experienced them during the process of occupational therapy. We planned to conduct a pilot study of how these factors contribute to recovery and the return to normal life. The result was that factors related to "awareness of somatic sensation," such as an increase in physical strength and an appropriate sensation of fatigue which facilitated sleeping at night, were identified as factors that contribute to the ability to live in society, and intervention that increases awareness of somatic sensation appeared to be one of the foundations of the treatment strategy in occupational therapy.

Accordingly, the purpose of the present study was to investigate the factors that are related to the "awareness of somatic sensation" in occupational therapy. If factors associated with "awareness of somatic sensation" that accompany occupational therapy intervention were illustrated in this study, it might be possible to identify the best factors to take into consideration and those which are expressed in the activities when actually carrying out occupational therapy with patients with schizophrenia. Moreover, when the association between "awareness of somatic sensation" and the ability to live in society as shown in the previous study is taken into consideration, it seems possible to propose a basis for an answer to the question: Why is occupational therapy that involves the use of activity effective in terms of recovery? In the present study, we defined "somatic sensation" as the sensation that the body experiences through the sense organs, and taking into consideration the fact that the depersonalization experience and ego defense implications for patients with schizophrenia may be linked to somatic sensation, we decided to try to identify the factors associated with "awareness of somatic sensation" in occupational therapy.

METHODS

Participants

The participants in the study were the inpatients in a psychiatric hospital in Nagoya city in Japan between October 2003 and May 2004 who met all four of the following criteria: (1) they were diagnosed with schizophrenia by a psychiatrist, based on the ICD-10 or DSM-IV; (2) they participated in occupational therapy during the period of the study; (3) they were able to understand the intent of the questions and to fill out the questionnaire; and (4) they were not seriously ill physically.

Procedure

Occupational therapy, consisting of an exercise program for 60 minutes, once a week, was conducted in the gymnasium. After preliminary calisthenics to loosen the major joints, the program conducted in this study was divided into approximately 20 minutes of stretching followed by approximately 30 minutes of a free event (soft volleyball, table tennis, badminton, basketball, aerobic walking, etc.). During the actual conduct of the program, one of the authors supervised the planned schedule of activities, and several occupational therapists supported the program by providing leadership, guidance, and safety management. During the 8-month period of the study subjects who met the eligibility criteria and who gave their consent to take part in the study participated in the exercise program, for 8 weeks (a total of 8 times) from the date they participated for the first time.

To collect data, we first conducted evaluations by using the RSOTE and the Rosenberg Self-Esteem Scale (RSES) (Rosenberg, 1965). Interviews were conducted twice, the first time within 1 week after the first day of participation in the exercise program, and the second time within 1 week after participation for the eighth time. The Japanese version of the Body Awareness Scale (BAS) (Yamamoto, 2003), described below, was used with individual participants during the sessions and after completion of the sessions.

Measures

Sociodemographic and Medical Data

Age, gender, work experience, number of hospital admissions, length of hospital stay, and doses of oral medication were evaluated by means of the subjects' charts as sociodemographic and medical data.

Rating Scale for Occupational Therapy Experience

The RSOTE was designed by the authors to identify the feelings the subjects associated with work activity and is composed of work activity and group factors. The items which evaluate work activity were selected by referring to a study reported by Trombly (1995), and the items which evaluate group factors were selected by referring to studies reported by the following: Yalom (1970), Corsini and Rosenberg (1955), Bloch and Crouch (1985), Webster and Schwartzberg (1992), and Maxmen (1973).

A factor analysis revealed a 3-factor structure (total of 12 items) consisting of "trial search and experience of success," "awareness of somatic sensation," and "structure of daily life." Reliability and validity testing confirmed that this scale is an evaluation method that can be used in occupational therapy for patients with schizophrenia. Since the results of our previous study suggested that one of the three factors, "awareness of somatic sensation," is an important factor that contributes to recovery of the ability to live in society (Shingu, 2004), we focused this study on "awareness of somatic sensation." The section of the scale on "awareness of somatic sensation" is composed of four questions, and the subject is required to reply to each question on a 4-point scale that ranges from 0 points for "I strongly disagree" to 3 points for "I strongly agree." Possible total scores range from 0 points to 12 points. Higher scores represent stronger feelings associated with work activity.

Rosenberg Self-Esteem Scale (RSES)

The RSES was developed by Rosenberg (1965) to measure self-esteem. It is a Guttman scale composed of 10 items, and its reliability and validity have been confirmed by the original author (Rosenberg, 1965). Half of the questions about sense of self-worth are posed in a positive manner, and the other half are posed in a negative manner. It is a self-report-type questionnaire on which the subjects themselves answer questions on a 4-point scale ranging from 0 points for "I strongly disagree" to 3 for "I strongly agree." The range of possible total scores is 0-30. Higher scores represent recognition of greater self-worth.

Japanese Version of the Body Awareness Scale (BAS)

The BAS was developed by Roxendal (1985) and is composed of 47 items that make it possible to evaluate physical exercise ability and its psychological components. The evaluation items are divided into three areas: (1) reported psychopathology (16 items), (2) observed psychopathology (13 items), and (3) evaluation by a movement test (18 items). Different evaluation methods are included: an interview, observation, and a movement test, and it is designed in such a manner in order not to be biased by the subjectivity of the evaluator. In 2003 Yamamoto translated the BAS into Japanese, completed a Japanese version of the BAS composed of a total of 43 items, and confirmed its reliability and validity (Yamamoto, 2003). The BAS requires replies to each question on a 4-point scale ranging from 0 points for "It isn't any problem at all" to

3 points for "It's a serious problem," and lower scores mean a more favorable state. Possible scores range from 0 to 45 points for (1) reported psychopathology (15 items), (2) 0-39 points for observed psychopathology (13 items), and 0-45 points for (3) evaluation on the movement test (15 items).

