Table 3. Factor structures of the original MPP and the MPP-J

Item No.	Factor	
	Revised 5-factor structure of the MPP-J	Parker *et al.* [18]
36	Emotional support	Support
37	Emotional support	Support
35	Emotional support	Support
41	Emotional support	Support
39	Emotional support	Support
45	Emotional support	Support
33	Emotional support	Support
42	Emotional support	Support
32	Emotional support	—
18	Medical information	Content
19	Medical information	Content
17	Medical information	Content
21	Medical information	Content
20	Medical information	Content
23	Medical information	Content
14	Medical information	—
13	Medical information	—
29	Medical information	Support
30	Medical information	Support
31	Medical information	—
10	Clear explanation	Facilitation
12	Clear explanation	—
22	Clear explanation	Content
15	Clear explanation	Content
16	Clear explanation	Content
43	Clear explanation	Support
44	Clear explanation	Support
24	Clear explanation	Content
1	Clear explanation	Facilitation
46	Clear explanation	—
28	Encouraging question-asking	Content
26	Encouraging question-asking	Content
34	Encouraging question-asking	—
40	Encouraging question-asking	—
27	Encouraging question-asking	—
38	Encouraging question-asking	—
25	Encouraging question-asking	Content
4	Setting	Facilitation
3	Setting	Facilitation
5	Setting	Facilitation
6	Setting	Facilitation
2	Setting	—
7	—	—
8	—	—
9	—	Facilitation
11	—	—

information and the expertise of the physician (e.g. discussion of treatment options and new experimental therapies).

Factor 3: Clear explanation. Eight items loaded on this factor, accounting for 11.5% of the total variance. These items focused on how the news was conveyed, such as delivering news directly and clearly in words that are easy to understand.

Factor 4: Encouraging question-asking. Nine items loaded on this factor, accounting for 9.9% of the total variance. These items involved question-asking, such as allowing the patient to ask questions and taking sufficient consultation time to answer the patient's questions completely.

Factor 5: Setting. Five items loaded on this factor, accounting for 6.8% of the total variance. These items dealt with where and when the information was conveyed and included privacy and having the physician's full attention.

The correlations among the five factors were significant and of moderate to high ($r = 0.58$–0.79) magnitude.

Fit and internal consistency of each MPP-J factor

A summary of the fit indices for each factor using the original MPP structure model and the revised MPP-J 5-structure model and the internal consistency of each factor are presented in Table 4. In the original 3-factor model, only the facilitation factor of the MPP-J had a GFI > 0.90 and a CFI > 0.90. In the revised 5-factor model, the emotional support factor and the setting factor had a GFI > 0.90. The emotional, encouraging question-asking, and setting factors had CFIs > 0.90. However, the other factors had GFIs < 0.90 and CFIs < 0.90. All of the factors had a good internal consistency (Cronbach's alpha coefficient > 0.80).

Associations between demographic, medical and psychosocial variables and patients' communication style preferences

A series of regression analyses were conducted to determine the unique contribution of the demographic, medical, and psychological status variables on each of the MPP-J subscales (Table 5). Three participants were excluded from this statistical analysis because of missing data. All the MPP-J factors received significantly higher ratings from the female patients than from the male patients. Furthermore, all the MPP-J factors except for emotional support received significantly higher ratings from patients with lower levels of education than from patients with higher levels of education. Medical information, clear explanations, and encouraging question-asking received significantly higher ratings from younger patients than from older patients. Encouraging question-asking received a significantly higher rating from patients without recurrence or metastasis than from patients with recurrence or metastasis. The fighting spirit and anxious preoccupation subscales of the MAC were positively correlated with all of the MPP-J factors. The total HADS score was positively associated with the emotional support factor.

Table 4. The internal consistency and the fit of the each factor the MPP-J

	Alpha[a]	GFI[b]	AGFI[c]	CFI[d]
Original MPP structure model by Parker *et al.* [18]				
Factor 1 (content)	0.93	0.818	0.745	0.840
Factor 2 (support)	0.91	0.794	0.702	0.769
Factor 3 (facilitation)	0.81	0.937	0.873	0.900
Revised MPP-J structure model				
Factor 1 (Emotional support)	0.90	0.913	0.855	0.924
Factor 2 (Medical information)	0.91	0.810	0.716	0.786
Factor 3 (Clear explonation)	0.89	0.855	0.772	0.818
Factor 4 (Encouraging to ask questions)	0.91	0.876	0.753	0.910
Factor 5 (setting)	0.83	0.963	0.889	0.952

[a] Cronbach's alpha coefficient.
[b] The goodness of fit index.
[c] The adjusted goodness of fit index.
[d] The comparative fit index.

Table 5. Variables associated with each factor of the MPP

Independent variables	Beta	*p*	*r*	R^2	Adjusted R^2
Factor 1 (emotional support)				0.138	0.132
Sex[a]	0.085	0.038	0.085		
MAC fighting spirit	0.235	<0.001	0.198		
MAC anxious preoccupation	0.170	0.001	0.107		
HADS total	0.136	0.009	0.085		
Factor 2 (medical information)				0.119	0.111
Age (year)	−0.118	0.009	−0.107		
Sex[a]	0.102	0.021	0.095		
Education (year)	0.171	<0.001	0.162		
MAC fighting spirit	0.113	0.009	0.108		
MAC anxious preoccupation	0.191	<0.001	0.183		
Factor 3 (clear explanation)				0.130	0.121
Age (year)	−0.148	0.001	−0.134		
Sex[a]	0.098	0.027	0.090		
Education (year)	0.201	<0.001	0.191		
MAC fighting spirit	0.161	<0.001	0.153		
MAC anxious preoccupation	0.113	0.008	0.108		
Factor 4 (encouraging to ask questions)				0.181	0.172
Age (year)	−0.172	<0.001	−0.156		
Sex[a]	0.158	<0.001	0.146		
Education (year)	0.193	<0.001	0.183		
Recurrence or metastasis	−0.085	0.040	−0.082		
MAC fighting spirit	0.147	<0.001	0.140		
MAC anxious preoccupation	0.197	<0.001	0.184		
Factor 5 (setting)				0.165	0.159
Sex[a]	0.235	<0.001	0.232		
Education (year)	0.200	<0.001	0.198		
MAC fighting spirit	0.182	<0.001	0.174		
MAC anxious preoccupation	0.177	<0.001	0.170		

[a] Coded as 0 = male, 1 = female.

