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Factors correlated with fatigue in disease-free breast cancer patients: application of the Cancer Fatigue Scale

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Abstract Fatigue is one of the most frequent symptoms in cancer patients. However, the precise causes of this fatigue are still unknown, and this situation makes it difficult to combat the problem. The present study was conducted to investigate factors correlated with fatigue in disease-free breast cancer patients. A group of 134 randomly selected ambulatory breast cancer patients who had undergone successful surgical treatment participated. They completed the Cancer Fatigue Scale, the Hospital Anxiety and Depression Scale, the Mental Adjustment to Cancer Scale, and an ad hoc questionnaire detailing physical symptoms, social support, and demographic variables at home and returned them by mail the following day. Multiple regression analysis revealed that fatigue was significantly correlated with dyspnea, insufficient sleep, and depression, and that these three variables accounted for a total of 46% of variance in fatigue. Factors concerned with the cancer and treatment, such as disease stage, lymph node metastasis, number of days since operation, past intravenous chemotherapy, radiotherapy, current use of fluoropyrimidine compounds, and current use of tamoxifen citrate were not correlated with fatigue. The results suggest that fatigue in this population is determined by current physical and psychological distress rather than by the cancer itself and prior cancer treatments, and that the management of dyspnea, insomnia, and depression might be important in reducing fatigue in this population.

Key words Cancer · Fatigue · Depression · Symptom management · Quality of life

Introduction

Fatigue is deleterious to the activities and quality of life of cancer patients [12, 33] and is one of the most frequent symptoms experienced by cancer patients [16], including long-term survivors. The reported frequencies of fatigue in cancer survivors range from 34% to 76% [4, 13]. However, no strategy for managing fatigue has yet been established [3]. Understanding the factors

that are correlated with fatigue is important for establishing a solution to the problem.

Why do disease-free cancer patients frequently experience fatigue even after successful treatment? The development of cancer medicine has contributed to improved cure rates and longer survival terms, and seems to have brought many patients freedom from cancer and the burdens associated with the disease. However, some studies have shown that many disease-free cancer patients still suffer from various kinds of problems [4, 13, 35]. These include prolonged physical symptoms of the cancer and delayed effects of cancer treatment. Psychological distress, including fear of recurrence and death and alteration in social support, have also been recognized as major problems [22]. Can these burdens be associated with patient fatigue?

No studies of disease-free cancer patients have investigated the association between fatigue and a broad range of factors, including demographic, physical, psychological, and social factors, although these associations are often postulated in existing theories of fatigue in cancer patients [36]. Mast et al. reported that fatigue in breast cancer survivors was significantly related to treatment with chemotherapy, irrespective of length of time since treatment, age, disease stage, or tamoxifen use [20]. Psychological variables were not included in their study. Some studies conducted in other populations of cancer patients have almost consistently found associations between fatigue and psychological distress, although disease variables such as cancer site, clinical stage, treatment, and demographic variables such as age, sex, marital status, and occupational status were often controversial [17, 18, 25, 30]. In a prior study, we investigated bio-psycho-social factors associated with fatigue in ambulatory mixed cancer patients and found six correlated factors: female sex, higher level of education, status as housewife as opposed to full-time worker outside the home, living alone, poor performance status, and depression [2]. The study revealed that the fatigue experienced by cancer patients may be associated with multiple factors, including demographic, physical, and psychosocial factors.

The purpose of this study was to investigate factors correlated with fatigue in disease-free breast cancer patients. Identifying these factors may provide clues to how fatigue may be ameliorated and contribute to a better understanding of fatigue in affected patients. Based on the studies mentioned above, we postulated that fatigue in disease-free cancer patients might be correlated with psychosocial factors after interfactorial associations are taken into account. Patients' fatigue was evaluated by using the Cancer Fatigue Scale, which is a cancer-specific fatigue scale with sufficient validity and reliability and consists of three subscales: physical, affective, and cognitive subscales [24]. We investigated factors correlated with the total score and those correlated with each subscale. The former may give clues to ameliorating fatigue, the latter to extracting particular effects of bio-psycho-social factors on fatigue in cancer patients.

Subjects, materials and methods

Subjects

The subjects were ambulatory, disease-free breast cancer patients who had undergone successful surgical treatment at the National Cancer Center Hospital East, Kashiwa, Japan.

