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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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

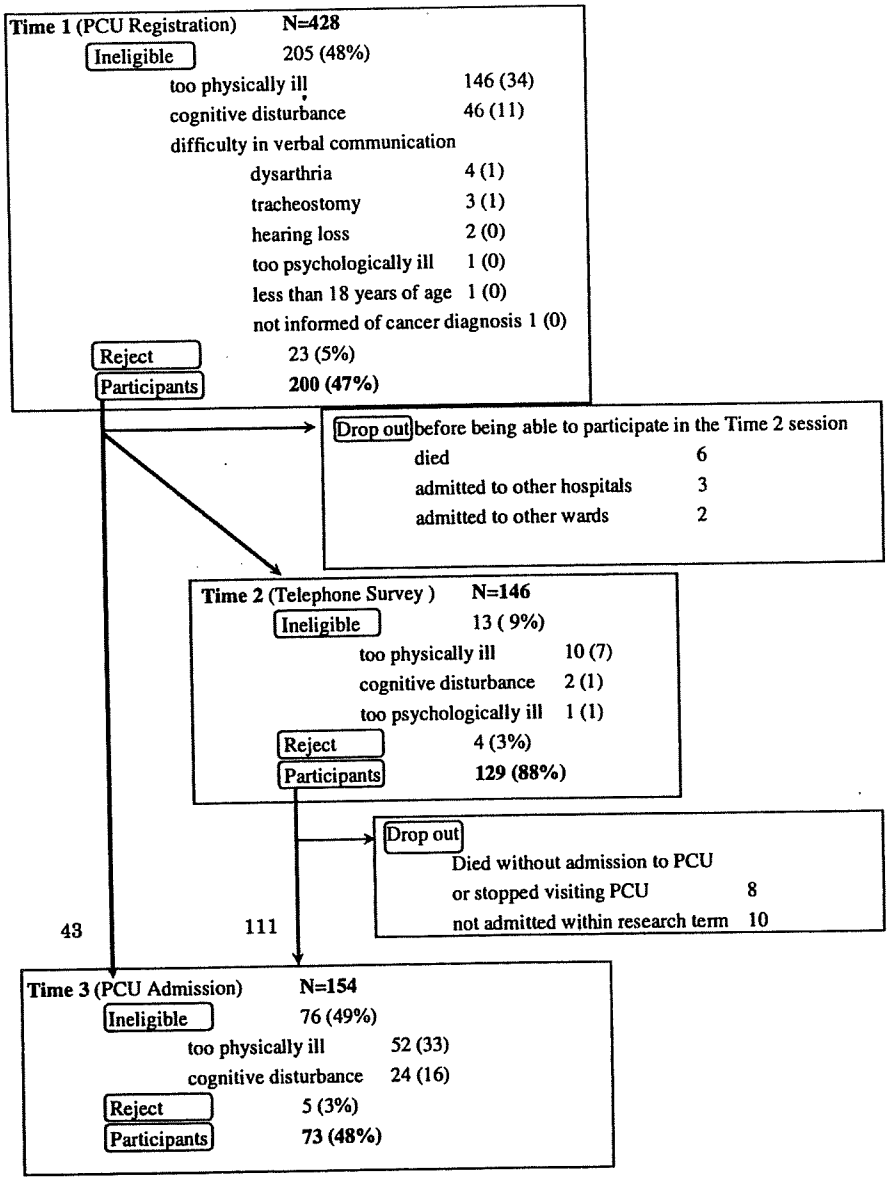

Fig. 1. Participant sampling. The participant sampling is summarized. Fifty-four patients dropped out or were admitted to the PCU before participating in the Time 2 session. PCU: Palliative Care Unit.

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 Iindex[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

Table 4
Multiple Regression Analyses—Factors Correlated with Fatigue

Model	Independent Variable	Coefficient	Standardized Coefficient	Multiple R^2	t	P
Model 1 ($n=192$)	Psychological distress[a]	0.69	0.48	0.30	8.23	<0.001
	Performance status[b]	−0.14	−0.22	0.10	−3.37	<0.001
	Dyspnea[c]	1.09	0.11	0.03	2.03	0.04
	Appetite loss[d]	1.59	0.15	0.06	2.52	0.01
Dependent variable: fatigue at Time 1, intercept = 19.30, multiple $R^2 = 0.50$, adjusted $R^2 = 0.49$						
Model 2 ($n=129$)	Psychological distress	0.32	−0.20	0.11	2.49	0.01
	Performance status	−0.16	−0.22	0.11	−2.85	<0.01
	Dyspnea	0.92	0.09	0.03	1.27	0.21
	Appetite loss	0.61	0.05	0.02	0.68	0.50
	Fatigue at Time 1	0.45	0.40	0.26	4.56	<0.001
	Interval between Time 1 and Time 2	0.09	0.06	0.00	0.97	0.33
Dependent variable: fatigue at Time 2, intercept = 13.13, multiple $R^2 = 0.53$, adjusted $R^2 = 0.51$						
Model 3 ($n=73$)	Change in psychological distress	0.49	0.32	0.12	3.76	<0.001
	Change in performance status	−0.11	−0.19	0.02	−2.20	0.03
	Change in dyspnea	2.40	0.25	0.05	3.11	<0.01
	Change in appetite loss	−0.01	0.00	0.00	−0.01	0.99
	Fatigue at Time 1	0.70	0.63	0.37	7.53	<0.001
	Interval between Time 1–3	−0.01	−0.12	0.02	−1.46	0.15
Dependent variable: fatigue at Time 3, intercept = 8.58, multiple $R^2 = 0.57$, adjusted $R^2 = 0.54$						