Discussion

The present study population was relatively large and heterogeneous. It included patients with several types and stages of cancers, both genders, and a broad age range. The participants' characteristics in the present study were similar to those in the original MPP study [18] in that they were outpatients at a teaching cancer center and the mean age and time since receiving the initial diagnosis were similar. The patient characteristics in this study differed from those in the original MPP study with regard to two primary variables, race and type of cancer (the participants in the original study had breast, gastrointestinal, gynecologic, and urologic cancers).

Overall, the mean scores of the majority of the items in the present study were lower than the

scores described in the original report. The rankings were partially similar to the results obtained in the US. For example, patients placed importance on receiving information about their cancer and its treatment, the physician speaking in a manner that is honest and easy to understand, and the physician offering support. However, the ranking of some items differed between the present study and the previous US study [18]. For example, compared with the US patients, Japanese cancer patients appeared to place more importance on having the physicians inform their family members about their diagnosis and prognosis (items 43 and 44 were ranked 18th and 23rd in the present study and 39th and 36th in the American study, respectively). This result is not surprising, given that a family-centered decision-making process [14] remains more dominant in Japan than in the US Japanese cancer patients also appeared to place less importance on the physicians giving the patients their full attention (item 5 was ranked 27th in Japan, and 10th in the US) and on physicians telling the patients about all the available treatment options (item 18 was ranked 30th in Japan and 9th in the US). This may reflect the more 'paternalistic' physician-patient relationship, in which the patients are deferential to their physicians regarding the scope and specifics of their treatment, that has traditionally dominated Japanese medical care.

Most of the items that were rated as most important were consistent with the communication styles advocated by published guidelines and recommendations on how to deliver bad news, such as delivering the news in person, discussing possible treatment options with the patient, and delivering the diagnosis honestly and in simple language [5–8]. However, two communication skills that are relevant in Western cultures may not be as important in Japan. First, though studies and guidelines typically recommend that physicians sit close to patients to facilitate physical contact [7,24], the Japanese patients in the present study did not rate having their physician hold their hand or touch their arm while telling them bad news as being important. This finding may represent a Japanese cultural norm in which 'formality' is more important than 'familiarity' during encounters with others. Second, the patients in the present study placed less importance on whether another health care provider was present during the consultation to offer support and information, a factor that has been recommended by previous guidelines. This may reflect a preference for privacy when communicating with their physician and a sense that the patient's family will provide sufficient support. Future studies in Japanese populations are needed to explore these issues.

The factor analytic structure in this study did not replicate the original MPP factor structure. This differs from a study conducted in Canada, which confirmed the factor structure of the original MPP [19]. The difference in the factor structures between North America and Japan may be due to cultural differences between these regions.

The exploratory factor analysis in our study showed a 5-factor structure, with the emotional support factor explaining most of the variance. The emotional support and setting factors were similar to the support and facilitation factors of the original MPP factor structure. Interestingly, the exploratory factor analysis included a new factor, the 'encouraging question-asking' factor; furthermore, the 'content' factor described in the original report was divided into two factors in our study, the 'medical information' factor and the 'clear explanation' factor. Items focusing on the encouragement of question-asking were rated highly by the patients (see items 40, 25, 38, 34, 26, 28, and 27 in Table 2). Patient–physician relationships in Japan have traditionally been based on a paternalistic and hierarchical culture that discourages patients from questioning doctors. For this reason, Japanese patients might need more time to ask questions, and to feel comfortable enough to ask any questions that they might have; they also like to be asked whether they have any questions. The new factor of encouraging question-asking might be related to the 'amae' culture described by Doi [25], which is a key concept for understanding typical interpersonal behaviors and interpersonal feelings among the Japanese. In Amae culture, people take it granted that they expect for another to behave and treat them guessing how they will feel and what they prefer. Our results suggest that it might be beneficial for physicians to encourage Japanese cancer patients to ask questions, to provide emotional support to their patients, and to understand their patients' communication style preferences regarding 'what information to receive' and 'how to receive it,' since patients might expect this information to be automatically provided by their physician.

Our findings indicated that female patients and patients with a fighting spirit or anxious preoccupation place greater importance on all aspects of physicians' communication styles when receiving bad news than male patients and those who scored lower on the fighting spirit scale. In addition, younger patients and patients with higher education levels rated medical information, clear explanations, and encouraging question-asking as being more important, compared with the ratings given to these items by older patients and those with less education. The setting variables were also given higher ratings by patients with higher education levels than by patients with lower education levels. These results were consistent with previous findings [16,18,26]. Furthermore, in the current study, patients who had higher levels of psychological distress indicated that they preferred having more emotional support from their

physicians, compared with the ratings given by less-distressed patients. Patients without recurrent or metastatic disease placed more importance on 'asking their physicians questions' than patients with recurrent or metastatic disease. Physicians should keep these results in mind when delivering bad news to Japanese cancer patients. Further study is needed to investigate other variables that were not considered in the present study and that may be associated with patients' communication style preferences. Some of these variables may include the estimated survival period and personality characteristics of the patients.

Three limitations of the present study should be noted. First, the cancer sites of the participants in the present study differed from those in the original study [18]. Therefore, the findings in the present study may have differed from those of the American study because the patients had different cancers. However, significant differences were not found between the types of cancer in the present study and the original study. The second limitation is that the study was conducted at a single teaching center specializing in cancer. Thus, the results of this study might not be representative of other cancer care settings. Nonetheless, because the consecutive sample included male and female patients with a variety of cancers, and disease stages, a wide range of ages, and different psychosocial characteristics, we believe that our results reflect the preferences of a broad range of patients. Another important limitation is that our study examined the preferences of patients at only one point in time. Thus, we cannot speculate on the stability of the measurements used in this study. Additionally, it is possible that a response shift occurred; that is, the patients' evaluations of their preferences may have changed as a result of a change in their personal standards or values or a reconceptualization of the construct [27]. Previous research has also found that patients' informational needs may change over the course of their illness and treatment [17]. Because of the cross-sectional nature of this study, we were not able to formally address this question. However, the amount of time that had elapsed since the patients received their initial diagnosis was not significantly associated with their preferences for communication.

