our results apply only to a clinic-based mild AD outpatient population. Further study is needed to clarify the neural substrates of the KPT among aged subjects with normal cognitive function or patients with dementias other than AD. Secondly, we compared rCBF between two groups with AD patients and found a difference in the SGC between two groups. It does not mean that the SGC is the only important area for performing the KPT. However, regardless of the above limitations, this is the first report to assess the neural substrates of performance on the KPT among patients with mild AD.

Conflict of interest

None.

Description of authors' roles

Y. Kishimoto was involved in data analysis and wrote the paper. S. Terada designed the study, analyzed the data and wrote the paper with Y. Kishimoto. S. Sato assisted in preparing the statistical design and supervised the statistical analysis. O. Yokota, H. Honda and N. Takeda collected the data. All authors discussed the results and conclusions. Y. Uchitomi supervised the study design, participated in data analysis and assisted with writing the paper.

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Perseverative errors on the Wisconsin Card Sorting Test and brain perfusion imaging in mild Alzheimer's disease

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ABSTRACT

Background: The Wisconsin Card Sorting Test (WCST) has long been used to investigate deficits in executive function in humans. The majority of studies investigating deficient WCST performance focused on the number of categories achieved (CA) and the number of perseverative errors of the Nelson type (PEN). However, there is insufficient evidence that these two measures reflect the same neural deficits.

Methods: Twenty AD patients with high PEN scores, and 20 age- and sex-matched AD patients with low PEN scores were selected. All 40 subjects underwent brain SPECT, and the SPECT images were analyzed by Statistical Parametric Mapping.

Results: No significant differences were found between high and low PEN score groups with respect to years of education, Addenbrooke's Cognitive Examination scores, and Mini-Mental State Examination scores. However, higher z scores for hypoperfusion in the bilateral rectal and orbital gyri were observed in the high PEN score group compared with the low PEN score group.

Conclusions: Our results suggest that functional activity of the bilateral rectal and orbital gyri is closely related to PEN scores on a modified WCST (mWCST). The PEN score on a mWCST might be a promising index of dysfunction of the orbitofrontal area among patients with mild AD.

Key words: Alzheimer's disease (AD), cerebral blood flow (CBF), perseveration, perseverative errors of Nelson type (PEN), Wisconsin card sorting test (WCST)

Introduction

Alzheimer's disease (AD) is the leading cause of late-onset dementia worldwide. Although the first neuropsychological deficit in AD is episodic memory loss (Perry and Hodges, 1999; Perry *et al.*, 2000), the presence of frontal or executive deficits in patients with even mild AD is now widely recognized (Perry *et al.*, 2000). Current evidence suggests that after an initial amnestic stage in AD, attention and executive functions are the first non-memory domains to be affected, before deficits in language and visuospatial functions occur (Perry and Hodges, 1999; Perry *et al.*, 2000). Moreover, perseveration errors are frequently found even in mild AD (Pekkala *et al.*, 2008). However, brain perfusion imaging evidence suggests the relative preservation of the frontal lobes in AD (Johnson *et al.*, 1987). It is, therefore, somewhat surprising that AD produces marked impairment in the attentional and executive functions, which have been linked with frontal lobe function, before deficits in language and visuospatial function occur (Perry and Hodges, 1999).

The Wisconsin Card Sorting Test (WCST) has long been used to investigate deficits in executive function in humans (Milner, 1963; Nelson, 1976). The subject is asked to match test cards to reference cards according to the color, shape, or number of stimuli on the cards. After a fixed number of correct matches, the sorting rule is changed without notice, and the subject must shift to a new mode of classification. Thus, the WCST measures cognitive flexibility, that is, the ability to alter a behavioral response mode in the face of changing contingencies (set-shifting) (Monchi *et al.*, 2001). Perry *et al.* found that 15% of minimally impaired patients with AD (Mini-Mental State Examination (MMSE)

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score 24–30) and 50% of mildly demented patients with AD (MMSE score 18–23) were impaired on the modified WCST (mWCST) (Perry *et al.*, 2000). The WCST is a complex problem-solving task that probably requires multiple cognitive processes rather than a single unitary function (Nagahama *et al.*, 2003). The majority of studies that investigated deficient mWCST performance in AD focused on the number of categories achieved (CA) and the number of perseverative errors of the Nelson (PEN) type (Perry *et al.*, 2000; Nagahama *et al.*, 2003). However, there is insufficient evidence that these two measures reflect the same neural deficit and that both measures equally indicate executive dysfunction (Takeda *et al.*, 2010). On the contrary, it has been reported that the CA and PEN scores of dementia patients are each related to regional cerebral blood flow (rCBF) in different brain regions (Takeda *et al.*, 2010).

As far as we could find, there have been only two studies of the relationship between WCST scores and rCBF in patients with dementia (Nagahama *et al.*, 2005; Takeda *et al.*, 2010). The first report by Nagahama *et al.* showed that the "stuck in set" type perseveration error (similar to the perseverative errors defined by Nelson) was associated with reduced rCBF in the rostrodorsal prefrontal cortex (PFC) in 72 elderly subjects including 51 patients with AD (Nagahama *et al.*, 2005). They used stereotaxic volume of interest analysis, and examined only four small areas in the frontal lobes (rostrodorsal PFC, posterior PFC, ventrolateral PFC and anterior cigulate area). Moreover, they did not include the effects of MMSE scores and CA scores of patients.

The second study (Takeda *et al.*, 2010) reported that PEN scores correlate with rCBF in the right thalamus of 77 subjects including 31 patients with AD. They analyzed the data using the rCBF quantification software program 3DSRT (Takeuchi *et al.*, 2002). The usefulness, validity, and objectivity of 3DSRT have been reported previously (Takeuchi *et al.*, 2002). However, these two studies include normal subjects and patients with dementias other than AD. There have been no studies on the relationship between PEN scores and rCBF in AD patients.

This study aimed to compare the rCBF of AD patients with high and low PEN scores on the mWCST, and to investigate the neural substrate important for the PEN scores on the mWCST of AD patients. Because functional neuroimaging studies of the WCST have confirmed the involvement of the PFC (Berman *et al.*, 1995; Monchi *et al.*, 2001; Konishi *et al.*, 2002), we predicted a relationship between PEN scores and prefrontal hypoperfusion among AD patients.

Methods

Modified Wisconsin Card Sorting Test

Owing to the long time required for administration of the original WCST and the refusal of some patients to complete the test due to frustration or fatigue, a number of modifications to the WCST have been developed (Nagahama *et al.*, 2003). We used this modification of Nelson's version using 48 (2×24) response cards that share one and only one attribute with the stimulus cards (Nelson, 1976). Patients were not informed of the correct sorting principle, nor were they told when the principle would shift during the test, but they were informed of the three possible categories before testing. The patients were required to determine which one was correct based solely on the feedback indicating whether each response was right or wrong. When the patient maintained a correct progression through six trials, the rule was changed without warning. The testing in this study continued until 48 cards were sorted (Nagahama *et al.*, 2005).