Statistical Analysis

The following analysis was performed to identify factors that contributed to the score for "awareness of somatic sensation" on the RSOTE after the intervention.

Associations between scores for "awareness of somatic sensation" on the RSOTE after the intervention, and sociodemographic and medical factors, as well as, changes in scores on the RSES and on the BAS (evaluation of reported psychopathology, observed psychopathology, and the movement test) were assessed by Spearman's rank correlation coefficient or the Mann-Whitney *U* test (univariate analysis). The RSES and BAS scores were analyzed after dividing the subjects into a cohort whose score improved and a cohort whose score deteriorated (this cohort includes subjects whose scores were unchanged).

A multiple regression analysis (forced entry method) was performed using the "awareness of somatic sensation" score after the intervention as the dependent variable and the associated factors identified in the univariate analyses, and the "awareness of somatic sensation" score before the intervention as the independent variables.

The P-values for all of the tests are two-tailed, and a P-value of < 0.05 was considered significant. The statistical Package for the Social Sciences (SPSS) 12.0J software was used to perform all of the statistical analyses.

RESULTS

Subjects' Participation

After excluding the 15 patients who refused to participate from the 50 patients who fulfilled the eligibility criteria, the remaining 35 served as the subjects for this intervention. Among the 35 patients there were 14 patients who did not participate in all 8 sessions during the course of the

program, and thus, 21 subjects were included in the final analysis. Table 1 shows the characteristics of the subjects of the final analysis.

Factors Associated with "Awareness of Somatic Sensation" After the Intervention

The results of the univariate analysis showed significant differences in "awareness of somatic sensation" after the intervention between the RSES-score-improvement cohort and RSES-score-deterioration cohort ($P = 0.03$), and between the BAS-observed-psychopathology-increase cohort and BAS-observed-psychopathology-decrease cohort ($P = 0.01$; Table 2).

Next, a multiple regression analysis was performed with the 2 factors having significant associations using the results of the univariate analysis and the "awareness of somatic sensation" scores before the intervention as independent variables and the "awareness of somatic sensation" scores after the intervention as the dependent variable. The results identified "observed psychopathology" alone as a significant factor (Table 3).

TABLE 1. Subjects' Characteristics (N = 21)

	N	Average (range)	Standard Deviation
Age (years)		45.4	14.2
		(21-69)	
Gender			
Male	11		
Female	10		
Work experience			
Presence	16		
Absence	5		
Number of hospital admissions		3.3	3.4
		(1-17)	
Length of hospital stay (years)		11.6	11.9
		(0.3-38)	
Mean dose of oral medication (mg)[a]		898.8	682.0
		(150-2,100)	

[a]Chlorpromazine conversion.

TABLE 2. Factors Related to Awareness of Somatic Sensation Score After the Intervention-Univariate Analysis

Variable	Correlation Coefficient	P-Value[a]
Age	0.16	0.50
Number of hospital admissions	0.17	0.46
Length of hospital stay	0.37	0.08
Total dose of oral medication	−0.56	0.81
	N	Mean Rank	P-Value[b]
Gender			
Male	11	9.68	0.30
Female	10	12.45	
Work experience			
Presence	16	11.50	0.50
Absence	5	9.40	
Self-esteem			
Improvement cohort	11	13.73	0.03
Deterioration cohort	10	8.00	
BAS			
Reported psychopathology			
Improvement cohort	13	11.88	0.61
Deterioration cohort	8	10.46	
Observed psychopathology			
Improvement cohort	11	14.60	0.01
Deterioration cohort	10	7.73	
Evaluation by a movement test			
Improvement cohort	16	13.40	0.31
Deterioration cohort	5	10.25	

[a]Spearman's rank correlation coefficient.

[b]Mann-Whitney U-test.

Changes in Scores for the Items on the BAS Subscale "Observed Psychopathology"

Change in scores on the BAS subscale "observed psychopathology" was identified as a factor associated with the "awareness of

TABLE 3. Factors Related to Awareness of Somatic Sensation Score After the Intervention-Multiple Regression Analysis

Variable	Coefficient	Standardized Coefficient	t	P-Value
Self-esteem[a]	0.14	0.94	0.62	0.54
BAS	0.45	0.80	2.30	0.03
Observed psychopathology[a]				
Awareness of somatic sensation score before the intervention	0.27	0.21	1.20	0.25

$R = 0.67$, Adjusted $R^2 = 0.35$.

[a]Coded as 0 = Deterioration cohort, 1 = Improvement cohort.

somatic sensation" score, after the intervention, in the "Factors Associated with 'Awareness of Somatic Sensation' After the Intervention" section above. The "observed psychopathology" subscale of the BAS is composed of 13 items, and the differences in scores for each of the subscale items before and after the intervention were evaluated by the Wilcoxon signed-ranks test to identify which of the 13 items showed differences in scores before and after the intervention. The results showed a significant difference in #17 Emotional change ($P = 0.02$: Table 4).

