

## 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.

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

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### 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  $\text{kg/m}^2$  ( $<18.5$ ,  $>18.5$ , 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 ( $<5$ ,  $\geq 5$ , 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 ( $\geq 5$ ) (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 <sup>2</sup> ) (%)								
< 18.5	11	10	12	8	8	3	26	25
≥ 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
≤ 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 <sup>a</sup> (%)								
IA-IB	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 <sup>b</sup> (%)								
0	39	39	27	21	56	63	47	50
I	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
≥ 5	53	51	69	38	54	51	47	42
Unknown	5	12	8	8	3	4	5	8

<sup>a</sup> Defined by TNM classification: International Union Against Cancer.

<sup>b</sup> 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 <sup>2</sup> )								
≥ 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	1.0 (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 <sup>a</sup>								
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 <sup>b</sup> (%)								
0	336	29.7 (3.1-66.3)	140	1.0 (referent)	207	33.9 (0.9-66.7)	51	1.0 (referent)
I	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)

<sup>a</sup> Defined by TNM classification: International Union Against Cancer.

<sup>b</sup> 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	Married	Widowed	Separate/divorced	Single
	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
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 (1.0-65.1)				
No. of death from all causes	481	31	20	16	121	31	9	7	602	62	29	23				
Unadjusted HR	1.0 (reference)	1.4 (0.9-1.9)	1.3 (0.8-2.0)	1.1 (0.7-1.9)	1.0 (reference)	0.9 (0.6-1.3)	0.9 (0.5-1.8)	1.8 (0.9-3.4)	1.0 (reference)	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 (reference)	1.4 (0.9-2.1)	1.1 (0.7-1.7)	1.1 (0.7-1.9)	1.0 (reference)	0.8 (0.5-1.3)	0.7 (0.3-1.4)	1.8 (0.8-3.9)	1.0 (reference)	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 (reference)	1.7 (1.2-2.5)	1.1 (0.7-1.7)	0.9 (0.5-1.5)	1.0 (reference)	0.7 (0.5-1.1)	0.5 (0.3-1.1)	1.2 (0.5-2.7)	1.0 (reference)	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 referral 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				<i>p</i>
	T1 (usual care)	T2 (original NASPRP)	T3 (modified NASPRP)	T4 (modified NASPRP)	
Total patients	134 (100)	157 (100)	160 (100)	129 (100)	
Age ( <i>M</i> ± <i>SD</i> )	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	

step. In the primary care setting, adding a question regarding assistance to the questionnaire, which was, "Is this something with which you would like help?" improved the screening performance (Arroll et al., 2005). Such a questionnaire may also give information about patients' needs, and adding a "help" question may be a clue to help us formulate our next step.

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REHABILITATION IN PRACTICE

Survey of the current status of cancer rehabilitation in Japan

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Abstract

**Purpose.** To elucidate the current status of cancer rehabilitation in institutions nationwide.

**Method.** A questionnaire survey regarding the current status of cancer rehabilitation in 1693 healthcare institutions was conducted by mail. The survey first asked whether rehabilitation was being conducted for cancer patients and, in facilities in which it was being conducted, it then asked about the content of the rehabilitation, the stage of the cancer patients, etc. Facilities in which cancer rehabilitation was not being conducted were surveyed in regard to whether there was a need for cancer rehabilitation.

**Results.** Valid replies were obtained from 1045 (62.0%) institutions and 864 (82.7%) of them conducted rehabilitation for cancer patients. A high proportion of the content of the rehabilitation was found to be related to physical function. Activities of daily living guidance and training were also found to be conducted in a high proportion. Low proportions of the facilities conducted content that was specialized for cancer. Of the 181 facilities in which rehabilitation was not being conducted for cancer patients, 171 (94.5%) replied that they felt that rehabilitation was needed for cancer patients.

**Conclusions.** Based on the results of this fact-finding survey it will be necessary to consider strategies for popularizing and developing rehabilitation programmes for cancer patients in Japan.