[a]Total score of HADS (Hospital Anxiety and Depression Scale).
[b]Defined by Karnofsky criteria.
[c]Assessed using a five-point Likert scale (1 = not at all to 5 = very much).
[d]Assessed using a three-point objective rating (1 = not at all to 3 = over threshold).

patients who suffered from cognitive dysfunction.[30] This problem should be considered in future studies of comparable populations. Another limitation was the use of invalid methods to assess symptoms other than fatigue. No comprehensive symptom inventories that were sufficiently brief and simple to use with severely exhausted patients were available at the time of protocol development.

In conclusion, this study revealed that fatigue in terminally ill cancer patients is closely correlated with both physical and psychological factors and that both of these factors may be closely related to the manifestations of fatigue. More attention to these factors could lead to a better understanding of fatigue in this population. Further research is required to examine whether the management of these factors may be effective for ameliorating fatigue. Also, patient suitability for the application of each mode of treatment should be clarified.

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Marital status and non-small cell lung cancer survival: the Lung Cancer Database Project in Japan

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Abstract

***Objective*: Previous studies have suggested that marital status is associated with survival from lung cancer; however, its association is not conclusive. The association between marital status and survival in Japanese patients with non-small cell lung cancer (NSCLC) was prospectively investigated.**

***Methods*: Between July 1999 and July 2004, a total of 1230 NSCLC patients were enrolled. The baseline survey consisted of the collection of clinical information and various demographic data, including marital status. A Cox regression model was used to estimate the hazards ratio (HR) of all-cause mortality adjustments for age, BMI, education level, performance status, histology type, clinical stage, smoking status, choice of definitive treatment, and depression.**

***Results*: The multivariable adjusted HR of male widowed patients versus male married patients was 1.7 (95% confidence interval = 1.2–2.5, $p = 0.005$). However, no significant increased risk of death in female widowed patients compared with female married patients was observed (HR = 0.7, 95% confidence interval = 0.5–1.1, $p = 0.15$). With regard to separated/divorced and single patients no significant increased risk of death in male and/or female compared with married patients was observed.**

***Conclusions*: The present data suggest that male widowed patients with NSCLC have a higher mortality rate than male married patients with NSCLC, after controlling for various factors.**

Keywords: marital status; non-small cell lung cancer; prospective study; survival

Introduction

Lung cancer is among the most common forms of cancer and is the most common cause of cancer-related death in the world [1,2]. Many studies have suggested that marital status is associated with survival from lung cancer; however, its association is not conclusive. Having a spouse die can significantly increase a person's risk of death; this 'widow/widower effect' is especially pronounced in men [3–6]. Therefore, the association between marital status and lung cancer survival should be clarified according to sex and subdivided marital status, such as married, widowed, separated/divorced, or single. However, only two studies have examined the association between marital status and lung cancer survival according to sex and subdivided marital status [7,8]. One study suggested that separated/divorced, single, and widowed patients had a higher risk of death compared with married patients, for both sexes [7]. The other one found no association between marital status and survival among divorced and widowed patients [8]. However, these studies were limited by small sample sizes [8] and a lack of differentiation between small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [7,8].

Possible associations between marital status and survival from lung cancer may be mediated by several factors. An unmarried status has been associated with an increased frequency of unhealthy life-style behaviors (especially with regard to smoking habits), maladjustment to the cancer diagnosis (especially among subjects who continue smoking even after they have been diagnosed as having cancer), psychological reactions (especially depression), delays in seeking treatment (more

advanced stages at the time of cancer diagnosis), and a lower likelihood of receiving definitive treatment [9–18]. However, previous studies did not consider these variables and did not clarify the effects of each factor on the associations between marital status and sex-specific survival from NSCLC.

In this prospective study, we investigated the influence of marital status on survival in patients with NSCLC in Japan. We were able to evaluate survival according to each sex and marital status in view of potential confounding factors and to clarify the effects of each modifying factor, such as smoking habits, psychological reactions, delays in seeking treatment, and likelihood of receiving definitive treatment, on the associations between marital status and survival. If several intermediate factors are provided, the physician could suggest possible means of improving the prognosis to their patients.

Methods

Participants

The design of this study, which was included as part of The Lung Cancer Database Project in Japan, has been reported in detail elsewhere [19]. Briefly, consecutive newly diagnosed lung cancer patients were invited to participate in the study, which was conducted at the Thoracic Oncology Division, National Cancer Center Hospital East, Kashiwa, Japan. Patients were included in the database study if they met all of the following criteria: informed of their lung cancer diagnosis; newly diagnosed patients with primary lung cancer; physically capable of completing the questionnaires; absence of cognitive impairment, such as dementia and delirium; ability to provide written consent; and no problems regarding the patients' participation in this project, as judged by their physicians.