For the mWCST, the number of CA and PEN were evaluated. In mWCST, the mean of the PEN score was reported to be 4.8 ± 5.6 among the normal elderly (mean age, 70.8) (Nagahama *et al.*, 2003). In this study, patients with a PEN score ≥ 16 (mean + 2SD among normal elderly) were placed in the high PEN score group, while patients with a PEN score ≤ 10 (mean + 1SD among normal elderly) were placed in the low PEN group.

Subjects

Twenty AD patients with dementia severity of 0.5 (suspicious) or 1 (mild) based on the Clinical Dementia Rating (CDR) (Hughes *et al.*, 1982) and whose PEN score on the mWCST was over 15, were selected from 227 consecutive Japanese patients who were fully examined at the Memory Clinic of Okayama University Hospital between April 2004 and March 2008. In addition, 20 AD patients at the Memory Clinic with low PEN scores on the mWCST, matched for age, sex ratio, education, Addenbrooke's Cognitive Examination (ACE) scores (Mathuranath *et al.*, 2000; Yoshida *et al.*, 2011), and CA scores on mWCST, were also selected.

They all (i) underwent general physical and neurological examinations and extensive laboratory testing, including thyroid function tests, serum vitamin B12, and syphilis serology; (ii) took the MMSE (Folstein *et al.*, 1975), ACE (Mathuranath *et al.*, 2000), and frontal assessment battery (FAB) (Dubois *et al.*, 2000; Kugo *et al.*, 2007) within one week of scanning; (iii) underwent brain SPECT as well as head MRI; and (iv) were diagnosed with probable AD according to the criteria formulated

by the NINCDS-ADRDA (McKhann *et al.*, 1984); (v) had a dementia severity of 0.5 or 1 on the CDR (Hughes *et al.*, 1982); and (vi) they or their nearest relatives gave written informed consent.

The exclusion criteria were: (i) complications from other neurological diseases or illnesses, (ii) history of mental illness or substance abuse prior to the onset of dementia, (iii) any evidence of focal brain lesions on head MRI, (iv) treatment with cholinesterase inhibitors, antipsychotics, antidepressants or anxiolytic drugs, and (v) left handedness or ambidexterity.

Information was also gathered from caregivers familiar with the patient's daily behavior. To serve as an informant, the caregiver was required to be living with the patient. The profile of each subject (age, sex, years of education, and years of disease duration) was recorded. The Physical Self-Maintenance Scale (PSMS) and the Lawton Instrumental Activities of Daily Living (IADL) scale (Hokoishi *et al.*, 2001) were scored based on the information from caregivers.

Other instruments

ACE was developed to provide a brief test sensitive to early stage dementia, and is capable of differentiating between dementia subtypes including AD, frontotemporal dementia, progressive supranuclear palsy, and other parkinsonian syndromes (Mathuranath *et al.*, 2000). ACE includes MMSE but extends it to encompass important areas not covered by MMSE, such as frontal-executive function and visuospatial skills. ACE has a sensitivity comparable to the Dementia Rating Scale (Mathuranath *et al.*, 2000), a well-established dementia screening tool that is widely used in research, but not in clinical practice because of its length and difficulty of administration. For this study, we used the Japanese version of the ACE described by Yoshida *et al.* (2011). The reliability of the Japanese version of ACE is excellent, and its validity is, to some extent, established (Yoshida *et al.*, 2011).

The FAB consists of six items, and the score on each item ranges from 0 to 3. A lower score indicates a greater degree of executive dysfunction. The six subtests of FAB explore (1) similarities (conceptualization), (2) lexical fluency (mental flexibility), (3) Luria motor sequences (programming), (4) conflicting instructions (sensitivity to interference), (5) a go/no-go test (inhibitory control), and (6) prehension behavior (environmental autonomy). For this study, we used the Japanese version of FAB described by Kugo *et al.* (Dubois *et al.*, 2000; Kugo *et al.*, 2007). The reliability of the Japanese version of FAB is good to excellent, and its validity is, to some extent, established (Kugo *et al.*, 2007).

The Physical Self-Maintenance Scale (PSMS) and Instrumental Activities of Daily Living Scale (IADL) are validated scales for the assessment of activities of daily living (ADL) (Hokoishi *et al.*, 2001). The PSMS is a six-item scale that rates self-care ability in toileting, feeding, dressing, personal hygiene and grooming, locomotion (physical ambulation), and bathing. The IADL scale assesses patients' ability to perform eight complex daily tasks: ability to use the telephone, shopping, food preparation, household tasks, laundry, mode of transportation, responsibility for medications, and ability to manage finances.

Ethics

The study protocol was approved by the Committee of Okayama University Hospital on Human Research. After providing participants with a complete description of the study, written informed consent was obtained.

Brain perfusion SPECT imaging

All subjects were examined by brain perfusion single-photon emission computed tomography (SPECT). Patients were examined in a comfortable supine position with their eyes closed in quiet surroundings. First, the passage from the heart to the brain was monitored after intravenous administration of 99mTc-ethylcysteinate dimer (ECD, 600 MBq, Daiichi Radioisotope Laboratories Ltd., Tokyo, Japan). Ten minutes after the angiography, SPECT images were obtained using a triple-head, rotating gamma camera interfaced to a minicomputer (GCA9300A/ DI; Toshiba, Tokyo, Japan) equipped with a fanbeam, low-energy, high-resolution collimator. Sixty projection images over a 360° angle in a 128 × 128 matrix were acquired. All images were reconstructed using ramp-filtered back-projection and then three-dimensionally smoothed with a Butterworth filter (order 8, cutoff 0.12 cycles/cm). The reconstructed images were corrected for gamma ray attenuation using the Chang method ($\mu = 0.09$).

Data analysis

Spatial reprocessing and statistical analysis of images was performed on a voxel by voxel basis using Statistical Parametric Mapping 2 (SPM2, Wellcome Department of Imaging Neuroscience, UK) running on MATLAB (The Mathworks, Inc., Natick, MA, USA). All SPECT images of each subject were normalized to the standard brain of the Montreal Neurological Institute (MNI), and spatial normalization was performed with 12-parameter

Table 1. Demographic characteristics and neuropsychological tests

	LOW PEN SCORES	HIGH PEN SCORES	p value
Number	20	20	
Age	70.0 ± 8.5	70.8 ± 11.4	0.778
Gender	10 M/10 F	10 M/10 F	–
Duration of disease	3.2 ± 2.1	3.0 ± 2.6	0.790
Education	10.7 ± 2.3	11.3 ± 2.9	0.478
Modified Wisconsin Card Sorting Test			
CA	0.9 ± 0.9	0.9 ± 0.9	0.856
PEN	7.3 ± 2.2	20.2 ± 6.3	0.000
ACE	68.3 ± 13.7	68.3 ± 13.3	0.991
Visuospatial	5.5 ± 2.6	5.0 ± 2.1	0.460
Language	26.0 ± 2.0	26.2 ± 2.0	0.701
Orientation	8.1 ± 2.6	8.3 ± 2.2	0.796
Memory	2.3 ± 2.7	2.5 ± 2.7	0.817
MMSE	23.2 ± 3.5	23.0 ± 4.4	0.814
FAB	12.0 ± 2.8	10.9 ± 3.0	0.232
Similarities	1.5 ± 1.1	1.2 ± 1.2	0.496
Lexical fluency	1.6 ± 0.9	1.7 ± 0.9	0.863
Luria*	1.7 ± 1.0	1.8 ± 1.0	0.754
Conflicting instructions	2.5 ± 1.0	2.2 ± 1.2	0.395
Go/no-go test	1.8 ± 1.1	1.1 ± 1.0	0.035
Prehension behavior	3.0 ± 0.0	3.0 ± 0.0	1.000
PSMS	5.3 ± 1.2	4.8 ± 1.5	0.208
IADL	4.9 ± 1.7	4.9 ± 1.7	1.000