**Keywords:** Cancer, current status, nationwide survey, rehabilitation in Japan

Introduction

In the year 2000 it was estimated that there were 538 345 new cancer cases in Japan and the number of new cases has continued to be high [1]. In 2004 the Ministry of Health, Labour and Welfare inaugurated the 'Third 10-Year Comprehensive Anticancer Strategy' and adopted 'Improving the Quality of Life (QoL) of Cancer Patients' as its principal focus. More specifically, the major tasks are (1) to proceed with the development of function-preserving and function-restoring therapy and the development of palliative therapy techniques and attempt to

popularize treatment methods with the aim of relieving cancer patient's distress and (2) to prepare a system that makes it possible to provide palliative therapy nationwide for terminally ill cancer patients in an attempt to improve QoL because of the need for support from a mental standpoint. Thus, it appears that there will be an ever greater increase in the need for rehabilitation, including mental and physical functions, to recover from symptoms and as a response to the needs of patients in the terminal stage [2–4].

As their condition deteriorates cancer patients experience a decrease in physical function, difficulty

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with movement and daily tasks [5-7] and a decrease in QoL [8-12]. In recent years progress has been made in research on rehabilitation for cancer patients and an ameliorating effect on QoL has been demonstrated by (1) exercise therapy designed to improve physical function [13-15], (2) psychosocial interventions designed to improve mental and psychological function [16-19] and (3) specialized methods for individual cancers (stoma care after surgery for colorectal cancer [20-22], shoulder exercise therapy for breast cancer patients [23], airway rehabilitation for lung cancer patients [24], training to cope with dysphagia [25] and voice and speech training [26,27] after surgery for head and neck cancer and improvement of transfer methods for terminal cancer patients) [28].

However, there has been little comprehensive rehabilitation research in Japan and no systematic cancer rehabilitation programmes have ever been popularized or developed. Thus, it will first be necessary to elucidate the situation regarding the conduct of cancer rehabilitation in healthcare institutions in Japan and its content. This study was carried out for the purpose of elucidating the current status of cancer rehabilitation at healthcare institutions nationwide by means of a questionnaire survey.

#### Subjects and methods

In March 2006, questionnaires regarding the conduct of cancer rehabilitation were mailed to departments associated with rehabilitation at 1693 healthcare institutions accredited as acute care hospitals, long-term care hospitals and multiple care hospitals according to the hospital function evaluation of healthcare institutions nationwide by the Japan Council for Quality Health Care in December 2005. In May a postcard requesting return of the questionnaire was sent to all healthcare institutions that had not returned them by the end of April 2006. This study adopted as the target population the 1686 facilities that remained after excluding the seven facilities whose accreditation in terms of the hospital function evaluation by the Japan Council for Quality Health Care had been withdrawn by the end of March 2006.

The survey asked:

- (1) the occupation and number of years of clinical experience of the responder to the questionnaire,
- (2) whether rehabilitation for cancer patients had been conducted in 2005, and the following in regard to the institutions that had conducted it:
- (3) the person engaged in rehabilitation (1: physician; 2: nurse; 3: nurse's aid; 4: nursing

care worker; 5: physical therapist; 6: occupational therapist; 7: speech therapist; 8: prosthetist; 9: psychotherapist; 10: social worker; 11: psychiatric social worker),