Women with a history of breast cancer had to fulfill the following eligibility criteria: (a) age 18 years or older, (b) surgical treatment at the National Cancer Hospital East, Japan, which was established in July 1992, (c) no current active cancer treatment such as surgery, intravenous chemotherapy or radiotherapy, (d) clinically free from evidence of metastatic or recurrent lesions, (e) ability to complete the questionnaires, and (e) freedom from severe mental or cognitive disorders.

A planned sample size was determined as follows. In a previous validation study of the Cancer Fatigue Scale (CFS) we had found significant associations ($r>0.45$ in Pearson's correlation) between the CFS scores and the depression score of HADS. Then, a desired sample size to find this association in univariate analysis was calculated as 66 when the two-tailed alpha error was set at 0.01 and the beta error was set at 0.10. When correlations between independent variables in multiple regression analysis are taken into account, planned sample size is required to be greater. Therefore, we determined the desired sample size as 132, which is double the desired size in univariate analysis.

This study was approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center. Written consent was obtained from each patient after she had been fully informed of the purpose of the study.

Methods

Every third patient on a planned visiting list, which is in alphabetical order, of the outpatient breast surgery clinic were selected as participants. After informed consent had been obtained, height, body weight, body temperature, and heart rate were measured, and the patients were asked at the same time whether they were using drugs regularly (especially nonsteroidal anti-inflammatory drugs, opioids, psychotropic drugs, or steroids). They were also asked to complete self-administered questionnaires (described below) at home and to return them by mail the following day. When inadequate answers were given clarification was sought over the telephone.

Patients' medical records provided information on clinical cancer stage grouping as defined by the Union Internationale Contre le Cancer (UICC), histological grade as defined by Bloom et al. [5], presence of metastasis, and past and current treatment, including current medication. Patients' performance status, as defined by the Eastern Cooperative Oncology Group (ECOG), was recorded by each patient's physician.

The Cancer Fatigue Scale

Subjects' fatigue was assessed using the Cancer Fatigue Scale (CFS), a brief self-rating scale for assessing cancer-related fatigue, which was designed specifically to reflect the nature of the fatigue

[24]. The scale development process involved (1) the development of a 58-item draft scale using in-depth interviews with cancer patients and discussions with medical experts, (2) completion of the draft questionnaire by 110 cancer patients, and (3) the development of the final Cancer Fatigue Scale (CFS) based on factor analysis. The reliability and validity of this scale have been established by a previous study. The scale consists of 15 items and three subscales – physical, affective, and cognitive – which are generated by factor analysis. Physical aspect of fatigue include being easily tired, an urge to lie down, exhaustion, a heavy and tired feeling, being fed up, reluctance, and not knowing what to do with oneself. Affective aspects of fatigue are lack of energy, lack of interests, lack of concentration, and not encouraging oneself to do anything. Cognitive aspects of fatigue are forgetfulness, errors while speaking, slower thinking, and carelessness. Each item is rated on a scale of 1 (not at all) to 5 (very much), and patients are asked to circle the one number that describes their current state. The possible responses for each subscale range from 0 to 28 for physical, 0 to 16 for affective, and 0 to 16 for cognitive. The maximum total score is 60. Higher scores reveal more severe fatigue. We reconfirmed the validity in this study. Pearson's correlation coefficients between the visual analogue scale (VAS) of fatigue and the total CFS score, which means convergent validity, was 0.66 ($P<0.001$). Factor analysis followed by varimax rotation, which indicates the construct validity, reproduced the same factor loading pattern as in the development study. Crohnbach's alpha coefficients for this sample were 0.87 (physical), 0.81 (affective), 0.76 (cognitive), and 0.84 (total).

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) was used to evaluate psychological distress. This questionnaire, developed by Zigmond et al., consists of a 7-item anxiety subscale and a 7-item depression subscale. It assesses patients over the week before its administration [37]. The particular feature of this scale is that it does not include any questions about physical symptoms. We have established the reliability and validity of the Japanese version of this questionnaire in cancer patients [19].

Mental Adjustment to Cancer scale

The Mental Adjustment to Cancer (MAC) scale is a self-rating scale for assessing subjects' styles of coping with cancer. This scale, developed by Watson et al., consists of five subscales: fighting spirit (16 items), anxious preoccupation (9 items), fatalism (8 items), helplessness or hopelessness (6 items), and avoidance (1 item) [34]. We have also established the reliability and validity of the Japanese version of this questionnaire [1].