In total, the project was explained to 2506 patients, and 2036 (81.3%) patients with newly diagnosed, untreated primary lung cancer were admitted during the project enrolment period. A total of 470 cases were ineligible for the following reasons: could not be contacted (49 cases), lung cancer diagnosis not confirmed at the time of admission (175 cases), non-lung cancer (120 cases), poor physical state (77 cases), refusal to participate in the project (43 cases), treated for lung cancer at another hospital (5 cases), and not yet informed of the diagnosis (1 case). For 40 of the 2036 patients, written informed consent could not be confirmed, and one patient withdrew consent during the follow-up period. Finally, the analyzed cohort consisted of 1995 patients.

As a result, the analytic cohort consisted of 1995 patients who were enrolled in the study between July 1999 and July 2004. The study protocol was approved by the institutional review board of the National Cancer Center, Japan. Each patient was fully informed of the purpose of the study before obtaining written consent and prior to participation in the study.

Exposure data

The patients completed the questionnaires during the waiting period prior to admission, and the questionnaires were collected after the patients were admitted. Questionnaires on demographic data and health habits (excluding the questionnaires on psychological factors) were distributed to all patients who had been registered by July 2004. Questionnaires on psychological factors were distributed only to patients who had registered by July 2003.

Demographic factors (age at cancer diagnosis, sex, education level, marital status, body mass index [BMI], smoking status, past history of cancer) and medical information (histology, clinical stage, PS, and first treatment) were obtained from the self-administered questionnaires and the patients' medical charts. PS was assessed by each attending physician using the Eastern Cooperative Oncology Group criteria [20].

To examine patient characteristics associated with variations in best-treatment practices, we defined, *a priori*, the minimally recommended initial therapies for each cancer stage at the time of diagnosis. As a practical matter, therapy for lung cancer is mainly decided, which take into account not only clinical stage but also age, comorbid illness, organopathy, and physical status. For the purposes of this analysis, the determination of the recommended therapies was based on pertinent information from medical literature published before 2004, including both randomized trials and meta-analyses of randomized trials, as well as the definitions of accepted therapy reflected in the Japan Lung Cancer Society clinical practice guidelines for the treatment of lung cancer, published in 2005 [21]. For tumor-node metastasis system stages I, II, and IIIA N0-1 surgical resection was considered the recommended initial therapy. For stage IIIA N2 patients, combination chemoradiotherapy was defined as the recommended therapy. For stage IIIB patients, combination chemoradiotherapy or chemotherapy alone was defined as the recommended therapy. For patients with stage IV disease, chemotherapy alone was considered the recommended therapy.

Depression symptoms were evaluated using the depression subscale of the Hospital Anxiety and Depression Scale (HADS) [22]. The HADS has

been used as a reliable and valid method of screening for depression in patients with cancer. Each item is rated on a scale of 0–3, with higher scores denoting a greater mood disturbance. The reliability and validity of the Japanese version of this questionnaire has been established in Japanese cancer patients [23]. The present study used a cutoff point of four out of five [23].

Follow-up

In order to follow up the subjects for vital status, confirmation was made by medical records, normal postal mail, and municipality registration data. The survival of subjects was followed from July 1999 to December 2004. The psychological questionnaire was only distributed to the patients who had registered by July 2003. In this study, we analyzed the subject who answered psychological questionnaire. Out of the remaining 1995 patients, 414 patients were excluded from the analysis because of lack of psychological questionnaires. A total of 351 cases were excluded from the analysis for the following reasons: double cancer (188 cases) or SCLC (163 cases). Finally, 1230 patients were included in the subsequent analyses.

The person-months of follow-up were counted for each subject from the date of enrollment in the study until death or the end of the study period (December 2004), whichever occurred first, and a total of 31 508 person-months (median, 24 months; range, 0–67 months) were accrued. During the follow-up period, 716 deaths from all causes were identified.

Statistical analysis

All statistical analyses were performed according to sex. Standard descriptive statistics were used to characterize the marital status. Thus, marital status was categorized into married, widowed, separated/divorced, and single. Intergroup comparisons of categorical and continuous variables were performed using chi-square tests and one-way analyses of variance, respectively. Hazard ratios (HRs) were computed as the number of deaths from all causes among the subjects in each marital status category versus the number of deaths from all causes among the respective reference category (married patients). A Cox proportional-hazards regression analysis was conducted to adjust for age at the time of cancer diagnosis, BMI in kg/m^2 (<18.5, >18.5, or unknown), education level (college/university or higher, or not), PS (0, 1, or 2–4) histological type (adenocarcinoma, squamous carcinoma, large, or other), smoking status (never-smoker, ex-smoker, or current smoker), clinical stage (IA–IIB, IIIA–IIIB, or IV), HADS depression score (<5, $\geqslant 5$, or unknown), and choice of cancer treatment (definitive treatment or non-definitive treatment) using the SAS PHREG procedure included in the SAS version 8.2 statistical software package (Cary, NC, USA). The assumption of proportional hazards was verified graphically. In all the statistical evaluations, p-values of less than or equal to 0.05 were considered to denote a significant difference. All p-values were two-tailed.

In secondary analyses, we also conducted stratified analyses to examine factors that markedly modified the associations between marital status and survival, such as smoking status, clinical stage, HADS-depression, or definitive treatment.