DISCUSSION

Content of the Program and Circumstances of Participation

Of the 50 patients who met the eligibility criteria, 21 remained as subjects in the final analysis. The reasons patients were excluded as subjects of the analysis after their informed consent had been obtained included mental symptoms, deterioration of physical condition, and participation in fewer sessions than the stipulated number because of being discharged from the hospital prior to completion. If only the numbers were examined, because of the many dropouts, the appropriateness of the program itself could be called into question. The program however was not devised just for research. It has generally been introduced into

TABLE 4. Comparison Between Scores for Each of the Items of the BAS Subscale "Observed Psychopathology" Before and After the Intervention

Item	Before the Intervention	After the Intervention	P-Value[a]
16. Hostility	0.05 (0.22)[b]	0.05 (0.22)	1.00
17. Emotional change	0.43 (0.68)	0.05 (0.22)	0.22
18. Lack of appropriate emotion	0.48 (0.51)	0.48 (0.51)	1.00
19. Autonomic disturbances	0.00 (0.00)	0.05 (0.22)	0.32
20. Sleepiness	0.14 (0.36)	0.14 (0.36)	1.00
21. Distractability	0.24 (0.63)	0.19 (0.40)	0.71
22. Withdrawal	0.24 (0.44)	0.14 (0.36)	0.32
23. Slowness of movements	0.33 (0.48)	0.29 (0.46)	0.56
24. Agitation	0.00 (0.00)	0.10 (0.30)	0.16
25. Involuntary movements	0.00 (0.00)	0.05 (0.22)	0.32
26. Muscle tension	0.38 (0.50)	0.38 (0.50)	1.00
27. Mannerisms and postures	0.14 (0.36)	0.10 (0.30)	0.56
28. Hallucinatory behavior	0.14 (0.36)	0.00 (0.00)	0.08

[a]Wilcoxon signed-rank test.
[b]Mean (standard deviation).

Japanese psychiatric occupational therapy and is implemented in the form of open groups in which participation is voluntary.

Factors Associated with "Awareness of Somatic Sensation" After the Intervention

Self-Esteem

The results of the univariate analysis showed that self-esteem was associated with the "awareness of somatic sensation" scores, but it was not identified as an explanatory factor in the multiple regression analysis.

Self-esteem means how one feels about oneself, including self-respect and self-acceptance, and is said to be a sense and feeling of one's own worth and ability. As in reports showing that the more patients are aware of their disease, the stronger their depressed mood and lower their self-evaluation tends to be. Whereas, the more the patients lack awareness of

their disease, the greater their delusions, grandiosity and lack of willingness, and their symptoms sometimes influence self-esteem. Moreover, the report by Marx, Test, and Stein (1973), who conducted a local program extending over 5 months and found that even though the degree of independence in daily living skills improved, there was no change in self-esteem. In addition the report by Okin, Dolnick, and Pearsall (1983), who claimed that even though social activity, interpersonal relations, and basic living skills had clearly improved 8 months after discharge, there were no differences in feelings of self-worth immediately after discharge, and then 8 months later. They suggested that even though the degree of independence in daily living skills had increased, self-esteem had not increased along with it.

Thus, self-esteem is affected by temporary factors, such as aggravation of symptoms, but it is also presumably characterized by not immediately increasing despite improvement in the ability to live in society as a result of intervention over an extended period. Factors that are considered problems from a longer perspective, including acceptance of impairments, are thought to intervene, and they may not have become clearly associated factors during a short-term intervention period of 8 weeks, as in this study.

Body Awareness (BAS)

Amanda (2001) described the body awareness of patients with schizophrenia as a function required to maintain body and mind in optimal condition, and mentioned that improving it may be linked to improvement in mental symptoms. Yamamoto (2003) focused on "body awareness" and used the BAS developed by Roxendal to investigate associations with mental symptoms in order to quantitatively evaluate the effect of physical exercise on patients with schizophrenia. Because the BAS scale is not biased toward the physical aspects, and its content is comprehensive and includes psychological aspects, in addition to the fact that patients with schizophrenia were used as the subjects and that the intervention was in the form of physical exercise in the present study, we concluded that the BAS is an appropriate scale for identifying changes in the somatic sensation of patients with schizophrenia.

The results of the multiple regression analysis identified only change in "observed psychopathology" on the BAS as a factor significantly associated with "awareness of somatic sensation." This finding showed that changes in "observed psychopathology" on the BAS were associated with the "awareness of somatic sensation" factor after the intervention,

regardless of the "awareness of somatic sensation" score before the intervention. Moreover, when we examined the changes in scores for the items in the "observed psychopathology" subscale in order to investigate the results in greater detail, we found a significant difference in emotional change ($P = 0.02$). This finding suggests that stabilization of emotions as a result of physical exercise, in particular, is associated with "awareness of somatic sensation."

Previous research showed an association between physical exercise and psychological aspects (Richardson et al., 2005; Paluska & Schwenk, 2000). Although those studies however touched on the favorable effect of physical exercise on emotional life, the authors did not go so far as to investigate how these effects are specifically expressed in the patients' ultimate condition. In the present study as well, it was impossible to go so far as to say anything about a cause-effect relationship between physical exercise and psychological well-being, but the suggestion of the possibility of a factor intervening between physical exercise and the psychological well-being can be described as new information. Two possible reasons for a change in observed psychopathology on the BAS that relates to "awareness of somatic sensation" are given below.