Ad hoc self-administered questionnaire

An ad-hoc self-administered questionnaire was used to obtain information on sociodemographic status, physical symptoms, and social support. Sociodemographic status included marital status, household number, having children (economically dependent, unmarried, or with health problems), level of education, employment status, and religiosity. Physical symptoms (pain, appetite, sleep, dyspnea, and fatigue) were assessed by the five-point Likert scale. Patients' use of confidants was used as an indicator of social support [21]. Patients were asked whether they had confided in someone, and if so, the type and number of confidants and their satisfaction with them. Changes in relationships with family members and others were also assessed by the five-point Likert scale, from a score of 1 (worsened considerably) to 5 (improved considerably).

Statistical analysis

Each CFS score was entered into the analysis as a dependent variable. First, we used univariate analysis between the CFS scores and the investigated factors to determine the potential fatigue-related factors; associated factors ($P<0.05$) were retained. Then we used backward stepwise multiple regression analysis to investigate these factors. Factors not having $P<0.05$ association were eliminated in this procedure. In all statistical analyses, we set the level of significance at $P<0.01$; probabilities of $0.01<P<0.05$ are reported as trends because of correction for multiple comparisons in the group effects. All P-values reported are two tailed. All statistical procedures were done with SPSS 8.0 J for Windows (SPSS, 1998).

Results

Subjects (Table 1)

The research was conducted from September to October 1997. In all, 139 randomly selected subjects were eligible for inclusion. Of these, 135 subjects (97.1%) agreed to participate in the study. Four subjects declined because of lack of time. There were no significant differences in age, clinical stage or performance status between patients who participated and those who refused. All patients had a performance status of 0, except for 1 with a performance status of 2 because of lumbago due to traumatic bone fracture. We excluded this subject from the analysis because of the heterogeneous nature of her case. Table 1 shows the demographic and clinical characteristics of the remaining 134 subjects. The mean number of days after surgery was 786 ± 463 (SD), and the mean number of days since the last chemo- and radiotherapy was 537 ± 458 days and 516 ± 364 days, respectively.

Frequency of fatigue

The patients' total CFS scores ranged from 1 to 42. The mean scores ± SD were: physical subscale, 5.3 ± 4.7; mental subscale, 7.1 ± 3.2; cognitive subscale, 4.1 ± 3.0; and total scale, 16.4 ± 7.9. According to the five-point Likert scale for fatigue, 75 (56.0%) of the subjects perceived their fatigue.

Results of univariate analysis between investigated factors and fatigue scores (Table 2)

Table 2 shows the results of univariate analysis for factors having <0.05 association with CFS scores. Among

Table 1 Demographic and clinical characteristics of patients ($n=134$; *ECOG* Eastern Cooperative Oncology Group, *HADS* Hospital Anxiety and Depression Scale)

Sample characteristic	*n*	%
Age (years)		
Mean 55.1 ± 10.3 (range 28–86)		
Median 55		
Education (years)		
≤9 (junior high school or less)	29	21.5
>9 (high school or more)	105	78.5
Marital status		
Married	115	85.9
Other	19	14.1
Household size		
Living alone	19	14.1
Living with others	115	85.9
Working outside the home		
Yes	58	43.0
No	76	57.0
Clinical stage[a]		
0	5	3.7
I	31	23.1
II	76	56.7
III	22	16.4
Type of surgery		
Mastectomy	103	77.0
Partial resection	31	23.0
No. of days after surgery		
Mean 789 ± 463 (range 59–1894)		
Median 723		
Past intravenous chemotherapy	38	28.1
No. of days after chemotherapy		
Mean 537 ± 458 (range 18–1543)		
Median 431		
Past radiotherapy	12	8.9
No. of days after radiotherapy		
Mean 516 ± 364 (range 104–1351)		
Median 402		
Current fluoropyrimidine compounds use	14	10.4
Current tamoxifen citrate use	55	40.7
Performance status 0 (ECOG)	134	100.0
Pain[b]		
Mean 1.4 ± 0.6 (range 1–3)		
Median 1		
Appetite[b]		
Mean 3.7 ± 0.9 (range 1–5)		
Median 4		
Sleep[b]		
Mean 3.6 ± 1.0 (range 1–5)		
Median 3		
Dyspnea[b]		
Mean 1.4 ± 0.6 (range 1–4)		
Median 1		
Fatigue		
Mean 1.8 ± 0.9 (range 1–5)		
Median 2		
HADS Depression score		
Mean 3.0 ± 2.7 (range 0–13)		
Median 2		
HADS Anxiety score		
Mean 4.4 ± 2.7 (range 0–12)		
Median 4		
Availability of confidants	123	91.8
Satisfaction with confidants[b]		
Mean 3.6 ± 1.0 (range 1–5)		
Median 4		
Religious belief[b]		
Mean 1.6 ± 1.0 (range 1–5)		
Median 1		