Results

The mean age of the subjects was 63.9 years, and the percentage of men was 70%. The proportions of married, widowed, separated/divorced, and single patients were 84, 9, 4, and 3%, respectively. The mean age differed significantly according to marital status for both male and female patients (Table 1). Moreover, the smoking status also differed significantly according to marital status for both male and female patients. In women, BMI, histology, and definitive treatment differed significantly according to marital status. No significant associations between marital status and any other variables were seen.

According to the univariate Cox proportional-hazards regression analyses, six demographic or clinical variables were significantly associated with increased HRs of lung cancer survival for male and female subjects versus their respective reference categories: BMI (<18.5), smoking status (ex-smoker and current smoker), clinical stage (IIIA–IIIB or IV), PS (1 or 2–4), histology type (squamous cell carcinoma or large cell carcinoma), definitive treatment (non-definitive), and HADS depression score ($\geqslant 5$) (Table 2).

Table 3 shows the HRs for lung cancer survival according to marital status. A univariate Cox proportional-hazards regression analysis showed no significant association between survival and marital status for male and female subjects (Table 3). These findings remained basically unchanged even after multivariate adjustments for age, BMI, education level, PS, histology type, clinical stage, smoking status, choice of definitive treatment, and HADS depression score. For male patients, however, a multivariate Cox proportional-hazards regression analysis showed a significant association between survival and marital status. The multivariable adjusted HRs of widowed, separated/divorced, and single patients versus married patients were 1.7 (95% confidence interval (CI), 1.2–2.5; $p = 0.005$), 1.1 (0.7–1.7; $p = 0.72$), and 0.9 (0.5–1.5; $p = 0.61$), respectively.

Table 1. Demographic, medical, and psychological characteristics in NSCLC patients to marital status

	Male				Female			
	Marital status				Marital status			
	Married	Widowed	Separate/ divorced	Single	Married	Widowed	Separate/ divorced	Single
No. of subjects	774	41	26	24	262	72	19	12
Demographic characteristics								
Mean age in years (SD)	64.3 (8.9)	70.5 (8.3)	62.7 (8.4)	50.0 (10.1)	61.9 (9.3)	69.6 (8.2)	59.6 (8.1)	59.7 (14.6)
Body mass index (kg/m^2) (%)								
<18.5	11	10	12	8	8	3	26	25
$\geqslant 18.5$	88	90	85	92	91	96	74	75
Unknown	1	0	4	0	1	1	0	0
Duration of education (%)								
>15 yr	23	20	27	29	6	4	0	17
$\leqslant 15$ yr	77	78	73	71	94	96	100	83
Unknown	1	2	0	0	0	0	0	0
Smoking status (%)								
Never-smoker	4	0	0	25	76	71	42	58
Ex-smoker	33	44	23	4	7	11	16	8
Current smoker	62	56	77	71	17	18	42	33
Medical characteristics								
Clinical stage[a] (%)								
IA–IIB	44	44	38	25	57	71	53	50
IIIA–IIIB	29	39	42	29	18	10	26	8
IV	27	17	19	46	25	19	21	42
Performance status[b] (%)								
0	39	39	27	21	56	63	47	50
1	55	59	65	79	39	36	42	42
2–4	6	2	8	0	5	1	11	8
Histology type (%)								
Adenocarcinoma	57	49	62	67	86	88	68	75
Squamous cell carcinoma	28	44	35	25	8	6	26	17
Large cell carcinoma	12	7	0	8	6	7	5	0
Other	3	0	4	0	1	0	0	4
Definitive treatment (%)								
Definite	85	85	73	83	91	94	74	83
Non-definitive	15	15	27	17	9	6	26	17
Psychological characteristics								
HADS depression (%)								
<5	42	37	23	54	43	44	47	50
$\geqslant 5$	53	51	69	38	54	51	47	42
Unknown	5	12	8	8	3	4	5	8

[a] Defined by TNM classification: International Union Against Cancer.
[b] Defined by Eastern Cooperative Oncology Group (ECOG).

For female patients, however, a multivariate Cox proportional-hazards regression analysis showed no significant association between survival and marital status. The multivariable HRs of widowed, separated/divorced, and single patients versus married patients were 0.7 (0.5–1.1; $p = 0.15$), 0.5 (0.3–1.1; $p = 0.10$), and 1.2 (0.5–2.7; $p = 0.71$), respectively.

In addition, we conducted an effect modification analysis to assess the effects of clinical stage, smoking status, choice of definitive treatment, and HADS depression score on the relationship between marital status and survival in male widowed patients. All of these factors had no significant effect on the association between male widowed patients and survival ($p > 0.05$ for all variables).

No survival differences were seen between married and unmarried (including widowed, separated/divorced, and single) patients. The multivariable adjusted HR of unmarried patients versus married patients was 1.0 (0.8–1.2; $p = 0.91$).