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CORRESPONDENCE

Smaller Regional Volumes of Gray and White Matter Demonstrated in Breast Cancer Survivors Exposed to Adjuvant Chemotherapy

We read with interest the article by Inagaki and colleagues, who reported on transient structural changes in selected areas of the brain associated with cognitive dysfunction in patients with breast cancer subsequent to adjuvant chemotherapy.[1] Although their article contributes to the understanding of an important, complex phenomenon, the results should be interpreted critically concerning their clinical relevance. In their study, there were methodological limitations, which were confirmed by the authors themselves, in addition to discrepancies with regard to previously published findings.[1]

The majority of the patients studied by Inagaki et al. did not receive a recommended, standard chemotherapy regimen (mainly cyclophosphamide, methotrexate, and 5-fluorouracil regimens). In addition, significantly more patients received adjuvant endocrine treatment among those who were exposed to chemotherapy. This should be taken into account, because cognitive dysfunction also has been observed in the context of endocrine treatment.[2] Finally, cognitive impairments have been observed before the start of adjuvant treatment in patients with breast cancer,[3] which was not taken into consideration in the report by Inagaki and colleagues.

We agree with the authors that the potential impact of adjuvant chemotherapy on the cerebral structure of breast cancer patients is of major interest. In the light of the increasing survival of patients with primary, high-risk breast cancer because of adjuvant chemotherapy, the control of therapy-associated, potentially long-term, persisting, adverse effects is essential. Therefore, additional, well-designed, prospective trials should be undertaken to study structural and functional changes in the brain of breast cancer patients. These investigations should focus on patients who are receiving standard chemotherapy regimens. In addition, because of the increasing number of patients undergoing dose-dense or dose-intense adjuvant chemotherapies, these subgroups also should be evaluated systematically. Future directions should combine structural and functional imaging of the brain as well as neuropsychological assessments in a longitudinal trial, including baseline findings before the start of any systemic therapy.

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Author Reply

We appreciate the comments of Dr. Eichbaum et al. on our study. They have made some important points regarding the interpretation of the observed findings.[1]

It is important to recognize that our study was not of a longitudinal design with baseline findings before the start of the patients' adjuvant chemotherapy. In addition, several potential confounding factors, such as endocrine treatment, need to be controlled in any future studies.

Regarding the clinical relevance of the results, the regimens of adjuvant chemotherapies that were used were not those that currently are recommended as standard chemotherapies that contain anthracyclines. The breast cancer surgeries in these patients were performed between 1992 and 2001. At that time, anthracycline-containing regimes were not standard. This circumstance may limit the clinical relevance of the current findings.

Our study also did not elucidate the mechanisms responsible for the effect on brain structure or on brain and cognitive functions. Further studies in animal models and using functional neuroimaging techniques in humans are needed to elucidate these mechanisms. Such elucidations would aid in the development of intervention strategies and new medications.

Management of the long-term, adverse effects of potentially curative cancer treatments is of great importance for optimizing the quality of life of cancer survivors. Although several controversial findings have been reported, many studies have demonstrated subjective and objective cognitive impairments in cancer patients receiving chemotherapy.[2] In light of this situation, the results of the current study should provide new insights for future research aimed at improving the quality of life of cancer patients.

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Short Communication

Relationship between heart rate and emotional memory in subjects with a past history of post-traumatic stress disorder

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Abstract Considerable evidence suggests that the adrenergic system plays an important role in the biological mechanism of post-traumatic stress disorder (PTSD). In the present pilot study the association between heart rate (HR) recorded prior to slide viewing and long-term emotional memory was compared between human subjects with a past history of PTSD ($n = 6$) and healthy women controls ($n = 12$). The correlation between HR during the anticipatory period and emotional memory was significant for the PTSD group ($r = 0.93$, $P < 0.001$) but not for the control group ($r = 0.21$, NS). The adrenergic reaction appears to be associated with emotional memory, which may be strengthened in subjects with a past history of PTSD.

Key words adrenergic system, emotional memory, heart rate, intrusive recollection, PTSD.

INTRODUCTION

Prior trauma is one of the important risk factors in post-traumatic stress disorder (PTSD).[1] The mechanism of the association has not yet been directly investigated, but a past history of PTSD would be a sensitizing factor for a new traumatic event. Because the experience of a stressful event might be accompanied by epinephrine release, the adrenergic system may play an important role in the enhanced encoding of trauma-related memories of PTSD patients.[2]

A previous study demonstrated that declarative memory for an emotional event was enhanced by post-learning epinephrine infusion.[3] That study indicated that an activated adrenergic system was associated with heart rate (HR) during or after slide viewing, while the possibility that 'priming' arousal may influence the enhanced memory was suggested.[3,4]

To our knowledge, the relationship between an anticipatory arousal measured by HR and long-term memory of emotional events has not been investigated in drug-naïve human subjects. The aim of the present pilot study was to examine the relationship between enhanced emotional memory and HR activity during the anticipatory period in subjects with a past history of PTSD and healthy controls.

METHODS

Subjects were recruited by advertisements in newspapers and regional flyers and consisted of six women (mean age, 48.7 ± 7.9 years; range, 35–59 years) with a past history of PTSD (past PTSD) as determined by the Structured Clinical Interview for DSM-IV and 12 healthy women (control mean age, 50.7 ± 6.0 years; range, 38–58 years) matched for age, education, and residency. The types of trauma were as follows: diagnosis of cancer in the partner in two; partner's sudden

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Table 1. Correlation (r_s) between HR and emotional memory score

	PTSD			Control			Total		
Memory score	Phase1	Phase2	Phase3	Phase1	Phase2	Phase3	Phase1	Phase2	Phase3
Pre-HR	0.71	0.93*	0.84	−0.35	0.21	−0.05	−0.06	0.47	0.34

* $P < 0.001$.
HR, heart rate; Pre-HR, heart rate during the anticipatory period; PTSD, post-traumatic stress disorder.

death in one; and disaster, child abuse, violence by her intimate partner in one each. They were currently free from major medical illnesses and psychopathology. There was no significant difference in the postmenopausal state between past PTSD and control subjects.