- (4) type of cancer (primary cancer only) of the patients receiving rehabilitation (1: brain, nerve, eye; 2: mouth, nose, pharynx, larynx; 3: lungs or bronchi; 4: breast; 5: gastrointestinal tract; 6: liver, gallbladder, pancreas; 7: urinary tract; 8: gynecologic; 9: skin; 10: bone or muscle; 11: blood or lymph);
- (5) stage of the cancer patients (1: early stage; 2: recurrence or advanced stage; 3: terminal stage),
- (6) number of patients (new patients only) who received rehabilitation in 2005 according to whether the patient was an inpatient or outpatient (1: fewer than 10; 2: 10-49; 3: 50-99; 4: 100 or more);
- (7) content of the rehabilitation (1: gait training; 2: muscle strengthening exercises; 3: range of motion exercises; 4: respiratory and pulmonary physical therapy; 5: analgesia, control of inflammation; 6: prosthetic hand and foot training after limb amputation; 7: guidance and training for activities of daily living (ADL); 8: functional restoration of the upper limb after breast cancer surgery; 9: care for lymphoedema; 10: care after surgery for head and neck cancer; 11: stoma care after surgery for colorectal cancer; 12: urostomy care after surgery for urinary tract cancer; 13: creative activities; and 14: psychotherapy and psychological counselling).

The healthcare institutions that did not conduct rehabilitation for cancer patients in 2005 were surveyed in regard to

- (8) whether there is a need for rehabilitation for cancer patients,
- (9) the situations in which they felt a need for rehabilitation for cancer patients (1: when patients request that they would like to stand and walk again; 2: when they teach methods of nursing care to families and caregivers for patients who are transferred to their homes; 3: when patients request that they wish to be able to use the toilet without depending on others; 4: when they wish to devise a method of moving patients who are bedridden and struggle with moving them; 5: when patients are isolated and do not find life worth living; 6: when attempting to deal with psychological distress, such as depression and anxiety; 7: when attempting to deal with mental pain);



- (10) the reason for the delay in introducing rehabilitation for cancer patients (1: absence of prescriptions for rehabilitation by attending physicians; 2: insufficient rehabilitation staff; 3: facility and equipment not prepared; 4: no economic support; 5: absence of any scientific basis for the efficacy of rehabilitation for cancer patients; 6: absence of feeling a need for rehabilitation for cancer patients), and
- (11) whether they had plans to conduct rehabilitation for cancer patients in the future.

The content of the above questions was thoroughly considered and decided on by physicians, nurses, physical therapists, occupational therapists, psychologists and epidemiologists who are knowledgeable about cancer rehabilitation and involved in the Third Term Comprehensive Control Research for Cancer Project 'Development of Strategies to Improve the QoL of Different Types of Patients'.

The 1045 of the 1059 institutions that mailed back the questionnaire and replied to the question asking whether they conducted rehabilitation for cancer patients were used as the denominator to calculate the percentage that conducted rehabilitation for cancer patients. The percentages for each item in the content of the survey on cancer rehabilitation were calculated by using the number of institutions that conducted rehabilitation and the number of institutions that did not conduct rehabilitation, respectively, as denominators.

The following definition of rehabilitation was provided on the first page of the questionnaire:

Rehabilitation means recovery of various abilities, including physical functions, daily living functions and activities of daily living. Methods include nursing, nursing care, physical therapy, occupational therapy, speech therapy and counselling. It is not limited to gait training or to muscles and joints, but includes support for daily living and social activities.

## Results

Valid replies were obtained from 1045 (62.0%) of the 1686 institutions nationwide. The most common occupation of those who filled out the questionnaire was physical therapist (78.7%), followed by physician (8.7%), occupational therapist (7.2%) and nurse (1.5%). Other occupations that can be cited are: speech therapist (0.5%), clerical staff (0.2%) and psychologist (0.1%). The proportions of institutions according to number of years of clinical experience of the responder were: 1-10 years, 30.9%; 11-20 years, 39.6%; 21 years or more, 28.6%. There were no significant differences in reply rates according to region of Japan (Hokkaido Region, 60.2%;

Tohoku Region, 59.1%; Kanto Region, 59.5%; Chubu Region, 71.3%; Kinki Region, 64.3%; Chugoku Region, 59.6%; Shikoku Region, 59.0%; Kyushu and Okinawa Region, 63.2%) ( $\chi^2=11.6$ ,  $p=0.11$ ).