All data are means ± SD. p value, unpaired and two-tailed t tests.
PEN = perseverative errors of the Nelson type; CA = categories achieved.
ACE = Addenbrooke's cognitive examination.
MMSE = Mini-Mental State Examination.
FAB = frontal assessment battery; Luria* = Luria motor sequences.
PSMS = Physical Self-Maintenance Scale.
IADL = Lawton Instrumental Activities of Daily Living.

affine and non-linear transformations (Friston *et al.*, 1995). The voxel sizes of the reslice option were 2 mm × 2 mm × 2 mm. The non-linear parameter was set at 25 mm cut-off basis functions and 16 iterations. All the normalized SPECT images were then smoothed with an isotropic gaussian kernel filter (12-mm full-width at half-maximum). To examine the images for specific regions showing differences in perfusion, two sample *t*-tests were performed. Global normalization was performed by proportional scaling with the mean voxel value. Masking was applied using the threshold method (0.8 times the global value). The analysis used a threshold of $p < 0.01$ at the voxel level and results were considered significant at $p < 0.05$ (corrected) at the cluster level.

Statistical analysis

Statistical analysis was performed using the SPSS 14.0J software program (SPSS Inc., Chicago, IL). The two groups were compared using independent sample *t*-tests. A value of $p < 0.05$ was accepted as significant.

Results

Clinical characteristics and neuropsychological tests

No significant differences were found between high and low PEN score groups with respect to age ($p = 0.778$), disease duration ($p = 0.790$), or years of education ($p = 0.478$) (Table 1).

With the exception of PEN scores on mWCST ($p < 0.001$), no significant differences were found between high and low PEN score groups in CA scores on the mWCST ($p = 0.856$), ACE ($p = 0.991$), MMSE ($p = 0.814$), FAB ($p = 0.230$), PSMS ($p = 0.208$), or IADL ($p = 1.000$) (Table 1). There were no significant differences between high and low PEN groups in the four subscale scores on ACE. Comparison of FAB subscales revealed that AD patients with high PEN scores got lower scores than those with low PEN scores in the subscale score of the go/no-go test (Table 1).

Regional cerebral blood flow (rCBF)

The areas of hypoperfusion in the high PEN score group that were not present in the low PEN score

Table 2. Significant regional uptake differences between AD patients with low and high PEN scores on mWCST

DIRECTION OF DIFFERENCE	NUMBER OF VOXELS	PEAK Z SCORES	COORDINATES (MNI) X	Y	Z
Decreased uptake in AD patients with high PEN scores on mWCST	528	2.89	−4	52	−10
		2.58	8	46	16
		2.57	2	42	18

AD = Alzheimer's disease; MNI = Montreal Neurological Institute; mWCST = modified Wisconsin Card Sorting Test.

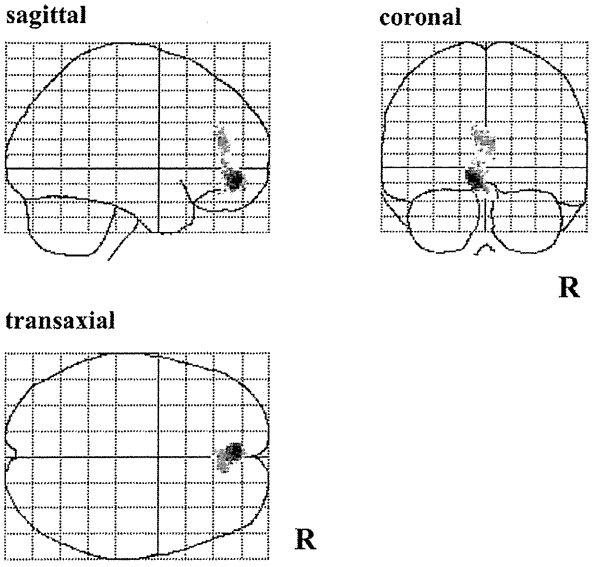

Figure 1. SPM (z) map of rCBF decrease in AD patients with high PEN scores on the modified WCST compared with AD patients with low PEN scores. Three-way-glass view of the area of significant hypoperfusion.

group according to the SPM analysis are shown in Figure 1 and Table 2. A similar test for areas of hypoperfusion in the low PEN score group that were not present in the high PEN score group found no cluster of voxels. Figure 1 shows the z score for each voxel in this cluster superimposed onto a 3-way glass brain view. Figure 1 shows a significant cluster of voxels in the left rectal gyrus extending to the right rectal gyrus and bilateral orbital gyrus (in the ventromedial PFC). Table 2 shows the probability results of the SPM analysis and the location of peak z scores in terms of MNI coordinates.

Discussion

Ventromedial PFC and WCST

We predicted hypoperfusion in the PFC among AD patients with high PEN scores, and we revealed in this study that rCBF in the bilateral rectal and orbital gyrus among AD patients with high PEN scores was lower than that among AD patients with low PEN scores. Therefore, the results are in accordance with our hypotheses. It was reported that all patients with lesions involving regions of the ventromedial PFC (vmPFC) were impaired on WCST, and that most patients without ventral prefrontal damage performed normally on WCST (Schnyer *et al.*, 2009). Our results also suggest the importance of the vmPFC in WCST.

The vmPFC is reported to play a key role in implementing probabilistic rules (Bhanji *et al.*, 2010), and patients with vmPFC damage show deficits in learning reward-punishment rules (Hartstra *et al.*, 2010). Moreover, vmPFC is involved in guiding decision-making when strategies change (de Wit *et al.*, 2009). Therefore, difficulty in changing a strategy when the rules are altered might cause the increase in PEN scores on WCST as a matter of course.

WCST and rCBF in AD and other neurodegenerative diseases

In this study, the PEN score of WCST was significantly associated with rCBF in the bilateral rectal and orbital gyrus. However, the results of other studies are not always consistent with our findings (Nagahama *et al.*, 2005; Takeda *et al.*, 2010). What causes the difference?

Nagahama *et al.* showed that the "stuck in set" type perseveration error was associated with reduced rCBF in the rostrodorsal PFC (Nagahama *et al.*, 2005). They did not examine rCBF in the ventromedial PFC and calculated the correlation of perseveration errors to rCBF without adjusting the CA scores. Therefore, if MMSE scores or CA scores correlate with rCBF in the rostrodorsal PFC, the correlation of perseveration error to rCBF in the rostrodorsal PFC is not specific to perseveration error. The CA score was reported to correlate with rostrodorsal PFC (Takeda *et al.*, 2010). Therefore, the correlation of perseveration error to rCBF in

the rostrodorsal PFC might be affected by the correlation of CA score to rCBF in the rostrodorsal PFC.