On the first test day the subjects viewed an emotionally arousing short story[5,6] on a 14-in (35-cm) color monitor while seated comfortably. Prior to slide viewing, each subject was fitted with electrodes for continuous HR monitoring (Biopac MP150 recording system, Monte System, Tokyo). The stories, consisting of 11 slides, were presented as a brief narrated slide show of approximately 5 min.[5] The story was divided into three phases: phase 1 (slides 1–4), phase 2 (slides 5–8), and phase 3 (slides 9–11). Phase 1 depicted a mother taking her son to visit his father at work. In phase 2, the boy is caught in a terrible accident, which critically injures him. In phase 3 the mother was shown leaving the hospital. One week later the subjects received an unexpected memory test, 5–9 multiple-choice questions per slide.[7] Memory scores were expressed as a percentage of the maximum of each phase. The Institutional Review Board and Ethics Committee of the National Cancer Center approved this study. All of the subjects gave informed consent, and received monetary compensation (¥4000) for their participation.

The pre-HR value was obtained from HR averaged across the 20 s prior to phase 1. At that time point, a slide gave the following instructions: 'Please watch the following slides carefully.' The memory scores and HR (pre-HR, phase 1–3) were assessed with a two-way repeated measures analysis of variance (ANOVA). Any relationship between HR and memory scores was calculated with the Spearman's correlation coefficient (r_s). Significant effects were assumed at $\alpha < 0.01$ from a two-tailed test. Data were analyzed using SPSS (Windows version 12.0; SPSS, Chicago, IL, USA). One set of the control group HR data was not obtained because of a technical error.

RESULTS

The mean recall scores (±SD) for each phase for the past PTSD and control groups were, respectively, phase 1: 53.6 ± 9.3, 48.8 ± 6.9; phase 2: 56.0 ± 14.4, 54.9 ± 8.7; and phase 3: 54.5 ± 14.0, 45.2 ± 8.5; The mean HR (±SD) for each phase for the past PTSD and control groups were, respectively, pre-HR: 71.5 ± 10.1 b.p.m., 75.8 ± 20.7 b.p.m.; phase 1: 72.1 ± 9.8 b.p.m., 72.4 ± 12.7 b.p.m.; phase 2: 69.1 ± 7.7 b.p.m., 69.7 ± 8.6 b.p.m.; and phase 3: 69.6 ± 8.6 b.p.m., 76.5 ± 27.2 b.p.m. The two-way ANOVA for repeated measures revealed no significant main effects and interactions.

The correlation between HR and memory scores was calculated using only the pre-HR because of no significant HR change during the experiment. As shown in Table 1, a significant correlation was seen between the pre-HR and memory score only on phase 2 in the PTSD group. There was no significant correlation between age and memory scores in either group.

DISCUSSION

To the best of our knowledge, the present findings are the first to indicate that the association between HR during the anticipatory period and emotional memory strengthens in the subjects with a past history of PTSD. This result supports the speculation of Cahill and Alkire that priming arousal could be associated with memory consolidation.[3] Priming arousal, that is, a high pre-HR in the present study, was associated with enhanced emotional memory. Although subjects were not required to infer their own emotions, we can speculate that a heightened pre-HR would be accompanied with an emotional state (e.g. anxiety) during the anticipatory period. It was found only in the past PTSD group, but it is premature to conclude that this relationship was specific in the past PTSD subjects because of the small sample size. Acquired knowledge in this pilot study is that the association may be strengthen in the past PTSD group.

Memory scores in the present study compared with previous studies[5,8] were low on phase 2 but comparable on phase 1 and 3. Subjects in the present study were older compared with previous studies (mean age in previous studies: 27.4–34.8 years).[5,8] Therefore, the

effect of emotional arousal on memory may be differentiated in different age groups.

For HR, there was no significant change during the experiment. The slides used in the present study may not be stressful enough to change the physiological response. Furthermore, HR may not be an appropriate index of the adrenergic system for these slides.

Finally, one possible interpretation could be advanced for the result of a strong relationship between adrenergic activation and emotional memory in the past PTSD group in the present study. There would be some people who had undergone prolonged states of adrenergic activation in the past PTSD group. Orr and Roth suggested that prolonged states of adrenergic activation increased the risk for PTSD through intensified fear conditioning.[9]

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Breast Cancer in First-degree Relatives and Risk of Lung Cancer: Assessment of the Existence of Gene–Sex Interactions

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Background: Previous studies have shown the sex differences in lung cancer and the associations between estrogen-related genes and non-small cell lung cancer. In the present study, we assumed the existence of shared candidate genes that are common in lung and breast cancers, and examined whether women with a family history of breast cancer are at increased risk of lung cancer compared with men, especially adenocarcinoma, in a case-only study.
Methods: This case-only study was conducted based on the Lung Cancer Database Project at the National Cancer Center Hospital East. A total of 1566 patients with newly diagnosed primary lung cancer were consecutively recruited between 1999 and 2003. Information on their family history of cancer and smoking habit was obtained from a self-administered questionnaire. To assess an interactions between two factors, odds ratios for interaction (ORis) and 95% confidence intervals (CIs) were calculated by case-only contingency table.
Results: A statistically significant ORi was observed between a family history of breast cancer in first-degree relatives (parent and siblings, not including children) and the sex of a patient (ORi: 2.22, 95% CI: 1.02–4.81). A stratified analysis by histologic subtypes showed a statistically significant ORi only for adenocarcinoma (ORi: 3.27, 95% CI: 1.19–8.98). No other family history of cancer, such as stomach, colon and lung cancer, showed a statistically significant ORi.
Conclusion: This study suggests the possibility of gene–sex interaction in lung cancer.