### Current status at facilities that conduct rehabilitation for cancer patients

In 2005, rehabilitation for cancer patients was being conducted at 864 facilities (82.7%). Physical therapists (97.3%) accounted for the occupation most commonly employed in departments associated with rehabilitation and were followed by physicians (74.9%), occupational therapists (64.6%) and speech therapists (57.1%) (Table I).

In the majority of facilities patients with primary cancer at the following sites received rehabilitation: gastrointestinal system (81.4%), lung and bronchi (64.7%), breast (63.4%), brain, nerves, eyes (59.0%), liver, gallbladder, pancreas (56.7%).

The proportions according to the stage of the cancer patients who received rehabilitation were: recurrence or advanced stage, 86.8%; terminal stage, 84.6%; and early stage in 79.6%, and a high proportion of facilities provided rehabilitation in all three stages.

The proportions of facilities that conducted rehabilitation for inpatients according to the numbers of cancer patients who received rehabilitation (new patients only) were: 10-49 patients, 44.9%; fewer than 10 patients, 34.1%; 50-99, 10.8%, and 100 or more, 8.1%, and the proportions for outpatients were: fewer than 10 patients, 65.6%; 10-49 patients, 8.6%; 50-99 patients, 1.4%; and 100 or more patients, 0.3%.

The content of the rehabilitation for cancer patients in terms of physical function consisted of gait training (92.1%), muscle strengthening exercises

Table I. Percentages of institutions according to the occupations of persons engaged in departments associated with rehabilitation (n=864).

Occupation	No. of institutions	%
Physical therapist	841	97.3
Physician	647	74.9
Occupational therapist	558	64.6
Speech therapist	493	57.1
Nurses' aide	137	15.9
Nurse	131	15.2
Social welfare worker	69	8.0
Psychotherapist	46	5.3
Prosthetist	28	3.2
Nursing care worker	23	2.7
Psychiatric social worker	9	1.0
Other	294	34.0

(88.9%) and range of motion exercises (85.6%) and the rates of conduct of rehabilitation were high. The content in terms of ADL consisted of guidance and training for activities of daily living (ADL) (adjustments to the environment, health care equipment, self-help devices) (73.6%) and the rates of conduct of rehabilitation were high. The results for content in terms of post-operative care showed that functional restoration of the upper limb after breast cancer surgery was performed at more than half of the facilities (56.6%), but that there were low rates of conduct of care for lymphoedema (43.4%), care after surgery for head and neck cancer (14.8%), stoma care after surgery for colorectal cancer (10.3%) and urostomy after surgery for urinary tract cancer (5.4%).

The rates for conduct of content focused on patients' mental and psychological aspects were low and the content consisted of creative activities (recreation, music, painting, handicrafts, etc.) (24.4%) and of psychotherapy and psychological counselling (7.6%) (Table II).

#### *Current status at facilities that do not conduct rehabilitation for cancer patients*

There were 181 facilities that did not conduct rehabilitation for cancer patients in 2005. Of them,

Table II. Numbers of institutions according to the content of the rehabilitation conducted for cancer patients.

Content	No. of replies	%
<b>Physical function</b>		
Gait training	796	92.1
Muscle strengthening exercises	768	88.9
Range of motion exercises	742	85.9
Respiratory and pulmonary physical therapy	536	62.0
Analgesia, control of inflammation, etc.	433	50.1
Prosthetic hand and foot training after limb amputation or dissection	193	22.3
<b>Daily living</b>		
Guidance and training for activities of daily living (ADL) (including adjustment of the environment, health care equipment, self-help devices)	636	73.6
<b>Care after cancer surgery</b>		
Restoration of upper limb function after breast cancer surgery	489	56.6
Care for lymphoedema	375	43.4
Care after surgery for head and neck cancer	128	14.8
Stoma care after surgery for colorectal cancer	89	10.3
Urostomy after surgery for urinary tract cancer	47	5.4
<b>Mental and psychological aspects</b>		
Creative activities (recreation, music, painting, handicrafts, etc.)	211	24.4
Psychotherapy and psychological counselling	66	7.6

171 health care institutions (94.5%) replied 'yes' to the question asking whether rehabilitation is needed for cancer patients. Only two (1.1%) replied 'no', that it is not needed; the other eight facilities (4.4%) did not reply to the question.