Our previous report showed that PEN scores correlate with rCBF in the right thalamus (Takeda *et al.*, 2010). Twenty-nine of 40 AD patients in this study were also included in the previous study. In that study, the data were analyzed, using the rCBF quantification software program 3DSRT (Takeuchi *et al.*, 2002). The 3DSRT divides each hemisphere into 12 arbitrary segments and each segment includes a relatively broad area. For example, the callosomarginal segment includes the superior frontal, medial frontal, and paracentral lobules, anterior cingulate, and subcallosal, orbital, and rectal gyri (Takeuchi *et al.*, 2002). Therefore, if PEN scores correlate strongly with only a small region in the frontal lobe, the correlation of PEN scores to a broad segment such as the callosomarginal segment in the 3DSRT could obscure statistically significant results in smaller regions. In this study, rCBF in whole voxels of brains of high and low PEN score groups were compared. This approach facilitates identification and analysis of smaller, discrete regions of interest. Moreover, both Nagahama *et al.* (2005) and Takeda *et al.* (2002) studied a mixture of subjects including different etiologies, MCI, and elderly subjects, whereas this study included only patients with AD. The difference in subjects might influence the results.

Ventromedial PFC and AD

We found a decrease in rCBF in the ventromedial PFC among AD patients with high PEN scores. Significant metabolic decreases in ventromedial prefrontal areas are reported to begin early in the course of AD (Fouquet *et al.*, 2009). In support of this contention, the same two medial prefrontal areas showed specific perfusion decreases from the entorhinal to the limbic neuropathologic Braak stages (Braak and Braak, 1991), corresponding to amnestic mild cognitive impairment and early AD, respectively (Bradley *et al.*, 2002). Our results suggest that some AD patients suffer from frontal neuropsychological deficits and frontal hypoperfusion in the early stage, and that those patients might be included in a so-called frontal variant of AD (Johnson *et al.*, 1999; Woodward *et al.*, 2010).

WCST and the go/no-go task

In this study, AD patients with high PEN scores got lower scores on the go/no-go task on FAB than those with low PEN scores. The go/no-go task, in which the participant must inhibit a response that was previously given to the same stimulus, can assess the difficulty in controlling impulsiveness (Drewe, 1975). Therefore, the go/no-go task is commonly used to investigate processes of selective attention or response inhibition (Ambach *et al.*, 2008). Response inhibition is difficult for patients with damage to the ventral part of the frontal lobes (Rolls *et al.*, 1994). Thus, the PEN score on mWCST may be a promising index to detect dysfunction of the orbitofrontal area among mildly affected AD patients, and equally these results suggest that the go/no-go task from the FAB may possess particular utility as a bedside test of orbitofrontal dysfunction in AD.

Limitations of this study

The results in this study should be interpreted with some caution: (1) the relatively small sample size, comprising only 20 AD patients with high CA scores and 20 AD patients with low CA scores, may limit the sensitivity to actual group differences and associations between neuropsychological functions and neural activation; (2) the low spatial resolution of SPECT scans may limit detection of alterations in small regions, thus increasing the risk of false negatives and interference from surrounding regions as well (Takeuchi *et al.*, 2002); (3) PEN and CA scores on mWCST were evaluated, but other subscales of WCST were not investigated and therefore we cannot discuss the relationship of other subscales with the PEN scores; and (4) stereotypical behaviors among AD patients were not scored. Future studies including such data will be important in relating or translating SPECT findings into clinically relevant understanding of behavior.

Conclusions

We compared rCBF between patient groups with high and low PEN scores on mWCST, and found that the high PEN score group showed lower rCBF in the bilateral rectal and orbital gyrus. Hypoperfusion of the orbitofrontal area might therefore be related to perseveration in AD patients. Further studies on the other scores on mWCST will shed light on the neural substrate of mWCST.

Conflict of interest

None.

Description of authors' roles

S. Terada designed the study, analyzed the data and wrote the paper. S. Sato assisted in preparing the statistical design and supervised the statistical analysis. H. Honda collected the data and was

involved in data analysis. O. Yokota, E. Oshima, Y. Kishimoto and N. Takeda collected data. All authors discussed the results and conclusions. Y. Uchitomi supervised the study design, participated in data analysis and assisted with writing the paper.

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Serum Brain-derived Neurotrophic Factor and Antidepressant-naive Major Depression After Lung Cancer Diagnosis

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Previous studies have reported the existence of an association between brain-derived neurotrophic factor and major depression. However, the possible role of brain-derived neurotrophic factor in the pathophysiology of major depression after cancer diagnosis has not yet been investigated. Subjects were collected using the Lung Cancer Database project. Using the cut-off scores on the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D), 81 subjects with depression (HADS-D > 10) and 81 subjects without depression (HADS-D < 5) were selected. The two groups were matched for age, sex, clinical stage and performance status. The serum brain-derived neurotrophic factor levels were measured using an enzyme-linked immunosorbent assay method. The serum brain-derived neurotrophic factor levels were not statistically different between the subjects in the depression group [29.1 (13.6) ng/ml; mean (SD)] and the non-depression group [31.4 (10.6) ng/ml] ($P = 0.22$). In a stratified analysis by gender, however, the mean serum brain-derived neurotrophic factor level in the depression group tended to be lower than that in the non-depression group among women ($n = 24$ pairs, $P = 0.06$). Major depression after cancer diagnosis is not associated with serum brain-derived neurotrophic factor levels.

Key words: major depression – BDNF – lung cancer – cancer diagnosis – stressful event

INTRODUCTION

Cancer is a common and worldwide fatal disease. Learning about the diagnosis of cancer is an extremely stressful life event, and major depression is common among patients with cancer (1). Stressful events are usually considered as strong risk factors for major depression (2). Therefore, the high

prevalence of major depression among cancer patients may be attributable to cancer-specific stressful events (3). However, the pathway by which stressful events lead to major depression among cancer patients has not yet been elucidated.

Recently, brain-derived neurotrophic factor (BDNF) has been recognized as an important factor in the pathophysiology of stress-related mental disorders, particularly major depression (4). In animal studies, the relationships between the stress and decreased expression of BDNF mRNA in the hippocampus and neocortex of rats (5,6), and increased synthesis of BDNF induced by interventions like depression treatments (7,8) were suggested. Patients with major depression had lower levels of serum BDNF than healthy controls (9–11), and the levels of serum BDNF changed to be normal after treatment for depression (9,11). However, with no such studies in the oncologic setting, we preliminarily planed to examine the difference in serum BDNF levels between subjects with and without antidepressant-naive major depression after being diagnosed as having lung cancer, which is a stressful life event and was not considered in the previous human studies (9–11). We hypothesized that the serum BDNF levels in the subjects developing major depression after being diagnosed as having lung cancer would be lower than in those without depression. We secondarily performed a stratified analysis by gender, because a previous study showed significantly low serum BDNF levels in depressive women, but not in depressive men (11).