[a] Clinical stage based on criteria of the Union Internationale Contre le Cancer

[b] Measured by a five-point Likert scale (*1* not at all to *5* very much)

demographic factors, household size and age were correlated with CFS scores. Among biological (medical) factors, current symptoms such as appetite, sleep, and dyspnea were significantly correlated with CFS scores. On the other hand, factors concerned with the cancer and treatment, such as disease stage, lymph node metastasis, number of days since surgery, type of surgery, past intravenous chemotherapy, radiotherapy, current use of fluoropyrimidine compounds, and current use of tamoxifen citrate, were not correlated with any CFS scores. In addition, neither the number of days since intravenous chemotherapy nor the number of days since radiotherapy was correlated with any CFS scores, and nor were body mass index and heart rate. Except for hypnotics, the drugs that patients commonly used were excluded from the analysis because only 2 subjects used anti-anxiolytics and none used other drugs. Among psychological factors, depression and anxiety correlated significantly with all fatigue scores, but no MAC subscore had any correlation with any CFS score. Among social factors, only satisfaction with confidants was significantly correlated with the CFS scores (apart from physical subscale).

Results of multiple regression analysis (Table 3)

Before analysis, we used univariate analysis of potential factors correlating with fatigue by using Pearson's correlation. Three correlation coefficients were >0.40 (maximum 0.67): these were between appetite and sleep, appetite and HADS depression score, and depression score and HADS anxiety score. We included these variables since all they were considered to be important for this study. Table 3 shows the results of multiple regression analysis of the factors correlating with each CFS score. Total fatigue was significantly correlated with dyspnea, insufficient sleep, and depression. Depression was significantly correlated with all dimension of fatigue. The selected independent variables of total, physical, affective, and cognitive scales accounted for 46%, 31%, 33%, and 25%, respectively, of the variance in each CFS score.

Discussion

This study yielded two main results. First, fatigue in disease-free breast cancer patients is determined mainly by dyspnea, insufficient sleep and depression. Second, various factors, including psychosocial factors, are associated with each dimension of fatigue.

Fatigue in this population is determined by current physical and psychological distress, rather than by the cancer itself and prior cancer treatments. It was an interesting and unexpected result that dyspnea was

Table 2 Potential factors correlating with fatigue and correlations with Cancer Fatigue Scale scores

Potential factors	*P*-values for univariate analysis with fatigue scores											
	n	Total			Physical			Affective			Cognitive		
		Mean	*t*	*P*	Mean	*t*	*P*	Mean	*t*	*P*	Mean	*t*	*P*
Demographic													
Household size													
Alone	19	–	–	n.s.	5.6	–3.46	0.001	–	–	n.s.	–	–	n.s.
With others	115	–			3.0			–			–		
Medical													
Current hypnotics use													
Yes	6	–	–	n.s.	–	–	n.s.	8.5	–3.28	0.005	–	–	n.s.
No	128	–			–			7.0			–		
Type of surgery													
Mastectomy	103	–	–	n.s.	–	–	n.s.	7.4	2.06	0.04	–	–	n.s.
Partial resection	31	–			–			6.1			–		
			r	*P*		*r*	*P*		*r*	*P*		*r*	*P*
Demographic													
Age	134		–	n.s.		–0.25	0.004		–	n.s.		–	n.s.
Physical													
Appetite[a]	134		–0.38	<0.001		–0.23	0.008		–0.37	<0.001		–0.24	0.005
Sleep	134		–0.38	<0.001		–0.19	0.03		–0.48	<0.001		–0.20	0.02
Dyspnea	134		0.34	<0.001		0.34	<0.001		0.17	0.05		0.31	<0.001
Psychological													
Depression (HADS)	134		0.63	<0.001		0.49	<0.001		0.42	<0.001		0.24	<0.001
Anxiety (HADS)	134		0.52	<0.001		0.44	<0.001		0.23	0.007		0.43	<0.001
Social													
Satisfaction with confidants[a]	134		–0.23	0.008		–	n.s.		–0.22	0.01		–0.25	0.004