Discussion

In this prospective study conducted in Japan, a significant association was found between marital status and survival in male patients with NSCLC. Male widowed patients had a higher mortality risk

Table 2. Results of univariate analysis for survival from lung cancer

	Male				Female			
	No. of subjects	Person-months median (range)	Cases	Univariate HR (95% CI)	No. of subjects	Person-months median (range)	Cases	Univariate HR (95% CI)
No. of subjects	865	21.6 (0.6–66.3)	548		365	26.8 (0.5–66.7)	168	
Demographic characteristics								
Age								
<49	58	20.5 (0.9–64.4)	38	1.0 (referent)	30	25.7 (1.8–56.7)	16	1.0 (referent)
50–59	193	21.8 (1.7–65.7)	125	1.0 (0.7–1.5)	95	28.1 (2.9–66.1)	42	0.7 (0.4–1.3)
60–69	350	20.7 (0.8–65.9)	221	1.0 (0.7–1.5)	136	28.2 (1.9–66.7)	63	0.8 (0.4–1.3)
70<	264	22.1 (0.6–66.3)	164	0.9 (0.7–1.4)	104	26.7 (0.5–63.7)	47	0.8 (0.4–1.4)
Body mass index (kg/m^2)								
⩾18.5	765	22.1 (0.6–66.3)	469	1.0 (referent)	330	27.3 (0.5–66.7)	146	1.0 (referent)
<18.5	93	14.4 (0.8–66.3)	73	1.6 (1.2–2.0)	31	18.6 (3.7–62.8)	20	1.9 (1.2–3.0)
Unknown	7	15.7 (5.6–58.6)	6	1.6 (0.7–3.6)	4	25.7 (11.7–30.7)	2	1.4 (0.3–5.5)
Duration of education								
>15 yr	197	20.3 (0.9–65.8)	122	1.0 (referent)	22	29.3 (3.4–45.2)	6	1.0 (referent)
⩽15 yr	661	21.9 (0.8–66.3)	423	0.9 (0.8–1.2)	343	26.7 (0.5–66.7)	162	1.8 (0.8–4.0)
Unknown	7	29.7 (0.6–63.9)	3	0.7 (0.2–2.3)	0	—	0	—
Smoking status								
Never-smoker	39	28.4 (2.4–63.9)	18	1.0 (referent)	265	28.3 (0.9–66.7)	110	10 (referent)
Ex-smoker	283	21.3 (0.8–66.3)	179	1.6 (0.9–2.6)	34	26.7 (0.5–54.8)	15	1.1 (0.7–1.9)
Current smoker	543	20.3 (0.6–66.3)	351	1.7 (1.1–2.8)	66	22.1 (1.8–63.6)	43	2.0 (1.4–2.9)
Medical characteristics								
Clinical stage[a]								
IA, IB, IIA, IIB	371	34.2 (3.1–66.3)	121	1.0 (referent)	216	35.2 (0.9–66.7)	45	1.0 (referent)
IIIA, IIIB	259	16.1 (0.6–65.9)	201	4.1 (3.3–5.2)	61	23.1 (3.2–65.6)	46	6.1 (4.0–9.3)
IV	235	8.0 (0.8–63.8)	226	9.8 (7.8–12.3)	88	11.3 (0.5–62.1)	77	12.0 (8.2–17.7)
Performance status[b] (%)								
0	336	29.7 (3.1–66.3)	140	1.0 (referent)	207	33.9 (0.9–66.7)	51	1.0 (referent)
1	482	15.6 (0.8–66.3)	363	2.8 (2.3–3.4)	141	21.5 (2.4–66.1)	100	4.2 (2.9–5.9)
2–4	47	4.1 (0.6–25.2)	45	12.7 (8.9–17.9)	17	5.7 (0.5–23.2)	17	28.9 (16.1–52.0)
Histology type								
Adenocarcinoma	490	23.0 (0.6–66.3)	306	1.0 (referent)	309	27.9 (0.5–66.7)	130	1.0 (referent)
Squamous cell carcinoma	252	20.7 (0.9–66.3)	157	0.9 (0.8–1.2)	32	24.9 (3.4–60.8)	23	2.2 (1.4–3.4)
Large cell carcinoma	99	14.6 (1.4–65.8)	72	1.4 (1.0–1.8)	21	22.5 (2.9–61.9)	14	1.8 (1.0–3.1)
Other	24	29.0 (2.8–65.6)	13	0.8 (0.4–1.3)	3	29.7 (22.9–57.6)	1	0.7 (0.1–4.8)
Definitive treatment								
Definitive	733	23.0 (0.8–66.3)	445	1.0 (referent)	331	27.9 (0.9–66.7)	140	1.0 (referent)
Non-definitive	132	10.1 (0.6–65.9)	103	1.9 (1.5–2.3)	34	12.9 (0.5–56.7)	28	3.2 (2.1–4.8)
Psychological characteristics								
HADS depression								
<5	452	23.5 (0.9–66.3)	265	1.0 (referent)	189	28.7 (0.9–66.7)	71	1.0 (referent)
⩾5	364	16.7 (0.8–65.9)	251	1.3 (1.1–1.6)	163	25.1 (0.5–66.1)	89	1.7 (1.2–2.4)
Unknown	49	24.4 (0.6–60.6)	32	1.1 (0.8–1.6)	13	38.6 (4.9–60.9)	8	1.6 (0.8–3.4)

[a] Defined by TNM classification: International Union Against Cancer.
[b] Defined by Eastern Cooperative Oncology Group (ECOG)

than male married patients. Our study had some methodological advantages over previous studies in that we were able to take into account differences in sex and marital status as well as potential modifying factors, such as smoking status, psychological variables, choice of definitive treatment, and disease stage at the time of diagnosis. The present study indicates that these potential modifying factors did not participate in association between marital status and survival in male patients with NSCLC. Further examinations are needed to clarify the details of this association.