PATIENTS AND METHODS

Study Design and Subjects

The present study used secondary samples from our previous study (12) on the Lung Cancer Database project (13). The project was a prospective cohort study to investigate the pathogenesis of and the development of new therapy for lung cancer. The project and the present study were approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center, Japan. All participants provided their written informed consent prior to enrollment.

The details of the inclusion and exclusion criteria of the present study were described in our previous report (12). In concise, patients newly diagnosed as having primary lung cancer were included, and patients with cognitive impairment, past or current histories of mental disorders, and brain neoplasms or brain metastasis were excluded. To remove the influence of severe physical status, patients with a performance status (PS) of 2 or higher were also excluded (PS was defined by Eastern Cooperative Oncology Group).

Assessment of Depression

Self-reported questionnaires, including the Hospital Anxiety and Depression Scale (HADS) (14), were completed during the waiting period prior to admission. The HADS consists of seven-item anxiety and seven-item depression subscales and is used to assess anxiety and depressive symptoms during the preceding week. The Japanese version of the depression subscale of the HADS (HADS-D) has two cut-off points that yield a good sensitivity and specificity for depression screening (10 out of 11; 82.4 and 95.1%, major depression only, 4 out of 5; 91.5 and 58.0%, adjustment disorder and major depression, respectively) (15). In this study, 'depression' was defined based on HADS-D scores without usual procedure such as the Structured Clinical Interview for DSM-IV.

Selection of Depression and Non-depression Groups

Subjects were selected according to the method used in our previous study (12), as follows: (i) all eligible subjects were classified into three groups according to the two cut-off points (10 out of 11 and 4 out of 5) for HADS-D; (ii) the number of subjects in the high-score group (>10) was used as the number of cases with major depression; (iii) the same number of controls in the low-score group (<5) was selected from the eligible subjects so that the two groups were matched for age, sex, PS (0 or 1) and clinical stage as assessed by the TNM classification (Ia–IIIa or IIIb–IV). To compare major depression with non-depression, the cases with high HADS-D scores (>10) were enrolled in the 'depression group', and the cases with low scores (<5) were included in the 'non-depression group'.

Measurement of Serum BDNF

Following an overnight fast, blood samples were collected by registered nurses in the morning (7–9 AM), a few days after admission. After storing the samples for about 2 h at 4°C, the serum was separated by centrifugation (1870*g*, 10 min) and stored at −80°C until further assay. The samples were thawed to 4°C and the serum BDNF levels were measured using an enzyme-linked immunosorbent assay kit (Promega, Madison, WI, USA) (9). The absorbance of samples at 450 nm was measured using an Emax automated microplate reader (Molecular Device, Tokyo, Japan).

Assessment of Demographical and Medical Backgrounds

Information regarding clinical, demographic and social factors were collected from the database and the patients' medical charts (13). These data consisted of sex, age, clinical staging as assessed by the TNM classification, PS, pathologic type of the lung cancer, educational level (longer/not longer than 9 years), smoking status, alcohol consumption status, presence/absence of breathlessness and pain, number of platelets and body mass index.

Statistical Analysis

To analyze the background factors, differences in continuous or categorical variables were analyzed by analysis of variance (ANOVA) and the χ^2 test, respectively.

As the primary analysis, the serum BDNF level was analyzed by ANOVA and analysis of covariance (ANCOVA). Background variables that were statistically significantly different between the two groups were examined as independent variables, with the serum BDNF level as the dependent variable, using the Spearman rank correlation coefficient (for continuous variables) or ANOVA (for categorical variables). Only factors that were related to both the background and the BDNF levels were used as covariates in the ANCOVA. As a secondary analysis, stratified analyses according to sex were also performed. All tests were two-tailed, with P values <0.05 indicating statistical significance. The statistical analyses were performed using the statistical software package SPSS for Windows (Version 16.0J, SPSS Japan Institute Inc.)

RESULTS

Participants

During the period of the study, 30 patients refused to participate, while 829 patients provided blood samples and completed self-reported questionnaires. Based on the inclusion/exclusion criteria, 717 patients were found to be eligible for enrollment in the present study (13). Of the 717 subjects, 81 had high HADS-D scores (>10) and were selected as the subjects of the depression group. Of the remaining 319 subjects with HADS-D scores of 4 or under, 81 subjects matched for age and sex were enrolled as controls in the non-depression group.

Group Backgrounds

Table 1 shows the background characteristics of the two groups, including some data that were reported in our previous study (12). The depression group contained more subjects with breathlessness than the non-depression group. Except for the breathlessness, no other variable differed significantly between the groups. The mean and standard deviation in the interval between completion of the HADS questionnaire and the blood sampling in all the subjects were 3.6 and 5.0 days, respectively; these values were similar for both groups [depression group; 3.9 (5.0) days; mean (SD), non-depression group; 3.8 (5.9) days] ($F = 0.04$, $P = 0.85$). The serum BDNF levels showed no significant differences between the subjects with breathlessness [$n = 82$; 28.7 (11.3) ng/ml; mean (SD)] and those without breathlessness [$n = 78$; 31.9 (13.0) ng/ml] ($F = 2.66$, $P = 0.11$).

Table 1. Background of all subjects ($n = 162$)

	Depression	Non-depression	χ^2 or F^a	P-value
HADS-D (score)	11–21	0–4		
Number	81	81		
Sex (male)	57 (70%)	57 (70%)	0.0	1.00
Age (y.o.)	65.1 ± 8.3	65.0 ± 8.3	0.003[a]	0.96
Performance Status (0/1)[b]	23/58	23/58	0.0	1.00
Clinical stage				
Ia–IIIa[c]	34 (42%)	34 (42%)	0.0	1.00
IIIb–IV[c]	47 (58%)	47 (58%)		
Educational level (>9 years)	52 (64%)	56 (69%)	0.46	0.50
Alcohol (>45 g/day)	14 (17%)	12 (15%)	0.38	0.54
Current smoker	33 (41%)	30 (37%)	0.23	0.63
Pathology				
Adenocarcinoma	42	45	1.49	0.83
Squamous cell	19	20		
Small cell	6	7		
Large cell	8	6		
Other	6	3		
Breathlessness (presence)	49 (60%)	33 (41%)	5.61	0.018
Pain (presence)	28 (35%)	31 (38%)	0.19	0.67
Body mass index (kg/m^2)	22.0 ± 3.5	22.1 ± 3.2	0.06[a]	0.80
Platelet ($10^4 \times \mu$l)	27.7 ± 9.3	28.3 ± 9.4	0.20[a]	0.66

Age, body mass index and platelet: mean ± SD. PS: number. Others: number and percentage.
[a]F-value.
[b]Defined by Eastern Cooperative Oncology Groups.
[c]Defined by TNM Classification, International Union Against Cancer.

Serum BDNF Levels in the Two Groups

Figure 1 illustrates the absence of any significant difference in the serum BDNF levels between the depression group and the non-depression group (ANOVA). The serum BDNF levels were normally distributed. Since no covariates were detected as statistically significant variables in the background analyses, ANCOVA was not performed. In the stratified analyses by gender, no significant differences were seen between the two groups among the men. The mean serum BDNF level was lower in the women with depression than in the women without depression, but the difference was not statistically significant.