[a] Measured by five-point Likert scale (*1* not at all to*5* very much)

Table 3 Multiple regression analysis of factors correlating with fatigue ($n=134$)

Fatigue	Variable	Coefficient	Standardized coefficient	Multiple R^2	*t*	*P*
Total[a]	Dyspnea[e]	2.23	0.17	0.07	2.53	0.01
	Sleep[e]	–1.36	–0.19	0.07	–0.26	0.01
	Depression[f]	1.58	0.53	0.34	7.81	<0.001
	Intercept = 13.60, multiple $R=0.69$, multiple $R^2=0.47$, adjusted $R^2=0.46$					
Physical[b]	Age	–0.09	–0.20	0.05	–2.75	0.007
	Dyspnea[e]	1.58	0.21	0.07	2.72	0.007
	Depression[f]	0.73	0.41	0.20	5.44	<0.001
	Intercept = 5.99, multiple $R=0.57$, multiple $R^2=0.32$, adjusted $R^2=0.31$					
Affective[c]	Type of surgery[g]	–1.22	–0.16	0.03	–2.24	0.03
	Sleep[e]	–1.26	–0.41	0.20	–5.48	<0.001
	Depression[f]	0.35	0.29	0.12	3.94	<0.001
	Intercept = 12.08, multiple $R=0.59$, multiple $R^2=0.35$, adjusted $R^2=0.33$					
Cognitive[d]	Dyspnea[e]	0.87	0.18	0.05	2.31	0.02
	Satisfaction with confidants[e]	–0.52	–0.18	0.05	–2.31	0.02
	Depression[f]	0.42	0.38	0.17	4.74	<0.001
	Intercept = 3.53, multiple $R=0.52$, multiple $R^2=0.27$, adjusted $R^2=0.25$					

[a] Total fatigue
[b] Physical aspect of fatigue
[c] Affective aspect of fatigue
[d] Cognitive aspect of fatigue
[e] Measured by five-point Likert scale
[f] According to HADS (Hospital Anxiety and Depression Scale)

strongly associated with fatigue in disease-free cancer patients. Dyspnea is also poorly understood, as well as fatigue [10]. Furthermore, no study of dyspnea was conducted in this population. It is thought of as a complex symptom with physiological, psychological and social components. We assume that dyspnea might be caused in this population by the delayed effect of cancer treatment, or that fear of recurrence may have a role in it,

since there is evidence that dyspnea is associated with psychological status in a healthy population [7] and in terminally ill cancer patients [8]. As far as the association between fatigue and dyspnea is concerned, Winningham et al. suggested in their theoretical model that other symptoms such as dyspnea might manifest secondary fatigue [36]. Our result may support their model. On the other hand, it was reported that cancer patients often used the term tired or fatigued when describing their dyspnea [6]. It might be said that dyspnea and fatigue have the same underlying etiology. Furthermore, these two symptoms may be causes and results each other. Further research is required before we can understand this phenomenon.

Patients with insufficient sleep had relatively higher fatigue, especially affective aspects of fatigue; this effect was independent of depression, although the association between depression and insomnia is well recognized. Graydon et al. reported that sleep was one of the most effective strategies to combat fatigue in cancer patients [15]. Our results might confirm this. Our results uncovered more details of the association between fatigue and depression, although the multidimensional nature of fatigue, including both physical and psychological aspects, has been noted [28, 29]. Depression is the most influential factor in all three aspects of fatigue, including physical aspects, and it explained 34% of the variance in the total score. Although fatigue is often noted as a physical symptom, health care professionals might pay more attention to the psychological state of a patient who complains of fatigue. On the other hand, we might question whether depression and fatigue are the same phenomenon. This study could not provide an adequate answer to this question because of its cross-sectional design. Our results may indicate that fatigue is not completely equal to depression, since that is established by both physical and psychological factors, although these two conditions overlap in a complex manner. Also, there is a report that fatigue does not follow a similar course to depression in patients treated by radiotherapy [32]. Furthermore, the possibility remains that this finding might be partly due to lack of specificity in the CFS. Further research is required to solve this complex phenomenon.