Of the three studies that examined the association between marital status and lung cancer survival according to sex and subdivided marital status [7,8]. Kravdal [7] followed up SCLC and NSCLC patients (number of patients were not specified) and documented 15 882 deaths in males and 3944 deaths in females. Single female patients had a higher risk of death than married patients. Lastly, Kvikstad *et al.* [8] followed up 333 female married, divorced, and widowed cases of SCLC and NSCLC for 6 years, revealing 268 deaths. No significant associations were found between marital

Table 3. Hazard ratios (HR) of cancer survival according to the marital status

	Male				Female				Total			
	Married	Widowed	Separate/ divorced	Single	Married	Widowed	Separate/ divorced	Single	Married	Widowed	Separate/ divorced	Single
No. of subjects	774	41	26	24	262	72	19	12	1036	113	45	36
Person-months of follow-up	21.8 (0.6–66.3)	17.0 (2.5–57.9)	23.7 (0.9–65.9)	19.1 (3.0–65.1)	26.5 (0.5–66.7)	30.5 (4.4–63.6)	28.1 (5.9–62.2)	23.6 (5.2–50.2)	23.6 (0.5–66.7)	25.9 (2.5–63.6)	27.2 (0.9–65.9)	21.0 (3.0–65.1)
No. of death from all causes	481	31	20	16	121	31	9	7	602	62	29	23
Unadjusted HR	1.0 (referent)	1.4 (0.9–1.9)	1.3 (0.8–2.0)	1.1 (0.7–1.9)	1.0 (referent)	0.9 (0.6–1.3)	0.9 (0.5–1.8)	1.8 (0.9–3.4)	1.0 (referent)	0.9 (0.7–1.1)	1.1 (0.7–1.5)	1.2 (0.8–1.8)
p-Value		0.08	0.26	0.62		0.45	0.84	0.23		0.32	0.77	0.39
Multivariable adjusted HR1	1.0 (referent)	1.4 (0.9–2.1)	1.1 (0.7–1.7)	1.1 (0.7–1.9)	1.0 (referent)	0.8 (0.5–1.3)	0.7 (0.3–1.4)	1.8 (0.8–3.9)	1.0 (referent)	0.9 (0.7–1.3)	0.9 (0.6–1.3)	1.2 (0.8–1.8)
p-Value		0.06	0.81	0.69		0.43	0.27	0.17		0.81	0.57	0.52
Multivariable adjusted HR2	1.0 (referent)	1.7 (1.2–2.5)	1.1 (0.7–1.7)	0.9 (0.5–1.5)	1.0 (referent)	0.7 (0.5–1.1)	0.5 (0.3–1.1)	1.2 (0.5–2.7)	1.0 (referent)	1.1 (0.9–1.5)	0.9 (0.6–1.3)	0.9 (0.6–1.4)
p-Value		0.005	0.72	0.61		0.15	0.10	0.71		0.41	0.42	0.65

HR1: age, BMI, education, PS, and histology type adjusted.
HR2: age, BMI, education, PS, histology type, smoke stage, definitive treatment, and HADS-depression adjusted.

status and survival among female divorced and widowed patients. The present study showed no significant association between marital status and survival when male and female patients were examined as a single group. On the other hand, when the subjects were divided into male and female patients, only the male widowed patients had a higher mortality risk than the male married patients. Having a spouse die significantly increases a person's risk of death in the general population, and this 'widow/widower effect' is especially pronounced in men [3–6]. In the present study, the findings for male patients with NSCLC are consistent with these previous results.

Possible associations between marital status and survival may be mediated by several factors. An unmarried status has been associated with an increased frequency of smoking, depression, advanced disease stage at the time of diagnosis, and a lower likelihood of receiving definitive treatment [9–13,15–18]. Previous studies did not consider possible modifying factors' effects to examine differences in sex and marital status [7,8]. Therefore, it is not clarified why single, separate/divorced, and widowed patients have a higher mortality compared with married patients. This is the first study to examine differences in sex and subdivided marital status as well as the effects of potential modifying factors, such as smoking status, psychological variables, choice of definitive treatment, and disease stage at the time of diagnosis, on the association between marital status and survival from NSCLC. In the present study, smoking status, disease stage at the time of diagnosis, choice of definitive treatment, and the HAD depression score did not have a significant modifying effect on the relationship between male widowed patients and survival. Thus, smoking status, disease stage at the time of diagnosis, choice of definitive treatment, and the HAD depression score might not have a major impact on the association between marital status and survival. However, an unmarried status has been associated with an increased chance of the patient continuing to smoke even after a diagnosis of cancer has been made [12]. The continuation of smoking even after a diagnosis of cancer has been made is known to be significantly associated with survival [12,14]. In this study, we could not evaluate this association because information on smoking continuation after cancer diagnosis was not available.

