~ 21	5 ~ 25
Avoidance	8	15	7 ~ 35	7 ~ 35
Hyperarousal	6	11	5 ~ 25	5 ~ 25
Fatigue	29	43	0 ~ 52	0 ~ 52
Anxiety	3	9	0 ~ 21	0 ~ 21
Depression	1	8	0 ~ 21	0 ~ 21

Univariate relationships among the study variables

Spearman correlation analyses were used to evaluate the bivariate relationship between sociodemographic and some clinical characteristics (age, education, cancer stage, hemoglobin level, and BMI), psychological factors (PTSD symptoms, fatigue, anxiety, and depression), and PCI. More PCI was significantly associated with lower education ($r = 0.18$, $P = 0.009$) and more PTSD symptoms ($r = -0.54$ for total score, -0.47 for re-experience, -0.45 for avoidance, and -0.57 for hyperarousal; $P < 0.001$), higher fatigue ($r = 0.48$, $P < 0.001$), anxiety ($r = -0.39$, $P < 0.001$), and depression ($r = -0.41$, $P < 0.001$).

The Mann–Whitney U test was used to compare PCI differences between two dichotomous groups: postmenopausal (yes/no), and receipt of chemotherapy, radiotherapy, and

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hormone therapy (yes/no). The results indicated that chemotherapy and radiotherapy were significantly associated with more PCI (Table 3).

Hierarchical linear regression models of PCI

The models were first assessed for absence of multicollinearity [VIF = (1.09–3.89) < 10]. There was no multicollinearity found, indicating that it was appropriate to include all independent variables in the regression models. The hierarchical linear regression model indicated that significant proportions of PCI variance were accounted for by PTSD symptoms and fatigue over and above chemotherapy and radiotherapy by controlling for age and education. As shown in Table 4, chemotherapy was significantly associated with PCI after controlling for age and education, but this was not the case for radiotherapy. In block 3, PTSD symptoms and fatigue entered the regression model and accounted for 26.0% of the variance in PCI. This model explained 38.3% of the PCI variance. In order to identify how the three PTSD symptoms were associated with PCI, a specific hierarchical linear regression model was performed with them instead of the total PTSD symptoms included in block 3. Among the three symptoms, only hyperarousal entered the model ($B = -1.24$, $SE = 0.33$, $\beta = -0.39$, $P < 0.001$; total $R^2 = 0.41$, $F = 13.34$, $P < 0.001$), and it, together with fatigue, contributed 28.8% of the PCI variance. The results showed that chemotherapy was significantly associated with PCI, and PTSD symptoms, especially hyperarousal and fatigue, were significantly associated with PCI beyond the other factors.

Table 3. Comparison of PCI as related to the clinical characteristics of the binary variables

	Median (25^{th}; 75^{th} quartiles)	*P*
Postmenopausal		0.778
Yes ($n = 55$)	63 (51; 71)	
No ($n = 147$)	64 (54; 70)	
Receipt of chemotherapy		0.000
Yes ($n = 101$)	67 (58; 72)	
No ($n = 101$)	61 (50; 68)	
Receipt of radiotherapy		0.006
Yes ($n = 9$)	64 (55; 70)	
No ($n = 193$)	52 (45; 60)	
Receipt of hormone therapy		0.374
Yes ($n = 11$)	64 (53; 70)	
No ($n = 191$)	58 (49; 70)	

Table 4. Hierarchical linear regression for variables associated with PCI ($n = 202$)

	B	*SE*	*β*	ΔR^2
Block 1				0.03*
Age	−0.08	0.09	−0.05	
Education	1.94	0.70	0.17**	
Block 2				0.09***
Chemotherapy	−4.08	1.50	−0.16**	
Radiotherapy	0.97	3.61	0.02	
Block 3				0.26***
PTSD symptoms	−0.39	0.10	−0.37***	
Fatigue	0.39	0.10	0.30***	
Anxiety	0.01	0.30	0.00	
Depression	0.25	0.34	0.08	
Total model				
R^2	0.38			
F	14.96***			

*$P < 0.05$,
**$P < 0.01$,
***$P < 0.001$

Discussion

This study sought to examine the relationships between chemotherapy, psychological factors, and PCI in Chinese patients with breast cancer. The results of this research suggested that PTSD symptoms, especially hyperarousal and fatigue, were associated with PCI over and above chemotherapy in patients with breast cancer after controlling for age and education. Specifically, PTSD symptoms and fatigue contributed much more to PCI than did chemotherapy.

To the best of our knowledge, this is one of the first published studies to examine cognitive changes in Chinese patients with breast cancer. Only one recent study reported the effects of cancer treatment on attentional functioning [36], and two more studies evaluated the neuropsychological cognitive changes of patients with breast cancer [37,38]. However, attentional function is only one of the domains of cognitive function. Difficulties in subjective cognitive function, rather than objective cognitive function, are most frequently associated with QOL and daily functioning [5,7]; therefore, it is crucial to assess subjective cognitive function (such as PCI) in addition to objective cognitive functioning.