The first possible reason is that it is an effect of the properties of the BAS evaluation scale. As stated above, the BAS combines different evaluation modalities: (1) reported psychopathology, (2) observed psychopathology, and (3) evaluation using a movement test. It is also characterized by having been devised to be unbiased by the subjectivity of the evaluator. Since the 8-week intervention period in this study was short and the content of the program was not designed for research purposes, a dramatic change in exercise ability would seem unlikely. It would also seem to take time for such a great change in consciousness to occur that subjects would be able to talk about changes in their emotional state and sense of reality in an interview. Thus, the only changes that can be objectively observed at 8 weeks after the start of the intervention are reflected in "observed psychopathology," and it is suggested that the changes that occurred as a result of occupational therapy, affected "awareness of somatic sensation."

The second possible reason is that the BAS contributed to the characteristics of the somatic sensations themselves. Patients with schizophrenia experience depersonalization, in which they feel a peculiar type of alienation and feeling of disconnection that pervades their waking consciousness. They have experiences associated with somatic sensations, and because of them complain that, "I don't feel that it's my body." It has long been pointed out that negative symptoms of schizophrenia are

associated with these experiences (Frith, 1992), and according to recent research based on both neuropsychological and psychophysiological aspects of these negative symptoms, it is now clear that these experiences are associated with a cognitive disorder that is an impairment of the integrative function that perceives, recognizes, and judges stimuli that have entered at the sensory level, and the outputs of this function. Furthermore, rehabilitation should be developed based on the fact that the nature of the cognitive disorder leads to secondary symptoms related to hypobulia (decline in volition) or to progressive deterioration (Rund, 1998), and that there is a close association between this cognitive disorder and social functioning (Green, Kern, & Braff, 2000). Against this background a variety of methods have also been made in occupational therapy for patients with schizophrenia and for other persons with mental disorders in which cognitive disorders are observed. For example, Yakobina, Yakobina, and Tallant (1997) reported on occupational therapy in which cognitive behavioral therapy was applied to the treatment of female outpatients with depression, and the author also tried an approach that emphasized cognitive issues in education sessions that in corporated the characteristics of a social reintegration program in participants who were long-term inpatients (Shingu, Ochiai, Kawai, & Ando, 2003). Thus, we suggest that the realistic sensations that accompany occupational therapy presumably assist recovery of the sense of self of patients with schizophrenia and have a calming effect on patients' moods and emotions. The results of this study showing that emotional change among the "observed psychopathology" items, in particular, was associated with awareness of somatic sensation appear to indicate that the effect was attributable to the action of the realistic sensations accompanying this sort of occupational therapy.

The design of this study made it impossible to draw any conclusions about cause-effect relationships with regard to whether the feelings acted on the somatic sensations or the somatic sensations acted on the feelings. It is very interesting however that the results suggested that a new factor that had never been focused on before might be associated with physical exercise in occupational therapy. Moreover, if the possibility that promoting somatic sensation contributes to improving the ability to live in society is taken into consideration, it seems to have been possible to hypothesize that there is an interaction of activity and sensation with psychological aspects (especially emotions) and thus establish treatment strategies for the future.

CONCLUSION

In this study, we investigated the factors that are related to the "awareness of somatic sensation" of inpatients with schizophrenia in occupational therapy. The results showed that observed psychopathology, specifically the sub-item "emotional change" alone, was extracted as a significant factor. The results suggested that a new factor that had never been focused on before might be associated with physical exercise in occupational therapy.

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Original Article

Factors Correlated with Fatigue in Terminally Ill Cancer Patients: A Longitudinal Study

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Abstract

Fatigue is among the most distressing symptoms experienced by terminally ill cancer patients. It is necessary to clarify factors correlated with fatigue to develop effective management strategies. A consecutive sample of cancer patients newly registered in the Palliative Care Unit (PCU) was assessed on three occasions: at the second visit to the outpatient clinic of the PCU (Time 1), three weeks after the Time 1 session over the telephone (Time 2), and at admission to the PCU (Time 3). The patients' fatigue and a broad range of biopsychosocial factors were assessed using the validated questionnaires, structured interviews, and medical record reviews at Time 1 and Time 3. Fatigue was the only factor assessed at Time 2. Two hundred patients participated in the Time 1 session, and 129 and 73 were followed at Time 2 and Time 3, respectively. Greater fatigue at Time 1 was significantly correlated with psychological distress, lower Karnofsky Performance Status score, dyspnea, and appetite loss (adjusted coefficients of determination [R^2] = 0.49). Greater fatigue at Time 2 was significantly correlated with psychological distress, lower Karnofsky Performance Status and fatigue at Time 1 (adjusted $R^2 = 0.51$). Greater fatigue at Time 3 was significantly correlated with changes for the worse in psychological distress, Karnofsky Performance Status, and dyspnea severity during the period between Time 1 and Time 3, after adjusting for Time 1 fatigue (adjusted $R^2 = 0.54$). The results indicate that fatigue in terminally ill cancer patients is determined by both physical and psychological factors. It may be important to include psychological intervention in the multidimensional management of fatigue in this population, in addition to physical and nursing interventions. J Pain Symptom Manage 2008;35:515–523. © *2008 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

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Fatigue, depression, terminal, palliative care, quality of life, symptom management, psycho-oncology, psychiatry, end of life