DISCUSSION

This is the first study, to the best of our knowledge, conducted to investigate the association between serum BDNF levels and major depression in the oncologic setting.

Unlike in previous studies (9–11), the serum BDNF levels were not lower in the subjects with major depression in the

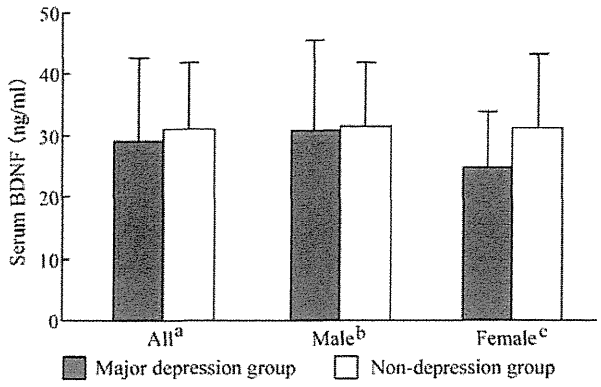

Figure 1. Serum levels of brain-derived neurotrophic factor (BDNF) in the depression group and in the non-depression group. [a]The primary analysis showed the absence of any statistically significant differences in the serum BDNF levels between the subjects in the depression group [$n = 81$; 29.1 (13.6) ng/ml; mean (SD)] and the non-depression group [$n = 81$; 31.4 (10.6) ng/ml] ($F = 1.53$, $P = 0.22$). [b]A stratified analysis by gender showed the absence of any statistically significant difference in the levels between the depression group [$n = 57$; 30.9 (14.8) ng/ml; mean (SD)] and the non-depression group [$n = 57$; 31.8 (10.2) ng/ml] ($F = 0.13$, $P = 0.72$) among men. [c]A stratified analysis by gender also showed the absence of any statistically significant difference between the depression group [$n = 24$; 24.7 (9.1) ng/ml; mean (SD)] and the non-depression group [$n = 24$; 30.7 (11.7) ng/ml] ($F = 3.87$, $P = 0.06$) among women.

present study. The lack of difference in the serum BDNF in our study might be related to the characteristics of depression in oncologic settings, which tends to be reactive to stressful event, mild and of short duration (3,16). In a previous study in which psychiatric patients without cancer were examined, the mean durations of depressive episodes were 0.78 years (9). Of the 81 cancer patients with major depression in the present study, 60 completed the HADS questionnaire within 1 month of the disclosure of their lung cancer diagnosis. None of the subjects in the major depression group visited the clinical psychiatric service or received antidepressants before or after their enrollment in this study. Although the duration of major depression was not directly assessed, the subjects with major depression in the present study might have had mild depression of short duration that remitted by themselves without antidepressants. The associations between peripheral BDNF and severity or duration of depressive episode were not concluded (17). Further study may be needed.

In the present study, depression was defined using the cut-off scores of the HADS-D and not by a structured psychiatric interview (such as the Structured Clinical Interview for DSM-IV). The one-point assessment of HADS-D might not always indicate a major depressive episode defined by DSM-IV; this could be a reason why the present result differ from previous studies' (9–11).

Although the P value did not reach statistical significance, our secondary analysis showed that women with major depression tended to have a lower serum BDNF level than women without depression. This result may support the result of a previous study suggesting an important role of reduced serum BDNF in depressive women, but not in men (11). Other studies reported an association between BDNF and the menstrual cycles in humans (18) and sex hormones in animals (19). Further studies examining these factors may be useful for elucidating the association between BDNF and major depression.

This study had the following limitations: (i) subjects with severe depression might have been excluded from this study because subjects with poor physical activity and cognitive impairment were ineligible and 30 subjects refused to participate in this study. (ii) Although peripheral BDNF was suggested to partly reflect the BDNF levels in cerebral spinal fluids (18,20), serum BDNF was mainly stored in platelets. Relation of serum BDNF levels to BDNF in hippocampus was uncertain. Further studies may be needed to reach definitive conclusions.

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Conflict of interest statement

None declared.

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Patients' Supportive Care Needs and Psychological Distress in Advanced Breast Cancer Patients in Japan

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Objective: Few studies have investigated the prevalence of the unmet needs among advanced or recurrent breast cancer patients in Asian countries and little is known about the relation between their unmet needs and psychological distress/quality of life.
Methods: The participants ($n = 87$) comprised randomly selected ambulatory female patients with advanced or recurrent breast cancer attending the Outpatient Department of Oncology, Immunology and Surgery of Nagoya City University Hospital. The patients were asked to complete self-administered questionnaires assessing the level of their physical and psychological symptoms, supportive care needs and socio-demographic and biomedical factors. The association between the patients' perceived needs and psychological distress/quality of life was then analyzed statistically.
Results: The patients had a mean ± standard deviation of 11 ± 7.7 and a median of 10 unmet needs. The prevalence of the 17 most frequent unmet needs was over 50%, and almost all of these unmet need items belonged to the Psychological or the Health system and information domain. The total Short-form Supportive Care Needs Survey Questionnaire with cancer score was significantly associated with the indices of psychological distress and quality of life. Most of the Short-form Supportive Care Needs Survey Questionnaire with cancer domains except Sexuality domain were also significantly associated with all the indices of psychological distress.
Conclusions: Psychosocial needs were strongly associated with psychological distress and quality of life. Quality of life and psychological distress may be improved if interventions for unmet needs, especially psychological and information needs, are made.

Key words: psycho-oncology – needs – psychological distress – quality of life – supportive care

INTRODUCTION

In Japan, breast cancer is the most common cancer among women, with 40 000 women being affected annually (1). The psychosocial impact of breast cancer deserves much clinical and research attention not only because of this high prevalence but also because of the magnitude of distress associated with the disease itself, treatment and the long duration of illness.

As a matter of fact, psychological distress, including anxiety and depression, are common among breast cancer patients, even years after diagnosis and treatment. The prevalence of psychiatric diagnoses (mainly depression and anxiety) among breast cancer patients reportedly ranges from around 20 to 40% (2–5). These psychological factors have been reported to predict subsequent quality of life (QOL) (6).

Women with advanced breast cancer, in particular, have high rates of psychiatric and psychological disturbances. A previous study showed that 42% of 227 women with advanced breast cancer had at least one psychiatric disorder and 36% had clinical depression and/or anxiety (3). Another study reported that 45% of the patients with recurrent breast cancer developed diagnosable depression and/or anxiety disorder within 3 months of their cancer diagnosis (4). Yet, another study showed that 42% of the patients with an initial breast cancer recurrence met the diagnostic criteria for major depressive disorder or adjustment disorder (5). Nevertheless, a previous study demonstrated that the distress of these patients remains inadequately diagnosed and treated (7). Furthermore, various barriers to the expression of psychological concerns among cancer patients have been reported (8).

Specific issues of needs as well as their perceived magnitudes should also be directly evaluated by need assessments. Such assessments are often used as a first step in the design of interventions to meet patients' needs (9–14). Evaluating patients' needs is important because unmet needs are correlated with a low QOL (15), since paying attention to psychosocial needs is associated with the satisfaction of patients with their medical care (16) and because unwanted interventions that do not match personal needs can have harmful effects. Inadequate attention to the needs of patients and their families may also lead to increased health care costs and unnecessary distress (17).