Key words: lung cancer – breast cancer – shared candidate genes – gene – sex interaction

INTRODUCTION

Lung cancer is the leading cause of cancer mortality for both men and women in the world (1). However, there is a large difference in the distribution of histologic subtypes and incidence rates between men and women. Squamous cell carcinoma is the predominant histological subtype in men while adenocarcinoma is the most common in women. The different proportions between men and women might be largely attributable to a gender difference in smoking habits. However, smoking-caused lung cancer is estimated to comprise only 18% in Japanese women (2). This observation suggests that there is a crucial need to explore other contributing factors in women's lung cancer.

Estrogen and estrogen-related genes, as well as breast cancer, are speculated to be associated with lung cancer in women, as well as sex differences in lung cancer. It has been shown that both normal lung cells and non-small cell lung cancer (NSCLC) cells express estrogen receptors and show biological responses to estrogen (3). Another study has shown that NSCLC cells respond to estrogens/anti-estrogens by altering endogenous gene expression (4). A large-scale prospective cohort study in Japan has reported an association between reproductive factors, estrogen replacement therapy

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and the risk of lung cancer (5). In addition, a recent case-control study in Japan has suggested a positive association between endogenous estrogenic exposure and NSCLC with epidermal growth factor receptor (EGFR) mutation (6).

In women, both lung and breast cancer incidence rates are still increasing. A previous study indicated that a positive family history of early onset lung cancer increased the breast cancer risk among first-degree relatives (7). A maternal history of breast cancer increased the risk of lung cancer in non-smokers (8). Based on prior evidence, estrogen-related genes might be the most plausible candidates linking breast and lung cancers. However, it is still not clear whether these genetic factors contribute to the sex differences in lung cancer.

Therefore, we hypothesized that the fact that adenocarcinoma is dominant among women due to the biological interaction between being women and having estrogen-related genotype susceptible to the breast cancer. In order to explore whether inherited genes that link lung and breast cancer susceptibilities contribute to the sex differences in lung cancer, we assumed that a family history of breast cancer is an indicator of genetic factors in the present study, though family history may reflect both genetic and shared environmental factors. We examined whether women with a family history of breast cancer are at increased risk of lung cancer compared with men, especially adenocarcinoma in a case-only study.

METHODS

Study Design

The data from the Lung Cancer Database Project at the National Cancer Center Hospital East were used in the present study (9). Participants of the database study completed the questionnaires during the waiting period prior to admission and the questionnaires were collected after the admission. The database included details about physical size, life style factors (smoking, diet), and medical information (histological subtypes and family history) obtained from both patients' medical charts and self-reported questionnaires. Blood and DNA samples were also available for the study. All patients gave their written informed consent before participating in the database study. This study was approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center.

Participants

All participants enrolled in this database study were patients with newly diagnosed primary lung cancer who were admitted to the Thoracic Oncology Division of the National Cancer Center Hospital East, Japan. The following criteria were applied for inclusion: patients were informed of their lung cancer diagnosis; the lung cancer diagnosis was confirmed by histological examination; patients were capable of completing the questionnaires; patients had an absence of cognitive impairment; patients had the ability to provide written informed consent; and no problems were foreseen regarding the patient's participation. In the present study, data from 1566 patients, collected during 1999–2003, with four major histologic subtypes (squamous cell carcinoma, adenocarcinoma, large cell carcinoma and small cell carcinoma) were submitted for analysis.

Statistical Analyses

Differences in the characteristics of patients with lung cancer were compared between men and women by the Student's t-test for continuous variables (age and number of siblings) and the χ^2 test for categorical variables (histology and smoking situation). Smoking situation was defined by pack-years, which is calculated by the multiplication of the number of packs of cigarettes smoked per day by the number of years smoked (never smokers, pack-years <20, 20–40 and >40).

The case-only study can provide increased statistical efficacy over case-control studies to detect gene–environment interactions (10–12), presenting the interaction parameter as an odds ratio for interaction (ORi). Under the assumption of independence between a family history of breast cancer and a patient's sex, ORis and their 95% confidence intervals (95% CIs) were calculated to estimate the departure from multiplicativity using multiple logistic regression models. The biases arising from non-independence between two variables can be removed using standard statistical multivariable techniques (13). ORis were adjusted for the potential confounding variables age (<65 or ≥ 65 years) and smoking situation. Stratified analyses were conducted by histological subtypes to further investigate the heterogeneity of results in different histological subtypes.

All statistical tests were two-sided and a P-value <0.05 was considered statistically significant. Participants with missing information for any of the variables in a regression model were omitted from the analyses. Data analyses were conducted using SAS statistical software (version 9.1 for Windows, SAS Institute, Inc., Cary, NC).

RESULTS

The patients' characteristics stratified by sex are shown in Table 1. The mean age at diagnosis was 64.9 ± 9.0 years for men and 63.7 ± 9.4 years for women ($P = 0.03$). There was no significant difference by sex regarding the number of siblings or family history of stomach, colon and lung cancer in first-degree relatives, but a significant difference was identified in the family history of breast cancer. Of the four major histologic subtypes, adenocarcinoma was the most frequent histologic subtype, especially predominant among women. Squamous cell carcinoma was the second most frequent histologic subtype, constituting about 30% of male lung cancer. The proportion of never smokers was approximately 14 times higher in women than in men. Similarly,

Table 1. Comparisons of baseline characteristics between males and females

Baseline characteristics*	Male ($n = 1116$)	Female ($n = 450$)	P-values†
Age at diagnosis (years)‡	64.9 ± 9.0	63.7 ± 9.4	0.03
Number of siblings‡	5.0 ± 2.3	5.0 ± 2.1	0.50
Family history of cancer in first-degree relatives			
Stomach cancer, yes	208 (18.6)	82 (18.2)	0.85
Colon cancer, yes	89 (8.0)	41 (9.1)	0.46
Lung cancer, yes	134 (12.0)	63 (14.0)	0.28
Breast cancer, yes	35 (3.1)	27 (6.0)	<0.01
Histology of lung cancer			
Adenocarcinoma	549 (49.2)	356 (79.1)	<0.01
Squamous cell	303 (27.2)	38 (8.4)	
Large cell	114 (10.2)	24 (5.3)	
Small cell	150 (13.4)	32 (7.1)	
Smoking situation			
Never smokers	53 (5.0)	298 (68.3)	<0.01
Pack-years <20	78 (7.3)	48 (11.0)	
20–40	244 (22.8)	47 (10.8)	
>40	695 (65.0)	43 (9.9)	

*Total number is different due to missing information.
†Student's t-test or χ^2 test.
‡Mean ± SD.

smoking dose has also been observed to be higher in male smokers than female smokers.