Introduction

Fatigue is a critical problem among terminally ill cancer patients. Previous studies have shown the prevalence of fatigue in this population to be between 52% and 81%.[1–3] Symptom management to improve the quality of life of patients with incurable cancer is the primary task of medicine. However, there are no established strategies for the management of fatigue.[4] The general strategy for symptom management is to correct the cause of the symptom. Therefore, the factors that are correlated with fatigue in cancer patients must be clarified before management strategies can be developed.[5]

Fatigue is thought to be associated with various factors. Physical factors include anticancer treatment;[6] other symptoms such as pain and dyspnea;[3,7,8] and anemia.[9] Among the psychological factors contributing to fatigue, the role of depressive mood has been most discussed. Our previous study and some other studies in cancer patients have confirmed this association,[7,10–12] but other studies have failed to find one.[3,13] Although the relative contribution of each factor is thought to vary over the course of the illness, few studies have applied a longitudinal design, or have been conducted in terminally ill cancer patients.

Only one previous study has investigated the factors associated with fatigue in terminally ill cancer patients.[3] A convenience sample of 95 cancer patients who were inpatients at a palliative care unit were compared with 98 healthy individuals. The results of a cross-sectional analysis revealed that pain and dyspnea were the only factors that were significantly correlated with fatigue in the patient group, whereas depression and anxiety were found to be significant in the control group. The study could not clarify any longitudinal associations between fatigue and these factors.

Taking this information into consideration, we assessed a broad range of psychosocial factors in a longitudinal study to clarify the factors correlated with fatigue in terminally ill cancer patients.

Patients and Methods

Consecutive outpatients with cancer, who had been seen at the Palliative Care Unit (PCU) of the National Cancer Center Hospital East, Japan, were asked to participate in the study. The eligibility criteria were (a) newly registered in the PCU, (b) not currently undergoing curative anticancer treatment, (c) informed of their cancer diagnosis, (d) well enough to complete the questionnaires and participate in at least a half-hour interview, and (e) not suffering from cognitive disorders, defined as a score of 24 or less on the Mini Mental State examination.[14] The Mini Mental State examination is a brief screening battery for detecting cognitive disturbances, and the Japanese version of the Mini Mental State examination has been validated.[15]

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

Three sessions were held: at the time of the patient's second visit to the outpatient clinic of the PCU (Time 1); three weeks later over the telephone (Time 2); and at the time just after being hospitalized to the PCU (Time 3).

Measurements Performed at the Time 1 and Time 3 Sessions

Fatigue. Fatigue was assessed using the Cancer Fatigue Scale (CFS), a 15-item self-rating scale for assessing fatigue in cancer patients.[16] The scale consists of three subscales (physical, affective, and cognitive) that address the multidimensional nature of fatigue. Each item has a five-point Likert scale (from 1 [not at all] to 5 [very much]), and the total fatigue score can range from 0 to 60, with higher scores

indicating greater fatigue. Separately from the CFS, a five-point Likert scale was also used at the same time to briefly assess fatigue (from 1 [not fatigued at all] to 5 [fatigued very much]).

Psychological Factors. The Hospital Anxiety and Depression Scale was used to evaluate the patients' psychological distress in the preceding week.[17] The Hospital Anxiety and Depression Scale consists of a seven-item anxiety subscale and a seven-item depression subscale but does not include questions about physical symptoms to avoid contaminating the mood assessments. Each item has a four-point Likert scale, and the total score can range from 0 to 42, with higher scores indicating greater distress. We previously established the reliability and validity of the Japanese version of this questionnaire in cancer patients.[18] The total score was used in the analyses because our interest was in the contribution of psychological distress to the manifestation of fatigue.

Physical (Including Medical) Factors. Medical information on each patient was obtained from their medical records. The Karnofsky Performance Status scale is a brief objective measure of a patient's functional status.[19] The score ranges from 100 (normal, no complaints) to 0 (dead). Independently, the attending physicians also clinically assessed the patients' Performance Status (PS), as defined by the Eastern Cooperative Oncology Group (ECOG). Patients were asked to express their severity of pain, dyspnea and constipation by selecting one score on a panel of from 1 (not at all) to 5 (very much). Appetite loss and insomnia were assessed in the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (revised) (SCID).[20] An investigator structurally questioned the patients regarding the severity of these symptoms and rated the patients as 1 (not at all), 2 (sub-threshold: present but does not reach the over-threshold criterion), 3 (over threshold: lasts more than two weeks and/or interferes with the patient's daily life). A physical examination, including measurements of height, body weight, body temperature and heart rate, was also performed for each patient. The body mass index (BMI) was calculated as the body weight / height^2.

Social and Demographic Factors. Sociodemographic data were obtained during a structured interview. The patients' use of confidants was used as an indicator of social support.[21] Patients were asked whether they had confided in anyone regarding their cancer, and if so, the type and number of confidants and their level of satisfaction with them. Changes in family and other relationships since their cancer diagnosis were also assessed using a 7-point Likert scale (1 [worsened considerably] to 7 [improved considerably]).

Measurements Performed at the Time 2 Session

Data were obtained during a structured telephone interview. Fatigue was assessed using the CFS at Time 2 also. The validity of the usage of the CFS over the telephone has been established.[16]

Statistical Analysis

Three models were analyzed using multiple regression analyses.