Our study had several limitations. First, the study was performed at a single National Cancer Center. Whether our results can be generalized to reflect other institutions remains unclear. Thus, further studies performed at multiple institutions are necessary to clarify the prognostic effects of marital status on the survival of lung cancer patients. Second, in this study the subjects were only NSCLC patients. Histological classification of

the lung cancers in our database at the National Cancer Center Hospital East (NCCHE), Japan, revealed that small cell carcinomas were much less common (11%) than NSCLC (89%); other reports have suggested that these cancers account for nearly 80 and 20% of all lung cancers, respectively [24]. Moreover, NSCLC and SCLC differ in terms of their prognosis as well as the therapeutic strategies employed [25]. Therefore, we clarified the association between marital status and survival using a homogeneous group, focusing only on NSCLC patients. Third, data on unhealthy lifestyle behaviors after a cancer diagnosis had been made were unavailable. An unmarried status has been associated with an increased frequency of maladjustment to the cancer diagnosis (especially among subjects who continue to smoke even after they have been diagnosed as having cancer) [12]. There is some possibility that the association between marital status and survival may be mediated by this factor. If data on unhealthy lifestyle behaviors after cancer diagnosis were made available, then the mechanism responsible for the association between marital status and survival could be clarified, and the physician could suggest possible means to improve the prognosis to their cancer patients.

In conclusion, our data indicated that marital status might influence survival among male widowed NSCLC patients in Japan. The present results indicate that potential modifying factors, such as smoking status, disease stage at the time of diagnosis, choice of definitive treatment, and the HAD depression score, did not participate in association between marital status and survival in male patients with NSCLC. Further research on marital status and survival in male patients with NSCLC within the potential modifying factors such as continued smoking and including a large population is needed to clarify the details of this association.

Conflict of interest

None of the authors have any conflict of interest with any aspect of submitting this article for publication.

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Clinical experience of the modified nurse-assisted screening and psychiatric referral program

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ABSTRACT

Objective: We previously reported that the nurse-assisted screening and psychiatric referral program (NASPRP) facilitated the psychiatric treatment of depressive patients, but the high refusal rate was a problem even though referral was recommended by the nurse to all positively screened patients. We modified the program so that the nurses could judge the final eligibility of referral using the result of the screening. This study assessed if the modified NASPRP led to more psychiatric referral of depressive patients.

Method: We retrospectively evaluated the annual change of the psychiatric referral proportion and compared the findings among the usual care term, the NASPRP term, and the modified NASPRP terms.

Results: The referral proportions of the modified NASPRP terms were 4.4% and 3.9%. These were not significantly higher than the usual care term (2.5%), and significantly lower than the NASPRP term (11.5%).

Significant of results: The modified NASPRP did not facilitate psychiatric treatment of depressive patients and another approach is needed.

KEYWORDS: Depressive disorder, Mass screening, Neoplasms, Psychiatry, Therapeutics

INTRODUCTION

Major depression and adjustment disorders are the most prevalent and burdensome psychiatric disorders in patients with cancer (Derogatis et al., 1983; Minagawa et al., 1996; Kugaya et al., 2000; Okamura et al., 2000; Akechi et al., 2001, 2004; Uchitomi et al., 2003). Although there are effective means of treating these disorders (Gill & Hatcher, 1999), these are often underrecognized by medical staff members (Fallowfield et al., 2001; McDonald et al., 1999; Passik et al., 1998), and National Comprehensive Cancer Network Clinical Practice Guideline recommends implementation of screening program.

We have developed and validated the Distress and Impact Thermometer (DIT) as a high-performance screening tool (Akizuki et al., 2005), and then the nurse-assisted screening and psychiatric referral program (NASPRP) was instituted, which was a clinical screening program combining implementation of DIT and recommendation for psychiatric

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referral for all positively screened patients, by nurses. We previously showed that introduction of the NASPRP resulted in more distressed patients referred to psychiatric consultation than before, but we also noted the high refusal rate for psychiatric referral when nurses recommended psychiatric referral to all positively screened patients (Shimizu et al., 2005).

The recommendation of psychiatric referral for patients who are not willing to undergo consultation can be a burden to those patients, because the stigma still attached to psychiatric illnesses makes many patients reluctant to acknowledge to themselves or their physicians that they are experiencing emotional distress (Goldman et al., 1999). It is also time-consuming for nurses in a busy clinical setting. We determined that the continuation of the original NASPRP was not reasonable and decided to modify the terms of NASPRP. In the process of the original NASPRP, nurses had lectures about depression and also experienced assessment of psychological distress and recommendation for psychiatric referral (Shimizu et al., 2005). We assumed such an experience period gave nurses the ability to detect among their patients those who had psychological distress and were willing to consult mental health professionals. We therefore modified NASPRP to allow the nurses to judge the final eligible patients for psychiatric referral after screening.

The ability of the modified NASPRP to facilitate psychiatric referral for depressive patients was not clear, however, and the aim of this study was to clarify this point. We hypothesized that the use of the modified NASPRP would achieve a higher proportion of referral of cancer patients to the psychiatric service for treatment of major depression and adjustment disorders than usual care and would not be inferior to the original NASPRP.

METHOD

Study Sample

This study was conducted by means of a retrospective analysis, and charts of consecutive patients admitted to the Oncology/Hematology Unit of the National Cancer Center Hospital East (NCCH-E), Japan, were eligible for review during the usual care period before the original NASPRP was introduced (T1), the period during which the NASPRP was used (T2), and the period during which the modified NASPRP was used (T3 and T4). The T1 period was the 3-month period from August to October 2002, and the T2, T3 and T4 periods were same 3 months in 2003, 2004, and 2005, respectively. Patients with a noncancer diagnosis and who were under 18 years of age were excluded.