Of the 171 facilities that replied that there is a need for cancer rehabilitation, the highest percentage, 69.1%, replied that the occasion when they felt the need for rehabilitation was 'when patients request that they would like to stand and walk again'. Other replies that exceeded 50% were: 'when teaching methods of nursing care to families and caregivers for patients who are transferred to their homes', 'when patients request that they wish to be able to use the toilet without depending on others', 'when wishing to devise a method of moving patients who are bedridden and struggling to move them' (Table III).

More than half of the institutions, 50.8%, gave 'absence of prescriptions for rehabilitation by attending physicians' as the reason for the delay in introducing rehabilitation for cancer patients and other reasons were 'insufficient rehabilitation staff, 30.4%; 'institution and facilities not prepared', 27.1%; 'absence of economic support', 23.8%; 'absence of any scientific basis for the efficacy of rehabilitation for cancer patients', 19.9%; and 'do not feel any need for rehabilitation for cancer patients', 5.5%.

Twenty-two (12.2%) of the 181 facilities replied that they 'have plans' to perform rehabilitation for cancer patients, while 58.6% 'have no plans' to perform it, 23.2% are 'considering it' and 6.1% did not reply.

## Discussion

In this study a survey targeting healthcare institutions in Japan was conducted in order to determine the

Table III. Occasions when the need for cancer rehabilitation was felt ( $n=171$ ).

Occasion	No. of replies	%
When patients request that they would like to stand and walk again	125	68.3
When teaching methods of nursing care to families and caregivers for patients who are transferred to their homes	123	67.2
When patients request that they wish to be able to use the toilet without depending on others	119	65.0
When wishing to devise a method of moving patients who are bedridden and struggling to move them	102	55.7
When patients are isolated and do not find life worth living	85	46.4
When attempting to deal with psychological distress, such as depression and anxiety	82	44.8
When attempting to deal with mental pain	48	26.2
Others	20	10.9



current status of rehabilitation for cancer patients. The results showed that rehabilitation for cancer patients is being conducted at more than 80% of the facilities and that ~95% of the facilities where it was not being conducted in 2005 recognized the need for it. Thus, it was found that both the rate of conduct of cancer rehabilitation in Japanese healthcare institutions and the need for it are high.

The percentages of facilities according to the content of the rehabilitation they conducted for cancer patients were, in descending order: gait training, muscle strengthening exercises, range of motion exercises and guidance and training for ADL. On the other hand, while the rate for conduct of functional restoration of the upper limb after breast cancer surgery as post-operative care exceeded 50%, the rates for conduct of specialized rehabilitation in the form of care for lymphoedema, care after surgery for head and neck cancer, stoma care after surgery for colorectal cancer and urostomy after surgery for urinary tract cancer were low. These findings regarding the current status of rehabilitation for cancer patients in Japan demonstrate that rehabilitation is conducted for the purpose of enabling basic living activities, but they also suggested that specialized rehabilitation programmes for cancer may not have been widely adopted. In the future it will be necessary to make an effort to popularize rehabilitation for individual types of cancer and after cancer therapy.