These results may suggest two fatigue-reducing strategies. First, treatment of other current symptoms such as dyspnea and insomnia might be effective. Second, psychosocial intervention might be effective at treating fatigue in this population. Some studies have indicated the effectiveness of group psychotherapy at ameliorating fatigue, although the goal of those studies was not to reduce patient fatigue [11, 14, 31]. We should confirm the efficacy of psychosocial intervention at reducing fatigue and determine which kinds of cancer patients are most likely to benefit from specific psychosocial interventions.

Each dimension of fatigue had another correlated factor other than the three factors discussed above. The physical subscale had a significant negative correlation with age. Only Peter et al. and Akechi et al. have reported a negative association between age and fatigue in cancer patients [2, 25], and neither could explain it. One explanation may be that younger subjects have more physical tasks to complete in their daily lives, which might induce fatigue. There was a nonsignificant trend toward lower affective aspects of fatigue in patients who had a partial resection than in those who had a mastectomy. Moyer reviewed the psychological outcomes of breast-conserving surgery versus mastectomy and found psychological benefits in breast-conserving surgery [23]. Our results indicate that the psychological impact of mastectomy might weakly influence affective aspects of fatigue over the years. The cognitive subscale had a nonsignificant negative association with satisfaction with confidants. Cognitive fatigue may interfere with the use of social supports, but this finding is also difficult to explain. Further research is required on this issue.

It seems to be an important finding that there are no significant relationships between fatigue and certain factors that have been investigated. Among physical factors, neither number of days after surgery or past chemotherapy or radiotherapy was significantly correlated with fatigue scores. Whether the experience of fatigue might alter on the patients' course through the cancer is an interesting issue. According to these results, we assume that fatigue might not be simply the consequence of aggressive cancer treatment, and therefore might not decrease with time, but is caused by concurrent physical and psychosocial factors at the time. Body mass index, body temperature, and heart rate, which were investigated as convenient indices of physical conditions of inflammation, cachexia and cardiovascular condition, respectively, were not associated with fatigue scores. Because the study included only 1 patient with a body mass index under 80%, which is commonly recognized as the threshold between lean and normal, we could not investigate the association between weight loss and fatigue. Because body temperature and heart rate are both strongly influenced by environment and situation, our results might be interpreted as preliminary.

Among psychological factors, styles of coping with cancer, measured by the MAC scale, had no associations with any CFS scores by univariate analysis, although behavioral factors have been suggested to be associated with fatigue [28].

Among social factors, satisfaction with confidants seems to have indirect effects on fatigue, because a significant negative correlation with total CFS score was observed in univariate analysis and was dissolved in multiple regression analysis. This might indicate that

provision of good social support indirectly contributes to the amelioration of fatigue.

There are many kinds of theoretical framework for cancer-related fatigue, and they encourage both researchers and clinicians to pay enough attention to multiple aspects of manifestation of fatigue. For example, Piper cites many potential factors related to fatigue, such as psychological features, symptoms, and environmental and social patterns [27]. Although these frameworks can be used as a guide to understanding fatigue and to planning intervention for it, no clear evidence supporting any of these hypotheses has emerged. Our results may prove the importance of three aspects of fatigue-related factors; physical, psychological, and social. On the other hand, Pawlikowska et al. reported following their population-based study that 40%, 17%, and 15% of patients cited psychosocial (work, family, lifestyle), psychological (anxiety, depression), and physical aspects as the reasons for their fatigue, respectively [26]. The framework of these three aspects, which Engel introduced as a new medical model in 1977 [9], may be important to the understanding of fatigue.

Finally, a causal interpretation of the results must be made with caution for at least three reasons. First, this study had a one-arm cross-sectional design. This means that the causality between fatigue and the factors investigated, and the difference between fatigue in disease-free cancer patients and persons in the general population could not be clarified. Second, the evaluation of other current illnesses besides cancer and of cancer treatment might have been insufficient. Third, the reliability and validity of the instrument used to measure other physical symptoms than fatigue was not established. Fourth, hematological and biochemical abnormalities were not investigated. However, the factors associated with fatigue accounted for more than 25% of the variance in each fatigue subscore and 46% in the total fatigue score.

Despite these limitations, we think this study gives clues to how fatigue might be ameliorated in this population and gives a better understanding of the relationships between fatigue and bio-psycho-social factors, especially the strong relationship between fatigue and depression. Further research is needed in two directions. First, we should find out the causality between fatigue and psychological distress. Second, prospective studies are needed to determine whether psychological intervention in disease-free cancer patients with fatigue would be an effective treatment.

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