Model 1: Cross-Sectional Analysis at Time 1. This model used a cross-sectional design to clarify the factors correlated with fatigue. Fatigue at Time 1 was entered as a dependent variable. The possible independent variables were the factors investigated at Time 1.

Model 2: Longitudinal Analysis 1. This model was designed prospectively to clarify the temporal relationships between fatigue at Time 2 and the factors extracted in Model 1. Fatigue at Time 2 was entered as a dependent variable. The independent variables were all factors retained from the final Model 1. Time 1 fatigue and the interval between Time 1 and Time 2 sessions were entered to adjust the results.

Model 3: Longitudinal Analysis 2. This model was used to clarify the factors involved in change in fatigue severity. Fatigue at Time 3 was entered as a dependent variable. The possible independent variables were changes in the investigated factors between Time 1 and Time 3. The change in each value was calculated by subtracting the Time 1 value from the Time 3 value. Unchangeable variables, such as the cancer site and demographic data, were not included in this model. Also, Time 1 fatigue and the interval between Time 1 and Time 3 sessions were entered to adjust the results.

To determine the potential factors, univariate analyses between each dependent variable

and the possible independent variables were performed using Pearson's correlations, Spearman's rank correlations and unpaired Student's *t*-tests, where appropriate, in Model 1. Since we recognized the scores from Likert scales as ordinal variables, we used the Spearman's rank correlations when assessing the correlations between fatigue and the scores obtained by using Likert scales. For descriptive purposes, however, we tabulated the means and standard deviations for these variables. Partial correlations controlling for Time 1 fatigue and the interval between Time 1 and Time 3 sessions were performed in Model 3. Significantly correlated factors ($P < 0.05$) were retained. Multicollinearity diagnostics were calculated and examined. In Model 1, we conducted each of the three systematic variable selection procedures (backward, forward, and stepwise) and checked the consistency of the three models. Consistent results were expected. If differences were found, one model was selected based on clinical plausibility. In Models 2 and 3, forced-enter multiple regression analyses were conducted.

Median survival was calculated using the Kaplan-Meier product limit method. The level of significance was set at $P < 0.05$ in all of the statistical analyses. All reported P values are 2-tailed. All statistical procedures were conducted using SPSS 10.0 J version software for Windows (SPSS Inc., 1999).

Results

Patients

Detailed subject recruitment and retention are described in Fig. 1. The sociodemographic and clinical characteristics of the participants at Time 1 are shown in Table 1. There was a significant difference in ECOG PS between the participants ($n = 200$) and the non-participants ($n = 228$) at Time 1 (1.5 vs. 2.3, $P < 0.001$, Mann-Whitney U test). However, no significant differences in age, gender, cancer site or clinical stage were seen. The median survival times at the Time 1 and Time 3 sessions were 95 and 45 days, respectively. The median intervals between the Time 1–Time 2 and Time 1–Time 3 sessions were 20 (mean ± SD: 23 ± 6 days) and 64 days (92 ± 102 days), respectively.

Prevalence of Fatigue

The prevalence of fatigue (a score of 2 or greater on a 5-point Likert scale) was 64.0, 65.9 and 82.2% at Time 1, Time 2, and Time 3, respectively.

Model 1: Cross-Sectional Analysis at Time 1. The patients' mean total CFS score was 21.7 (± 9.5), significantly greater than the reference data obtained in disease-free breast cancer patients in our previous study (16.4 ± 7.9) ($t = 5.44$, $P < 0.001$, *t*-test).[7] Tables 2 and 3 show the results of the univariate analysis. The three multiple regression models using stepwise, forward, and backward variable selection procedures consistently showed that psychological distress, a lower Performance Status score and appetite loss were significantly correlated with Time 1 fatigue. Dyspnea was significantly correlated only in the backward model. Since a previous study reported an association between fatigue and dyspnea in advanced cancer patients,[3] we chose the results of this backward model. The final results of the model are shown in Table 4.

Model 2: Longitudinal Analysis 1. Fatigue decreased significantly between Time 1 and Time 2 (20.7 [SD = 9.2] and 18.2 [SD = 10.4], respectively, $t = 3.48$, $P = 0.001$, paired *t*-test). Psychological distress and Performance Status at Time 1 significantly predicted Time 2 fatigue, after adjusting for Time 1 fatigue (Table 4).

Model 3: Longitudinal Analysis 2. Fatigue increased significantly between Time 1 and Time 3 (21.9 [SD = 8.7] and 26.4 [SD = 9.7], respectively, $t = -4.62$, $P < 0.001$, paired *t*-test). Partial correlations showed that only changes in psychological distress level, Performance Status and dyspnea severity were significantly correlated with fatigue at Time 3 (Table 3). These results were almost consistent with the results of Model 1. Thus, we decided to use the same variable set of independent variables as that used in Model 1. A multiple regression analysis revealed that changes in psychological distress, Performance Status, dyspnea, and fatigue at Time 1 were significantly correlated with changes in fatigue (Table 4). Associations with changes in medication could not be