The three points described below can be cited as the merits of this study. First, this is the first study to assess a survey of the current status of cancer rehabilitation in Japan. The results of this survey have demonstrated the current status of the conditions of conduct and the content of cancer rehabilitation in healthcare institutions and they have clarified the need to consider strategies for popularizing and developing rehabilitation programmes for cancer patients. Secondly, letters urging institutions to reply were sent out to the target institutions in order to increase the reply rate in this study and, since a high reply rate of 62.5% was achieved with no significant differences in reply rate among the regions, the results of this study appear to reflect the situation in Japanese healthcare institutions as a whole. Thirdly, the questions in the survey were carefully examined by a study group that was well versed in rehabilitation and the questions were drawn up based on a thorough assessment by physicians, nurses, physical therapists, occupational therapists, psychologists and epidemiologists. Thus, the questions that were posed incorporated the opinions of each occupation and they appear to better reflect the current status of cancer rehabilitation.

The following three points can be cited as limitations of this study. First, according to occupation, physical therapists accounted for the highest proportion of persons who filled out the questionnaire (78.7%). Although physical therapists were found to be the major occupation that conducts rehabilitation for cancer patients, the replies regarding the conduct of rehabilitation in this survey may have been biased toward the occupation of physical therapist. Secondly, the definition of rehabilitation may have been vague. A definition of rehabilitation was stated in the questionnaire (see Methods section), but the definition of rehabilitation may vary from individual-to-individual and from occupation-to-occupation and as a result there may have been slight changes in the rates of conduct of rehabilitation and rates of conduct of the content of the rehabilitation. Thus, caution is required when interpreting the results of this questionnaire. Thirdly, analysis according to hospital size and type (university hospital, general hospital, specialized hospital, etc.) was impossible in this study and the possibility of the content of the rehabilitation differing according to the size and characteristics of the hospital cannot be ruled out.

Based on the above points, in order to popularize rehabilitation for cancer patients in the future it will first be necessary to establish its validity according to cancer type, cancer stage and method of cancer therapy. It will also be necessary to assess how to popularize cancer rehabilitation according to method of cancer therapy.

## Conclusions

The results of a survey of the status of rehabilitation for cancer patients in healthcare institutions in Japan showed that more than 80% of them conducted it. The highest proportions in regard to content were related to physical function and daily living. Many of the facilities where it was not being conducted felt a need for it. Based on the results of this survey it appears necessary to assess strategies for popularizing and developing rehabilitation programmes for cancer patients.

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## Hippocampal and Amygdalar Volumes in Breast Cancer Survivors with Posttraumatic Stress Disorder

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*Although smaller hippocampi and amygdalae were found in cancer survivors with intrusions, associations between cancer-related posttraumatic stress disorder (PTSD) and these volumes are unknown. The authors performed MRI volumetric analyses of these regions in 15 cancer survivors with PTSD, 15 cancer survivors without PTSD, and 15 healthy comparison subjects. The authors also examined the correlation between PTSD symptom scores of the Impact of Event Scale and these volumes in the PTSD group. These volumes were not significantly different among the groups, but the intrusion score was inversely associated with the hippocampal volume. Results suggest intrusions, not PTSD diagnosis, might be associated with hippocampal volume.*

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Cancer is a life-threatening illness and has been recognized as a stressor precipitating posttraumatic stress disorder (PTSD). The incidence of PTSD ranges from 3% in patients with early stage cancer to 35% in patients after treatment.<sup>1</sup> PTSD symptoms cause much distress for cancer patients and are associated with a reduced quality of life.<sup>2</sup> Thus, this issue requires both clinical attention and research.

The cancer experience contains multiple and chronic stressors at each step of diagnosis, treatment, progression, and recurrence. It differs from other types of

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trauma in that the traumatic stressor never disappears and can cause strong future-oriented anxiety regarding cancer recurrence and death.<sup>3</sup> In addition, the cancer threat originates from within the body; as a result, the patients are never free from the source of their traumatic fears. These unique characteristics of cancer-related trauma suggest that cancer-related PTSD might have a different neurobiological basis, meriting separate study from other types of PTSD. However, to our knowledge, no previous study has focused on this issue.