Few studies, however, have investigated the prevalence of the unmet needs among advanced or recurrent breast cancer patients in Asian countries. In past studies conducted in occidental countries, 20–40% of the incurable cancer patients were shown to have unmet needs in psychological and medical communication/information areas, in addition to 20–30% with physical unmet needs (18–21). For advanced breast cancer patients, the highest prevalence of unmet needs was observed in the psychological and health information domains (22).

Although some effective interventions for improving psychological distress, such as cognitive therapy, multifaceted psychosocial intervention and supportive care intervention (23–25), as well as pharmacotherapy, are available, these interventions are not always easy to provide in busy clinical oncology settings. Thus, brief and effective interventions are needed for cancer patients. Negative attitudes toward mental illness and psychological problems also remain a problem among cancer patients (26). By using an unmet needs assessment, rather than a direct mood assessment, we may be able to develop new interventions that are easily accepted by patients. However, little is known about the relation between patients' unmet needs and psychological distress and/or QOL in advanced cancer patients.

The purposes of the present study were to report the frequency of unmet needs in advanced breast cancer patients and to investigate the association between patients' unmet needs and psychological distress/QOL. We hypothesized that the prevalence of unmet needs would be high among them and a greater than moderate association would exist between the patients' perceived needs and psychological distress/QOL.

PATIENTS AND METHODS

Subjects

The study subjects were ambulatory female patients with advanced breast cancer who attended the outpatient clinic of the Oncology, Immunology and Surgery Department of Nagoya City University Hospital. Potential participants were sampled at random using a visiting list and a random number table.

The eligibility criteria for inclusion in the study were as follows: (i) women with a breast cancer diagnosis, (ii) an age of 20 years or older, (iii) informed of the cancer diagnosis, (iv) well enough to complete the survey questionnaire [Eastern Cooperative Oncology Group (ECOG) performance status of 0–3] and (v) clinical stage of breast cancer is IV or recurrence. The exclusion criteria included (i) severe mental or cognitive disorder, or (ii) an inability to understand the Japanese language.

This study was approved by the Ethics Review Committee of Nagoya City University Graduate School of Medical Sciences, Japan, and was conducted in accordance with the principles laid down in the Helsinki Declaration. Written consent was obtained from each patient after the provision of a thorough explanation of the purpose and method of the study.

Procedure and Measures

After informed consent had been obtained, the patients were asked to complete the self-administered questionnaires described below while they were at home and to return them on the next day. In the case of incomplete answers, clarifications were sought over the telephone.

Patient's Perceived Needs: Short-form Supportive Care Needs Survey Questionnaire with Cancer

The Short-form Supportive Care Needs Survey Questionnaire (SCNS-SF34) with cancer consists of 34 items covering five domains of need: psychological (10 items), health system and information (11 items), physical and daily living (5 items), patient care support (5 items) and sexuality (3 items). Respondents were asked to indicate the level of their need for help over the last month in relation to their having cancer using the following five response options [1, no need (not applicable); 2, no need (satisfied); 3, low need; 4, moderate need; 5, high need]. The subscale scores were obtained by summing the individual items. In addition, the total score was obtained by summing all the subscale scores (range, 34–170). Higher scores indicated a higher perceived

need. As an alternative use, the scale can be used to obtain information on the presence/absence and number of the perceived unmet needs (a rating of 3 or higher was regarded as unmet need), depending on the researcher's clinical question. The validity and reliability of the Japanese version of the SCNS-SF34 have been established (27).

Psychological Distress: Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is used to detect the states of depression and anxiety in medically ill patients, and questions about physical symptoms are excluded. This scale is composed of a self-reported questionnaire consisting of 14 items, and subjects rate how they felt during the previous week using a four-point Likert scale. The HADS consists of an anxiety and a depression subscale (0–21 points each), and the total score can range from 0 to 42. Higher scores indicate more severe depression and anxiety (28). The Japanese version of the HADS has been validated for cancer populations (29). The optimal screening cut-off point for adjustment disorder and/or major depressive disorder was 10/11, whereas the cut-off for major depression was 19/20.

QOL: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30

Patient's QOL was assessed using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). The EORTC QLQ-C30 is a 30-item self-reported questionnaire covering functional and symptom-related aspects of QOL for cancer patients. The validity and reliability of the Japanese version of the EORTC QLQ-C30 have been confirmed (30). In this study, the Global Health Status score was used. Higher Global Health Status scores indicate a higher QOL.

Socio-demographic and Biomedical Factors

An *ad hoc* self-administered questionnaire was used to obtain information on socio-demographic factors, including the marital status, level of education and employment status. The ECOG performance status was evaluated by the attending physicians. All other medical information (duration since diagnosis, clinical stage and anti-cancer treatment) was obtained from the patients' medical records.

Statistical Analysis

To investigate the association between the patients' perceived needs and psychological distress and/or QOL, the Spearman correlation coefficients and their 95% confidence intervals were calculated. All statistical procedures were conducted using the SPSS 17.0J version software for Windows (SPSS Inc., 2008)

RESULTS

Patient Characteristics

A random sample of 87 patients was identified. Two patients were excluded: one because she refused to participate and one for not providing responses despite consenting to participate. The socio-demographic and clinical characteristics of the remaining 85 patients (response rate: 97.7%) are shown in Table 1.

More than 80% of the subjects suffered from recurrent breast cancer, and about 90% of the patients did not have any impairment of physical functioning. The mean ± standard deviation (SD) and median number of months after the initial breast cancer diagnosis were 63.2 ± 78.4 and 42.8 (0–597.2), respectively. Among the participants, 74 patients (87.1%) had received surgery, 69 patients (81.2%) had received chemotherapy and 59 patients (69.4%) had received hormonal therapy.

Table 1. Characteristics of study participants ($n = 85$)

Characteristics	*n*	Percent
Age (years)	Mean: 58.6 (SD = 11.9), median: 59 (range, 32–89)	
Marital status		
Married	68	80
Employment status		
Full-time/part-time	29	22.6
Clinical stage		
IV	13	15.3
Recurrence	72	84.7
Performance status		
0	58	68.2
1	19	22.4
2	4	4.7
3	4	4.7
4	0	0
Current anti-cancer treatment		
Surgery	7	8.2
Chemotherapy	40	47.1
Trastuzumab	12	14.1
Hormonal therapy	34	40
Radiation therapy	0	0
HADS total score	Mean: 11.0 (SD = 7.54), median: 10.0 (range, 0–36)	
Adjustment disorder defined by HADS	28	32.9
Major depressive disorder defined by HADS	12	14.1

HADS, Hospital Anxiety and Depression Scale.

Frequency of Unmet Needs

Each patient scored a mean of 11 (SD = 7.7) and a median of 10 unmet needs. Table 2 shows the most common unmet needs (rated 3 or more on the five-point Likert scale). The most common unmet need was 'Fears about the cancer spreading' (78.8%) followed by 'Feeling I can do nothing about the result of treatments', 'Having one member of hospital staff with whom you can talk to about all aspects of your condition, treatment and follow-up', 'Being afraid of worried by people around' and 'Being informed about things you can do to help yourself to get well'. The prevalence of the 17 most frequent unmet needs were over 50%, and almost all of these unmet need items belonged to the Psychological domain or the Health system and information domain.