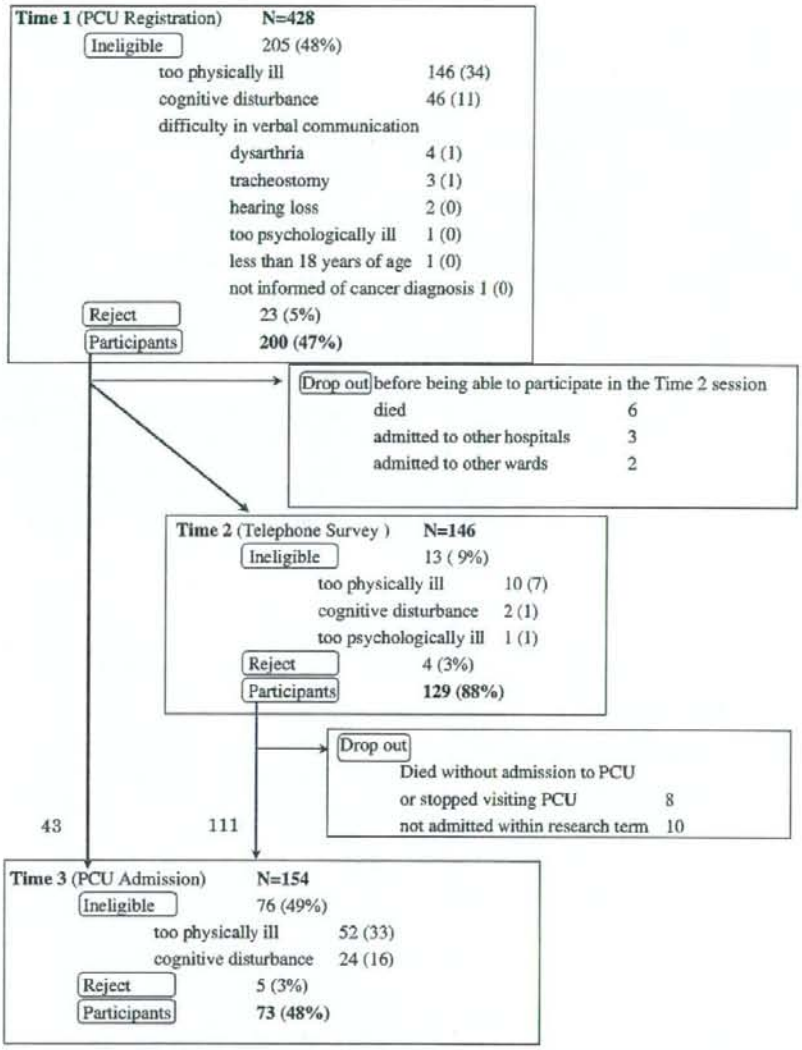

Fig. 1. Participant sampling. The participant sampling is summarized. Fifty-four patients dropped out or were admitted to the PCU before participating in the Time 2 session. PCU: Palliative Care Unit.

analyzed because the number of relevant patients was too small.

Association Between Physical Component of Fatigue and Psychological Distress

Since we were interested whether the physical component of fatigue itself associated with psychological distress, we additionally investigated the correlates of the physical subscale of the CFS in the same manner. The results were consistent: a significant correlation was observed between the physical component of fatigue and psychological distress in all three models (multiple R^2 for psychological distress was 0.20, 0.11, and 0.08 in Models 1, 2, and 3, respectively).

Discussion

This is the first longitudinal study to clarify that both physical and psychological factors

Table 1
Demographic and Clinical Characteristics of the Patients at Time 1

Characteristics	*n*	%
Age (years), mean ± SD (median)	61.0 ± 10.2 (61)	
Gender		
Female	69	35
Education level		
Junior high school or less	58	29
Marital status		
Married	74	87
Household size		
Lives alone	10	5
Cancer site		
Lung	79	40
Colon	24	12
Head and neck	15	8
Stomach	13	7
Liver	13	7
Other	56	28
Clinical stage		
Recurrence	34	17
Metastatis		
Presence	184	92
History of anti-cancer therapy (multiple choice)		
Surgery	84	42
Chemotherapy	115	58
Radiotherapy	71	36
Performance status[a] ≤60	55	28

[a]Defined by Karnofsky criteria.

Table 2
Associations Between Potential Factors and Time 1 Fatigue ($n = 200$)[a]

		Association with Time 1 CFS Total Score		
Potential Factors	*n*	Mean	*t*	*P*
Education				
Junior high school or less	58	18.6	−2.93	0.04
Other	142	22.9		
Current medication				
Anxiolytics				
Presence	23	25.5	−2.08	0.04
Absence	177	21.2		
Opioids				
Presence	54	24.4	−2.57	0.01
Absence	146	20.6		
Antiemetics				
Presence	38	24.8	−2.27	0.02
Absence	162	20.9		
Laxatives				
Presence	86	23.4	−2.30	0.02
Absence	114	20.3		

[a]Factors with $P < 0.05$ are shown.

independently play important roles in the development of fatigue in terminally ill cancer patients. Three factors were consistently found to be correlated with fatigue: psychological distress and the Karnofsky Performance Status in all three investigated models, and dyspnea in Models 1 and 3. This consistency indicates the stability of these results. Also, the high coefficients of determination in each model confirm the adequate validity of the results.

The effectiveness of psychological interventions for the amelioration of fatigue has been reported, although the goal was not to reduce patient fatigue and the subjects were not terminally ill cancer patients in most of those studies.[4] Among psychotropics, the usefulness of methylphenidate (a type of psychostimulant) in the amelioration of fatigue has been suggested from preliminary experiments in terminally ill cancer patients,[22] but a recent randomized controlled trial failed to find significant superiority over placebo.[23] Another study indicated that paroxetine (a selective serotonin reuptake inhibitor antidepressant) had no influence on fatigue in patients receiving chemotherapy.[24] Further research is required to confirm the effectiveness of psychological intervention strategies, including these approaches.