Table 2 shows the interaction between a family history of breast cancer and the sex of a patient with lung cancer calculated as ORi. The ORi for the female patients who had a parent with breast cancer was significantly high after adjustment for age and smoking situation (ORi: 6.17, 95% CI: 1.36–27.98). However, no significant interaction was observed in the analysis of siblings (ORi: 1.51, 95% CI: 0.61–3.73). The ORi for the female patients who had a family history of breast cancer in first-degree relatives (parent and siblings, not including children) was approximately two times higher (ORi: 2.22, 95% CI: 1.02–4.81). Further adjustment for the number of sisters, educational background, or fruit and vegetable intake did not substantially affect the results (data not shown). In order to confirm site specificity for this interaction, we calculated ORis for family history of stomach, colon and lung cancer in first-degree relatives and the sex of patients, but none of these ORi showed statistical significance: ORi: 0.89, 95% CI: 0.60–1.34 for stomach cancer; ORi: 0.75, 95% CI: 0.44–1.28 for colon cancer; and ORi: 1.29, 95% CI: 0.81–2.04 for lung cancer (data not shown in Table 2).

Table 3 further represents the different ORis in each histologic subtype. After adjustment for possible confounding factors, only adenocarcinoma showed a statistically significant difference for interaction (ORi: 3.27, 95% CI: 1.19–8.98).

Table 2. Family history of breast cancer and patient's sex

Family history of breast cancer	No. of patients		ORi (95% CI)*	ORi (95% CI)†
	Male	Female		
First-degree relatives				
No	1081	423	1.0	1.0
Yes	35	27	1.99 (1.19–3.34)	2.22 (1.02–4.81)
Parent				
No	1111	442	1.0	1.0
Yes	5	8	3.90 (1.27–12.01)	6.17 (1.36–27.98)
Siblings				
No	1086	431	1.0	1.0
Yes	30	19	1.63 (0.91–2.93)	1.51 (0.61–3.73)

ORi, odds ratio for interaction; CI, confidence interval.
*Adjusted for age.
†Adjusted for age and smoking situation.

DISCUSSION

Previous studies revealed the sex differences in lung cancer and associations between estrogen, estrogen-related genes and NSCLC. We now show that female patients who have a family history of breast cancer in first-degree relatives are at a greater risk of lung cancer compared with male patients, especially adenocarcinoma. The results of this study indicate the possible existence of a gene–sex interaction, which may be associated with sex differences in lung cancer.

Accumulated evidences suggest that there are genetic contributions in lung cancer susceptibility, although the environment has predominance over genes (14,15). Although a previous population-based case-control study had already shown the association between a family history of breast cancer and lung cancer risk (8), most inherited genetic factors make a minor contribution to cancer susceptibility. Genetic effects can be substantially modified by interactions with the environment. The main finding of this case-only study is that inherited genes that link lung and breast cancer susceptibilities may be associated with the increased risk in women's adenocarcinoma.

Estrogen-related genes are most plausible candidate genes that link breast cancer and adenocarcinoma of the lung. Based on the results of this study, we suggest that estrogen-related genes play an important role in sex differences in lung cancer such as histologic distributions and prognosis (16). A recent study has shown that women with estrogen receptor (ER) β-positive tumors had a 73% ($P = 0.1$) increase in mortality, whereas men with ER β-positive tumors had a 55% ($P = 0.04$) reduction in mortality

Table 3. Breast cancer in first-degree relatives and patient's sex stratified by lung cancer histology

	No. of patients		ORi (95% CI)*	ORi (95% CI)†
	Male	Female		
Adenocarcinoma				
No	528	333	1.0	1.0
Yes	21	23	1.75 (0.95–3.21)	3.27 (1.19–8.98)
Squamous cell				
No	297	36	1.0	1.0
Yes	6	2	2.90 (0.56–14.95)	1.31 (0.12–14.36)
Large cell				
No	111	23	1.0	1.0
Yes	3	1	1.70 (0.17–17.46)	1.86 (0.13–26.03)
Small cell				
No	145	31	1.0	1.0
Yes	5	1	0.92 (0.10–8.16)	0.74 (0.06–8.86)

ORi, odds ratio for interaction; CI, confidence interval.
*Adjusted for age.
†Adjusted for age and smoking situation.

compared with those with ER β-negative tumors (17). Combined targeting of the ER and the EGFR in NSCLC shows enhanced antiproliferative effects, suggesting an interaction between the ER and the EGFR pathways (18).

The rapid progress in genome science has enabled us to perform genome-wide association studies. A genome-wide scan of women's adenocarcinoma of the lung with and without a family history of breast cancer is likely to detect shared susceptible genes between lung and breast cancers, merging new genome research with traditional epidemiological studies. Lung and breast cancers are serious concerns for women today. Identification of shared candidate genes will contribute to an understanding of the genetic association with sex difference in lung cancer, the development of new effective therapeutics treatments, and better targeting of high risk groups, especially women more susceptible to adenocarcinoma of the lung.

Four major limitations must be considered when interpreting the present results. First, this study does not consider the effect of shared environmental factors. Lifestyle factors, such as diet and smoking, are often shared by family members. There remains some possibility that the results of this study may reflect genetic factors, shared environmental factors, or both. However, it has been shown that most familial cases of lung cancer cannot be attributed to shared smoking habits (19). In the present study, adenocarcinoma showed an increased ORi while squamous cell carcinoma showed a decreased ORi after adjustment for the smoking situation. At the least, bias arising from different smoking situations seems to be properly adjusted. Given that further adjustment did not substantially affect the results and that we confirmed site specificity of the observed interaction, our findings are unlikely to be influenced by shared environmental factors.