Consistent with prior studies, chemotherapy here is shown to have a significant relationship with PCI [1–4,9]. Many mechanisms by which chemotherapy impacts cognitive functioning have been postulated, including direct neurotoxic injury, immunologic changes, and endocrine disorders, but no single mechanism can explain the cognitive changes observed in patients with cancer after chemotherapy [9]. 'Chemo-brain' or 'chemo-fog' is recognized as a cognitive impairment, an adverse effect of chemotherapy, and most of the existing studies focus on chemotherapy as the reason for cognitive decline. Recently, some longitudinal studies have found that patients with breast cancer perform worse in comparison to matched healthy controls on cognitive function examinations before chemotherapy begins [10,11]. Results from a functional magnetic resonance imaging study indicated that patients

with breast cancer perform worse on selective attention and working memory tasks before chemotherapy compared with healthy controls [39]. The results of this current study emphasize the importance of considering psychological factors, especially PTSD symptoms, in conjunction with chemotherapy in an effort to understand the factors that contribute to cognitive disturbances of patients with breast cancer.

This study adds to the existing literature by showing that PTSD symptoms and fatigue are associated with cognitive changes, even in the absence of chemotherapy. Among the psychological variables, fatigue has been investigated most frequently, with strong evidence from prior literature supporting the idea that cancer-related fatigue is associated with PCI [12,40] and with the objective cognitive functioning of patients with breast cancer [41]. Fatigue and cognitive changes possibly share the underlying mechanisms that are influenced as a result of the secondary effects of systemic inflammation. TNF-α, as a marker of inflammation, was reported to be associated with cancer-related fatigue [42] and increased memory complaints [43].

Most evidence suggests that people with PTSD exhibit poorer performance in cognitive tests compared with those without PTSD [16,17]. A breast cancer diagnosis is traumatic for many women, and 20.1% may report cancer-related PTSD symptoms at 3 months post-surgery [14]. However, PTSD is first evidenced as one of the associated factors of cognitive decline in patients with breast cancer in the present study, even though one of the studies we mentioned earlier regarded it as merely a result of stress [23]. One explanation of the association between PTSD and cognitive functioning in patients with breast cancer is the theory of self-regulation, which considers that the resources used for behaviors requiring self-control is limited [19]. Patients with breast cancer use their resources to focus on the perceived threat (the diagnosis of breast cancer); thus, there is a shortage of resources available for use in other tasks, and this can result in problems with logical thinking and reasoning, cognitive extrapolation, reading comprehension [44], and working memory [45], all of which are important cognitive domains. Hyperarousal symptoms were common in patients with cancer, and the patients became highly sensitive to physical symptoms for the fear of relapse [46]. Although there is little evidence regarding the association between hyperarousal and PCI, researchers have found that hyperarousal is related to lower levels of energy/vitality and subjective emotional health [47,48], all of which have been demonstrated to be related to PCI [7,12].

Nonetheless, this study reveals that the effects of anxiety and depression on PCI fail to reach statistical significance, and this is inconsistent with previous results that showed how anxiety and depression are associated with subjective cognitive deficits. The possible reasons for this result include a stronger influence of PTSD on PCI or interference from core PTSD symptoms (e.g. hyperarousal, including difficulty concentrating) on PCI.

One of the limitations of this study is that we cannot report the incidence of significant PCI because there is no cutoff score for the FACT-Cog; however, the FACT-Cog is a comprehensive self-report scale and has been robust enough to evaluate the PCI of patients with cancer until now [4]. Patients with breast cancer in Singapore rated their PCI as a median score of 63 with chemotherapy and 68 with no chemotherapy [4]. A median score of 61 with chemotherapy and 67 with no chemotherapy was reported in our study. This indicates that patients in this study reported similar cognitive functioning with the Singapore patients.

However, some other limitations of this study should be discussed. First, we did not assess objective cognitive functions to evaluate whether they were consistent with subjective cognitive functions. Second, the results cannot be generalized to older patients because patients older than 60, who are naturally at greater risk of cognitive decline, were excluded [49]. Their children do not often tell them of their breast cancer diagnoses because they want to protect them from feelings of fear and despair. This is consistent with traditional Chinese attitudes and behaviors. Based on this tradition, another limitation was the generalization of our results to patients living in different cultures (e.g. Western countries). However, cancer, as one of the most life-threatening illnesses, can be traumatic to women living in any culture.

In conclusion, chemotherapy is associated with PCI in Chinese women with breast cancer. PTSD symptoms, especially hyperarousal and fatigue, are risk factors of PCI independent of chemotherapy. This pilot study points to the necessity of investigating the PCI situation in Chinese patients with breast cancer and the role PTSD may play in any possible intervention. Further longitudinal design studies are needed in order to corroborate the results of the present study and to add an examination of more objective measures of cognitive functioning, as well as an investigation of the mechanisms underlying the results.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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