We previously reported smaller hippocampi<sup>4</sup> and amygdalae<sup>5</sup> in cancer survivors with intrusive recollections, a symptom of PTSD. However, whether these volumetric alterations in cancer patients were related to the entire PTSD entity or only to intrusive recollections remained unclear. With regard to PTSD resulting from other types of traumas, adults with PTSD related to combat exposure or childhood abuse have been repeatedly shown to have smaller hippocampi.<sup>6</sup> These subjects differ from breast cancer survivors in that combat veterans are typically male and childhood abuse victims are traumatized early in life. In addition, a meta-analysis<sup>7</sup> suggested that elderly subjects with severe PTSD tend to have smaller hippocampi. Although the relatively advanced age of patients at the time of cancer onset might contribute to the smaller hippocampi in patients with cancer-related PTSD, the unique characteristics of cancer-related traumas might suggest a different pathophysiology of cancer-related PTSD, compared with other types of PTSD. With regard to amygdalar volume, no reports of significant alterations in patients with PTSD have been made.

The aim of the present study was to examine the hippocampal and amygdalar volumes in breast cancer survivors who had experienced cancer-related PTSD for approximately 1 year since their cancer diagnosis. We hypothesized smaller hippocampal and amygdalar volumes in breast cancer survivors with cancer-related PTSD. Additionally, we examined the possible correlation between regional brain volumes and cancer-related PTSD symptoms.

## METHOD

### Subjects

This study was approved by the institutional review board and the ethics committee of the National Cancer

Center in Japan and was performed after obtaining the written informed consent of all the subjects. All the subjects were part of a data set from a longitudinal prospective study investigating distress and brain volumes in breast cancer survivors. The subjects were recruited from the outpatient clinic of the Division of Breast Surgery, National Cancer Center Hospital East, between 1998 and 2002. A trained psychiatrist (YM) interviewed the subjects using the clinical version of the Structured Clinical Interview for DSM-IV (SCID-I)<sup>8</sup> to diagnose PTSD and other axis I psychiatric illnesses. A sample of 30 subjects assessed by two raters was used to assess the interrater reliability in a preliminary study. The interrater agreement for the diagnosis of PTSD was excellent ( $\kappa = 1.0$ ). Subjects were excluded if they met any of the following criteria: double cancer or evidence of residual or recurrent cancer detected by an attending oncologist (SI); current comorbid DSM-IV axis I diagnosis at the time of the investigation; psychotropic medication within the previous month; any history of neurologic disorder or traumatic brain injury with loss of consciousness; or cognitive impairment (less than 24 on the Mini-Mental State Examination<sup>9,10</sup>). Fifteen cancer survivors with a current ( $N = 5$ ) or past ( $N = 10$ ) history of cancer-related PTSD were eligible and were included in the present study. The subjects in the present study were newly recruited and totally different from those in previous studies.<sup>4,5</sup>

As control subjects, 15 breast cancer survivors without any history of psychiatric illness and 15 healthy comparison subjects were individually matched to the subjects with PTSD according to age ( $\pm 2$ ) and, as closely as possible, to height, years of education, and lifetime alcohol consumption. PTSD symptoms, such as intrusion and avoidance, were assessed using the Impact of Event Scale<sup>11</sup> in all cancer survivors. The Impact of Event Scale is a well-validated, 15-item self-reported questionnaire for measuring intrusive ideation and avoidance and has been used to evaluate cancer-related stress reactions.

The effect sizes for reported differences in hippocampal volume between trauma-exposed subjects with or without PTSD were 1.76<sup>12</sup> for the right, and 1.23<sup>13</sup> and 3.67<sup>12</sup> for the left. For the smallest of these effect sizes, 10 subjects in each group were needed for a two-tailed alpha of 0.05 and a beta of 0.20, suggesting an adequate statistical power for the detection of volumetric differences in the present study.

### MRI Image Acquisition and MRI Volumetry

The methods of MRI acquisition and data analysis are described in detail elsewhere.<sup>4,14</sup> Briefly, MRI scans were