The second limitation, which is critically important in any case-only study, is the validity of the independence assumption. Women may be more likely than men to recall a family history of breast cancer. While the independence between two variables cannot be verified without control subjects, it may be tenable in this study because only adenocarcinoma shows an increased ORi. If recall bias existed, increased ORis would be observed in all histologic subtypes.

The third limitation is the validity of data on the family history of cancer. An evidence-based analysis showed that patient-reported family cancer histories for first-degree relatives were accurate and valuable for breast and colon cancer risk assessments (20). This might not be directly applicable to our study, however, given that Japanese physicians historically have tended not to disclose cancer diagnoses to their patients (21). If inaccurate reports were collected in the present study, the subsequent misclasssification might tend to have caused a null result. The significant ORis, however, were unlikely to have been affected by such misclassification.

We found that women with a family history of breast cancer in first-degree relatives were at increased risk of adenocarcinoma of the lung compared with men. This finding provides an interesting insight into sex differences in lung cancer and may hint at an explanation for sex-related biological differences. It should be interpreted cautiously, however, because of the small number of subjects in the stratified analysis by histologic subtype, which is indeed a fourth limitation. Thus, a full understanding of the relationship between genetic factors and sex differences in lung cancer will require not only further epidemiological confirmation but also more genetic and mechanistic studies.

Allowing for these limitations, this study showed that women with a family history of breast cancer are at an increased risk of adenocarcinoma of the lung compared with men, which might imply a possible gene–sex interaction in lung cancer.

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Conflict of interest statement
None declared.

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Conclusion: This study suggests the possibility of gene–sex interaction in lung cancer.

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INTRODUCTION

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Statistical Analyses

Differences in the characteristics of patients with lung cancer were compared between men and women by the Student's *t*-test for continuous variables (age and number of siblings) and the χ^2 test for categorical variables (histology and smoking situation). Smoking situation was defined by pack-years, which is calculated by the multiplication of the number of packs of cigarettes smoked per day by the number of years smoked (never smokers, pack-years <20, 20–40 and >40).

The case-only study can provide increased statistical efficacy over case-control studies to detect gene–environment interactions (10–12), presenting the interaction parameter as an odds ratio for interaction (ORi). Under the assumption of independence between a family history of breast cancer and a patient's sex, ORis and their 95% confidence intervals (95% CIs) were calculated to estimate the departure from multiplicativity using multiple logistic regression models. The biases arising from non-independence between two variables can be removed using standard statistical multivariable techniques (13). ORis were adjusted for the potential confounding variables age (<65 or ≥ 65 years) and smoking situation. Stratified analyses were conducted by histological subtypes to further investigate the heterogeneity of results in different histological subtypes.

All statistical tests were two-sided and a P-value <0.05 was considered statistically significant. Participants with missing information for any of the variables in a regression model were omitted from the analyses. Data analyses were conducted using SAS statistical software (version 9.1 for Windows, SAS Institute, Inc., Cary, NC).

RESULTS

The patients' characteristics stratified by sex are shown in Table 1. The mean age at diagnosis was 64.9 ± 9.0 years for men and 63.7 ± 9.4 years for women ($P = 0.03$). There was no significant difference by sex regarding the number of siblings or family history of stomach, colon and lung cancer in first-degree relatives, but a significant difference was identified in the family history of breast cancer. Of the four major histologic subtypes, adenocarcinoma was the most frequent histologic subtype, especially predominant among women. Squamous cell carcinoma was the second most frequent histologic subtype, constituting about 30% of male lung cancer. The proportion of never smokers was approximately 14 times higher in women than in men. Similarly,

Table 1. Comparisons of baseline characteristics between males and females

Baseline characteristics*	Male ($n = 1116$)	Female ($n = 450$)	P-values†
Age at diagnosis (years)‡	64.9 ± 9.0	63.7 ± 9.4	0.03
Number of siblings‡	5.0 ± 2.3	5.0 ± 2.1	0.50
Family history of cancer in first-degree relatives			
Stomach cancer, yes	208 (18.6)	82 (18.2)	0.85
Colon cancer, yes	89 (8.0)	41 (9.1)	0.46
Lung cancer, yes	134 (12.0)	63 (14.0)	0.28
Breast cancer, yes	35 (3.1)	27 (6.0)	<0.01
Histology of lung cancer			
Adenocarcinoma	549 (49.2)	356 (79.1)	<0.01
Squamous cell	303 (27.2)	38 (8.4)	
Large cell	114 (10.2)	24 (5.3)	
Small cell	150 (13.4)	32 (7.1)	
Smoking situation			
Never smokers	53 (5.0)	298 (68.3)	<0.01
Pack-years <20	78 (7.3)	48 (11.0)	
20–40	244 (22.8)	47 (10.8)	
>40	695 (65.0)	43 (9.9)	

*Total number is different due to missing information.
†Student's t-test or χ^2 test.
‡Mean ± SD.

smoking dose has also been observed to be higher in male smokers than female smokers.

Table 2 shows the interaction between a family history of breast cancer and the sex of a patient with lung cancer calculated as ORi. The ORi for the female patients who had a parent with breast cancer was significantly high after adjustment for age and smoking situation (ORi: 6.17, 95% CI: 1.36–27.98). However, no significant interaction was observed in the analysis of siblings (ORi: 1.51, 95% CI: 0.61–3.73). The ORi for the female patients who had a family history of breast cancer in first-degree relatives (parent and siblings, not including children) was approximately two times higher (ORi: 2.22, 95% CI: 1.02–4.81). Further adjustment for the number of sisters, educational background, or fruit and vegetable intake did not substantially affect the results (data not shown). In order to confirm site specificity for this interaction, we calculated ORis for family history of stomach, colon and lung cancer in first-degree relatives and the sex of patients, but none of these ORi showed statistical significance: ORi: 0.89, 95% CI: 0.60–1.34 for stomach cancer; ORi: 0.75, 95% CI: 0.44–1.28 for colon cancer; and ORi: 1.29, 95% CI: 0.81–2.04 for lung cancer (data not shown in Table 2).