Needs by Domain

The mean/median numbers of unmet needs in each domain were as follows: Psychological needs (total of 10 items), 6.3/8; Health system and information needs (total of 11 items), 6.1/7; Physical and daily living needs (total of 5 items), 2.1/2; Patient care and support needs (5 items), 2.3/2; Sexuality needs (3 items), 0.4/0.

Association Between Patients' Perceived Needs and Psychological Distress and/or QOL

The total SCNS-SF34 score was significantly associated with both psychological distress (HADS total: $r = 0.65$, $P < 0.01$; HADS anxiety: $r = 0.66$, $P < 0.01$; HADS depression: $r = 0.57$, $P < 0.01$) and QOL (Global Health Status: $r = -0.53$, $P < 0.01$). Each needs subscale score of the SCNS-SF34, including Psychological, Health system and information, Physical and daily living and Patient care and support, was significantly associated with all the types of psychological distress evaluated in the current study (anxiety, depression and total HADS score). The correlation coefficients ranged from 0.42 (the association between HADS depression and information need, $P < 0.01$) to 0.69 (the association between HADS total and psychological need, $P < 0.01$). Regarding the relation between patients' needs and QOL, each needs score of the SCNS-SF34, including Psychological, Health system and information, Physical and daily living and Patient care and support, was also significantly associated with the Global Health Status. The correlation coefficients ranged from -0.41 (the association between Global Health Status and information need, $P < 0.01$) to -0.69 (the associations between Global Health Status and Physical and daily living need and Psychological need, $P < 0.01$) (Table 3).

DISCUSSION

Advanced breast cancer patients had many unmet needs, and half of the SCNS-SF-34 items were unmet in more than 50% of the patients. Most of the common unmet need items belonged to the Psychological domain or the Health system and information domain. In addition, patients' needs were strongly associated with psychological distress and moderately associated with QOL.

To the best of our knowledge, the present report is one of the few studies to investigate the prevalence of unmet needs among patients with advanced breast cancer. The prevalence of unmet needs found in our study is nearly two times as high as those in previous reports examining patients with advanced cancer (21,22). An Australian study investigated the needs of 105 metastatic breast cancer patients using SCNS and found that the prevalence of unmet needs in the psychological domain was between 24 and 41%, whereas the prevalence of unmet needs in the information domain ranged from 26 to 41% (22). A British study showed that the prevalence of unmet needs among 246 patients with mixed advanced incurable cancer assessed using the Need Assessment for Advanced Cancer Patients (NA-ACP) was 39–40% for unmet needs in the psychological or emotional domain and 31–35% for unmet needs in the medical communication and information domain (21).

A larger number of unmet needs were observed in the present study, compared with previous studies. The findings may indicate that there are fewer social supports available for patients with advanced breast cancer in Japan (31). In addition, although differences in symptom reporting among culture were limited (32), there may be variances when people report their perceived needs. To consider the discrepancy among cultures, further studies which find out patients' perceived needs from cross-cultural viewpoints are needed.

This is the rare study to examine the association between the unmet needs of patients with advanced breast cancer and psychological distress and/or QOL. We found a significant correlation between unmet needs and psychological distress and/or QOL. As this was a cross-sectional study, conclusions regarding the causal correlation cannot be made. However, our findings suggested that interventions based on unmet needs might reduce the distress of advanced cancer patients and enhance their QOL.

A brief nurse-delivered intervention addressing the needs of 105 women with advanced breast cancer was reported in Australia. This intervention consisted of identifying individual unmet needs and information, coaching and practicing self-care and communication strategies, and the distribution of relevant information cards. However, no significant differences between the intervention and usual care groups were observed (33). Another trial obtained feedback on patient-reported outcomes, with patient-reported outcomes summarized on feedback sheets. For the intervention groups, the information on the feedback sheet was sent to a telephone caseworker or the patient's oncologist/general practitioner. However, no overall intervention effects were observed (25). These results suggest that interventions targeting only the

Table 2. Items of moderate/high unmet needs among advanced breast cancer patients ($n = 85$)

Rank	Item	Percent (moderate/ high need)[a]	95% CI	Domain
1	Fears about the cancer spreading	78.8	70–88	Psychological
2	Worry that the results of treatment are beyond your control	71.8	62–81	Psychological
3	Concerns about the worries of those close to you	68.2	58–78	Psychological
4	Having one member of hospital staff with whom you can talk to about all aspects of your condition, treatment and follow-up	67.1	57–77	Health system and information
5	Being informed about things you can do to help yourself to get well	65.9	56–76	Health system and information
5	Anxiety	65.9	56–76	Psychological
7	Feeling down or depressed	62.4	52–73	Psychological
7	Uncertainty about the future	62.4	52–73	Psychological
7	Feeling about death and dying	62.4	52–73	Psychological
10	Having access to professional counseling if you, family or friends need it	57.6	45–66	Health system and information
11	Feelings of sadness	56.5	46–67	Psychological
11	Learning to feel in control of your situation	56.5	46–67	Psychological
11	Reassurance by medical staff that the way you feel normal	56.5	46–67	Patient care and support
11	Being informed about your test results as soon as feasible	56.5	46–67	Health system and information
15	Being adequately informed about the benefits and side effects of results before you choose to have them	55.3	45–66	Health system and information
15	Being treated in a hospital or clinic that is as physically pleasant as possible	55.3	45–66	Health system and information
17	Being informed about cancer which is under control or diminishing	54.1	44–65	Health system and information
17	Being treated like a person not just another case	54.1	44–65	Health system and information
19	Being given written information about the important aspects of your care	52.9	42–64	Health system and information
20	Keeping a positive outlook	49.4	39–60	Psychological
21	Lack of energy/tiredness	48.2	38–59	Physical and daily living
21	Being given information about aspects of managing your illness and side effects at home	48.2	38–59	Health system and information
21	Being given explanations of those tests for which you would like explanations	48.2	38–59	Health system and information
24	More choice about which cancer specialists you see	47.1	36–58	Patient care and support
25	Not being able to do the things you used to do	45.6	35–56	Physical and daily living
26	Hospital staff acknowledging, and showing sensitivity to, your feelings and emotional needs	44.7	34–55	Patient care and support
27	Hospital staff attending promptly to your physical needs	43.5	33–54	Patient care and support
28	Pain	42.4	32–53	Physical and daily living
28	More choice about which hospital you attend	42.4	32–53	Patient care and support
30	Feeling unwell a lot of the time	38.8	28–49	Physical and daily living
30	Work around the home	38.8	28–49	Physical and daily living
32	Changes in sexual feelings	15.3	8–23	Sexuality
32	Changes in your sexual relationships	15.3	8–23	Sexuality
34	To given information about sexual relationships	10.6	4–17	Sexuality

CI, confidence interval.
[a]Moderate/high unmet need: rated 3 or more on the five-point Likert scale on each item of the Short-form Supportive Care Needs Survey Questionnaire.