In contrast to our results, Stone et al. failed to find an association between fatigue and psychological distress in their study in a palliative care setting.[3] This discrepancy may be explained by the following three differences between the two studies. First, differences in the instruments applied to assess fatigue may account for the discrepancy; they used the Fatigue Severity Scale, which was developed for patients with collagen disease. Second, the patient characteristics differed. They used a convenience sample population and did not exclude patients with cognitive dysfunction using neuropsychometric tests. Third, other factors, such as cross-cultural differences in the perception and expression of fatigue, may also influence this phenomenon. However, there are no studies that confirm this assumption.

Karnofsky Performance Status was revealed to be significantly correlated with fatigue, in addition to psychological distress. Disability in cancer patients may arise from a number

Table 3
Correlations Between Potential Factors and Time 1 ($n = 200$) or Time 3 ($n = 73$) Fatigue

Potential Factors	Descriptive Statistics (Mean ± SD, Median)[a]		Correlation with Time 1 CFS Total Score		Correlation Between Times 1–3 Change and Time 3 CFS Total Score	
	At Time 1	At Time 3	Correlation coefficient[b]	*P*	Correlation coefficient[c]	*P*
Physical factor						
Performance status (Karnofsky Performance Status)[d]	73.5 ± 14.6, 70	52.7 ± 16.6, 50	−0.45*	<0.001	−0.31	<0.01
Body Mass Index[e]	20.7 ± 3.4, 20.7	20.1 ± 3.7, 19.6	−0.21*	<0.01	−0.14	0.31
Pain[f]	1.9 ± 0.9, 2	2.1 ± 1.2, 2	0.23	0.001	0.05	0.65
Dyspnea[f]	1.9 ± 1.0, 2	2.0 ± 1.0, 2	0.36	<0.001	0.32	<0.01
Constipation[f]	1.8 ± 1.1, 1	2.0 ± 1.3, 1	0.24	0.001	−0.02	0.86
Diarrhea[f]	1.2 ± 0.5, 1	1.5 ± 1.0, 1	<0.01	1.00	0.04	0.76
Appetite loss[g]	1.9 ± 0.9, 2	2.2 ± 0.8, 2	0.42	<0.001	0.05	0.69
Sleep disturbance[g]	1.6 ± 0.7, 1	1.8 ± 0.8, 2	0.26	<0.001	0.12	0.32
Psychological factor						
Total score of HADS	11.6 ± 6.7, 11	14.8 ± 7.5, 15	0.62*	<0.001	0.46	<0.001
Social factor						
Satisfaction with confidants[h,i]	5.5 ± 1.4, 6	5.7 ± 1.5, 6	−0.17	0.02	−0.11	0.36

HADS=Hospital Anxiety and Depression Scale.
[a]Mean and SD of the ordinal variables were calculated also for descriptive purposes.
[b]All correlation coefficients are Spearman rho correlation coefficients, except for * Pearson *r* correlation coefficients.
[c]Partial correlation coefficient controlling for Time 1 CFS total score and interval between Times 1–3.
[d]Defined by Karnofsky criteria.
[e]Body Mass Index, calculated as body weight/height^2.
[f]Assessed using a five-point Likert scale (1 [not at all] to 5 [very much]).
[g]Assessed using a three-point objective rating (1 [not at all] to 3 [over threshold]).
[h]Assessed using a seven-point Likert scale(1 [not satisfied at all] to 7 [very much satisfied]) at Time 1.
[i]Assessed using a five-point Likert scale(1 [very much worse] to 7 [very much improved]) at Time 3.
HADS=Hospital Anxiety and Depression Scale.

of causes, including the direct effects of the cancer itself or of anticancer treatment, as well as indirect effects, such as cancer-related symptoms and deconditioning, which refers to the negative effect of prolonged bed rest and immobility upon various body systems.[25] The effectiveness of exercise for improving physical functions[26] and reducing fatigue[27] has been reported, although most of this evidence was not obtained in terminally ill cancer patients. Individualized, adequate interventions to maintain or gain physical activity, including exercises or a scheduled rest–activity pattern, may be beneficial for reconditioning body systems, even in terminally ill cancer patients.

The present results also suggested an association between dyspnea and fatigue, although the causality could not be determined. Interactions between multiple symptoms are an important area of symptom management research.[28] Most patients have multiple symptoms. Concurrent symptoms may share the same biological mechanisms, and an intervention to alleviate one symptom may also improve another symptom. Unfortunately, cancer-related dyspnea is not well understood.[29] Although the elucidation of a causal association remains to be made in future studies, the management of dyspnea should be attempted and may be helpful in ameliorating fatigue.

Some methodological qualifications deserve mention. First, the heterogeneity of the study population needs to be discussed. The patients had cancers that were at different sites and stages, and had different metastatic lesions, courses, and prognoses. Second, we observed considerable patient attrition because of physical and cognitive deterioration, which hampered participation in the study. The condition of non-participants was more serious, as shown in the Results. Thus, the prevalence of fatigue may have been underestimated in this study. Also, it may not be possible to generalize our findings to all terminally ill cancer patients. However, in this type of research field, such limitations are unavoidable. In fact, the minimal attrition rate may indicate the appropriateness of our research methodology. We also noticed a high prevalence of