Table 3 further represents the different ORis in each histologic subtype. After adjustment for possible confounding factors, only adenocarcinoma showed a statistically significant difference for interaction (ORi: 3.27, 95% CI: 1.19–8.98).

Table 2. Family history of breast cancer and patient's sex

Family history of breast cancer	No. of patients		ORi (95% CI)*	ORi (95% CI)†
	Male	Female		
First-degree relatives				
No	1081	423	1.0	1.0
Yes	35	27	1.99 (1.19–3.34)	2.22 (1.02–4.81)
Parent				
No	1111	442	1.0	1.0
Yes	5	8	3.90 (1.27–12.01)	6.17 (1.36–27.98)
Siblings				
No	1086	431	1.0	1.0
Yes	30	19	1.63 (0.91–2.93)	1.51 (0.61–3.73)

ORi, odds ratio for interaction; CI, confidence interval.
*Adjusted for age.
†Adjusted for age and smoking situation.

DISCUSSION

Previous studies revealed the sex differences in lung cancer and associations between estrogen, estrogen-related genes and NSCLC. We now show that female patients who have a family history of breast cancer in first-degree relatives are at a greater risk of lung cancer compared with male patients, especially adenocarcinoma. The results of this study indicate the possible existence of a gene–sex interaction, which may be associated with sex differences in lung cancer.

Accumulated evidences suggest that there are genetic contributions in lung cancer susceptibility, although the environment has predominance over genes (14,15). Although a previous population-based case-control study had already shown the association between a family history of breast cancer and lung cancer risk (8), most inherited genetic factors make a minor contribution to cancer susceptibility. Genetic effects can be substantially modified by interactions with the environment. The main finding of this case-only study is that inherited genes that link lung and breast cancer susceptibilities may be associated with the increased risk in women's adenocarcinoma.

Estrogen-related genes are most plausible candidate genes that link breast cancer and adenocarcinoma of the lung. Based on the results of this study, we suggest that estrogen-related genes play an important role in sex differences in lung cancer such as histologic distributions and prognosis (16). A recent study has shown that women with estrogen receptor (ER) β-positive tumors had a 73% ($P = 0.1$) increase in mortality, whereas men with ER β-positive tumors had a 55% ($P = 0.04$) reduction in mortality

Table 3. Breast cancer in first-degree relatives and patient's sex stratified by lung cancer histology

	No. of patients		ORi (95% CI)*	ORi (95% CI)†
	Male	Female		
Adenocarcinoma				
No	528	333	1.0	1.0
Yes	21	23	1.75 (0.95–3.21)	3.27 (1.19–8.98)
Squamous cell				
No	297	36	1.0	1.0
Yes	6	2	2.90 (0.56–14.95)	1.31 (0.12–14.36)
Large cell				
No	111	23	1.0	1.0
Yes	3	1	1.70 (0.17–17.46)	1.86 (0.13–26.03)
Small cell				
No	145	31	1.0	1.0
Yes	5	1	0.92 (0.10–8.16)	0.74 (0.06–8.86)

ORi, odds ratio for interaction; CI, confidence interval.
*Adjusted for age.
†Adjusted for age and smoking situation.

compared with those with ER β-negative tumors (17). Combined targeting of the ER and the EGFR in NSCLC shows enhanced antiproliferative effects, suggesting an interaction between the ER and the EGFR pathways (18).

The rapid progress in genome science has enabled us to perform genome-wide association studies. A genome-wide scan of women's adenocarcinoma of the lung with and without a family history of breast cancer is likely to detect shared susceptible genes between lung and breast cancers, merging new genome research with traditional epidemiological studies. Lung and breast cancers are serious concerns for women today. Identification of shared candidate genes will contribute to an understanding of the genetic association with sex difference in lung cancer, the development of new effective therapeutics treatments, and better targeting of high risk groups, especially women more susceptible to adenocarcinoma of the lung.

Four major limitations must be considered when interpreting the present results. First, this study does not consider the effect of shared environmental factors. Lifestyle factors, such as diet and smoking, are often shared by family members. There remains some possibility that the results of this study may reflect genetic factors, shared environmental factors, or both. However, it has been shown that most familial cases of lung cancer cannot be attributed to shared smoking habits (19). In the present study, adenocarcinoma showed an increased ORi while squamous cell carcinoma showed a decreased ORi after adjustment for the smoking situation. At the least, bias arising from different smoking situations seems to be properly adjusted. Given that further adjustment did not substantially affect the results and that we confirmed site specificity of the observed interaction, our findings are unlikely to be influenced by shared environmental factors.

The second limitation, which is critically important in any case-only study, is the validity of the independence assumption. Women may be more likely than men to recall a family history of breast cancer. While the independence between two variables cannot be verified without control subjects, it may be tenable in this study because only adenocarcinoma shows an increased ORi. If recall bias existed, increased ORis would be observed in all histologic subtypes.

The third limitation is the validity of data on the family history of cancer. An evidence-based analysis showed that patient-reported family cancer histories for first-degree relatives were accurate and valuable for breast and colon cancer risk assessments (20). This might not be directly applicable to our study, however, given that Japanese physicians historically have tended not to disclose cancer diagnoses to their patients (21). If inaccurate reports were collected in the present study, the subsequent misclasssification might tend to have caused a null result. The significant ORis, however, were unlikely to have been affected by such misclassification.

We found that women with a family history of breast cancer in first-degree relatives were at increased risk of adenocarcinoma of the lung compared with men. This finding provides an interesting insight into sex differences in lung cancer and may hint at an explanation for sex-related biological differences. It should be interpreted cautiously, however, because of the small number of subjects in the stratified analysis by histologic subtype, which is indeed a fourth limitation. Thus, a full understanding of the relationship between genetic factors and sex differences in lung cancer will require not only further epidemiological confirmation but also more genetic and mechanistic studies.

Allowing for these limitations, this study showed that women with a family history of breast cancer are at an increased risk of adenocarcinoma of the lung compared with men, which might imply a possible gene–sex interaction in lung cancer.

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Conflict of interest statement

None declared.

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