Because this study was a retrospective review for the purpose of comparing three clinical practices, written consent and institutional review board approval were not obtained.

Modified NASPRP

The original NASPRP was instituted from August until October, 2003, in the Oncology/Hematology Unit, a 42-bed unit of the NCCH-E (Shimizu et al., 2005). The modification of the NASPRP started gradually after the completion of the original NASPRP and reached its present form at the beginning of 2004. The details of the original NASPRP and modified NASPRP are described in Table 1.

Analysis

The ability of the modified NASPRP to facilitate psychiatric referral for depressive patients was evaluated by calculating the referral proportion, which is the proportion of patients referred to the psychiatric service and treated for a diagnosis of major depression or adjustment disorders among all patients admitted. Intergroup comparisons of the proportion referred were performed between groups by the chi-squared test, respectively. All tests were two-tailed.

Table 1. *Details of the original NASPRP and modified NASPRP*

	Original NASPRP	Modified NASPRP
Step 1	All patients admitted to the hematology/oncology ward were invited to fill out the Distress and Impact Thermometer.	Same as original NASPRP.
Step 2	All patients who scored above cutoff points of the DIT were eligible on this step and were recommended for psychiatric referral by nurses in charge.	Eligible patients on this step were determined by nurses' conference based on the result of the DIT, patient's background, and patient's statement and appearance on admission and recommended for psychiatric referrel by nurses in charge.
Step 3	With patients' agreement for referral, psychiatrists see patients and start treatments when patients were distressed with any psychiatric diagnoses.	Same as original NASPRP.

All analyses were performed using SPSS 14.0 J for Windows statistical software (SPSS Japan Institute).

RESULTS

Patients' characteristics, number of patients referred to psychiatry, and referral proportion are shown in Table 2. The characteristics of the eligible patients in each period were comparable in terms of age and sex, but not about cancer sites. There existed significant differences concerning the proportion of primary unknown cancer patients.

During the T3 period, 7 patients were referred to the psychiatry division and diagnosed as having an adjustment disorder among 160 admitted patients, and during the T4 period, 5 patients were referred with an adjustment disorder among 129 admitted patients. The referral proportion during the T3 period was 3.9%, and this was not significantly different from that in T1 (3.0%, 4/134; $p = .53$) when usual care was provided and significantly lower than that in T2 (11.5%, 18/157; $p = .02$) when the original NASPRP was used. The referral proportion during T4 period was 4.4%, and this was also not significantly different from that in T1 ($p = .69$) and significantly lower than that in T2 ($p = .02$). With regard to the difference concerning cancer sites, we also analyzed this with the exception of the primary unknown cancer patients, and the results were the same.

DISCUSSION

The result of this study demonstrated that the modified NASPRP was not useful compared to usual care and inferior to the original NASPRP regarding detection of major depression and adjustment disorders in cancer patients. With the nurses' experience of concentrated psychological care in the original NASPRP term, we assumed nurses could be a primary assessment team to decide eligibility to recommend psychiatric consultation, but our assumption was incorrect.

In this study, there were many limitations due to the study design, and we could evaluate only referral proportion and not for the process of the modified NASPRP. Why this modified program was not useful is not clear, but previous study demonstrates nurses tend to underestimate patients' depression (McDonald et al., 1999), and this may have happened in this program also.

Empirical evidence showed that even though patients screened positively and were suggested as having severe psychological distress, many of them did not proceed to adequate treatment due to the refusal of the patients (Roth et al., 1998; McLachlan et al., 2001; Shimizu et al., 2005). Very few studies have elucidated why patients refuse to proceed to treatment (Curry et al., 2002), and we have no useful tactic to change their behavior so far. As it now stands, it is important to detect those patients who are distressed and willing to get consultation adequately and to treat them first. To compose an effective program, we should assess not only the patients' depressive symptoms but also the patients' need for consultation with a mental health professional. We expected the modified NASPRP could be such a strategy, but our assumption was not true, and we must pursue another way as the next

Table 2. *Characteristic of patients and number of referred patients in each term*

	No. of patients				
	T1 (usual care)	T2 (original NASPRP)	T3 (modified NASPRP)	T4 (modified NASPRP)	*p*
Total patients	134 (100)	157 (100)	160 (100)	129 (100)	
Age ($M \pm SD$)	57.4 ± 13.4	56.4 ± 13.0	58.4 ± 13.1	56.7 ± 13.8	.365
Male (%)	58 (43.3)	71 (45.2)	68 (42.5)	61 (47.2)	.855
Primary cancer site					
Hematopoietic and lymphatic tissue	40 (29.9)	56 (35.7)	62 (38.8)	45 (34.9)	.461
Head and neck	19 (14.2)	37 (23.6)	28 (17.5)	27 (20.9)	.198
Breast	42 (31.3)	30 (19.1)	45 (28.1)	30 (23.3)	.081
Primary unknown	15 (11.2)	12 (7.6)	5 (3.1)	1 (0.8)	.001
Other	18 (13.4)	22 (14.00)	20 (12.5)	26 (20.2)	.275
Referred patients					
Adjustment disorders	2	11	7	5	
Major depression	2	7	0	0	
Referral proportion (%)	3.0	11.5	4.4	3.9	