Table 2 • Health-Related Quality of Life (HRQOL) in Survivors of Pediatric Brain Tumors (N = 104)

	Mean	SD	Q_L	Median	Q_H	Cronbach's α Coefficient
QLQ (n = 51)						
Physical functioning	83.8	21.6	80.0	86.7	100	.88
Role functioning	84.0	21.6	66.7	83.3	100	.73
Emotional functioning	82.7	17.0	75.0	83.3	100	.73
Cognitive functioning	79.4	25.7	83.3	83.3	100	.73
Social functioning	82.7	22.4	66.7	100	100	.69
Fatigue[a]	26.6	20.1	11.1	22.2	33.3	.67
Insomnia[a]	13.7	20.2	0	0	33.3	NA
Communication deficit[a]	19.2	27.2	0	11.1	33.3	.92
Drowsiness[a]	32.0	29.8	0	33.3	33.3	NA
PedsQL (n = 53)						
Child report						
Physical functioning	90.7	15.0	85.9	100	100	.85
Emotional functioning	86.0	15.9	75.0	90.0	100	.71
Social functioning[b]	85.4	23.2	80.0	98.0	100	.91
School functioning	83.6	16.2	75.0	90.0	95.0	.67
Cognitive problems	77.7	21.8	62.5	82.1	96.4	.89
Movement and balance	89.0	20.3	87.5	100	100	.83
Perceived physical appearance[b]	83.2	22.1	75.0	91.7	100	.69
Communication[b]	84.3	20.5	75.0	91.7	100	.82
Parent report						
Physical functioning	92.0	14.1	90.6	100	100	.85
Emotional functioning	92.2	9.9	90.0	95.0	100	.56
Social functioning	84.4	22.3	75.0	100	100	.92
School functioning	85.3	16.0	75.0	90.0	100	.65
Cognitive problems	79.0	25.4	64.3	92.9	100	.95
Movement and balance	89.2	22.4	87.5	100	100	.94
Perceived physical appearance	84.4	20.9	75.0	91.7	100	.86
Communication	78.5	24.1	66.7	83.3	100	.56

All scales ranged from 0 to 100. In most scales, a higher score indicates better HRQOL.
Abbreviations: NA, not applicable because scales contained 1 item; PedsQL, Pediatric Quality of Life Inventory: Q_H, higher quartile; Q_L, lower quartile; QLQ, Quality of Life Questionnaire.
[a]Lower scores indicate better HRQOL.
[b]n = 52 because of partially missing response.

reported by the previous studies, indicating the clinical significance of the result of this study. Nurses and other health professionals need to recognize the survivors' important aspects of HRQOL influenced by each late effect.

Our findings extend previous research indicating a link between late effects and HRQOL in survivors of pediatric cancer 18 years or older and support the findings of Blaauwbroek et al,[42] who showed that neurological late effects deteriorated physical aspects of HRQOL. Seizure adversely affects social functioning in survivors 18 years or older, and these survivors also report increased drowsiness. Consequently, older survivors may need additional support to promote social functioning by finding ways to manage seizures, drowsiness, and communication deficits. For example, drowsiness may be an adverse effect of antiseizure drugs, which could be alleviated by supervised management of drug therapy.[43] Seizure symptoms and drowsiness may be controlled by drugs and timing medication, study, and work to avoid overlap of study/work time and drowsiness. When survivors are employed as nonclerical workers with irregular or long hours, or both, it is imperative to ensure that they are able to take antiseizure drugs at a regularly scheduled time.

However, study or workplaces may not be able to respond adequately to the survivor's need to manage the combined effects of seizure and induced drowsiness. In addition, we found that survivors experiencing seizures may also report communication deficits. In such circumstances, physicians and nurses can explain to the survivor how to manage seizures and drowsiness and advise the survivor about ways to explain these symptoms to his/her study/workplace. Nurses may also assist in directly explaining, in writing, these late effects to a survivor's school or workplace to ensure that the survivor's communication deficit does not hinder the management of the late effects. Before doing so, the nurse would need to carefully consult with the survivor and family regarding the nature of the information to be disclosed to others. The explanation should be based upon the age and maturity of the survivor as well as the survivor's ability to communicate about deficits. Communication between nurses and school or workplace needs to be shared with the survivors and their families, and this sharing may enhance survivors' ability to explain their needs to others.

Although Blaauwbroek et al[42] did not find a significant link between ocular/visual impairment and any aspect of HRQOL among survivors of pediatric cancer, our results demonstrate that

Table 3 • Impact of Late Effects on Health-Related Quality of Life (HRQOL) in Survivors of Pediatric Brain Tumors 18 Years or Older (N = 51)

		Physical Functioning[a]	Role Functioning[a]	Emotional Functioning[a]	Cognitive Functioning[a]	Social Functioning[a]	Fatigue[b]	Insomnia[b]	Communication Deficit[b]	Drowsiness[b]
Motility disturbance of limb(s)	Impact	−16.3[c]	−7.0	5.9	−15.0	3.7	−5.5	−0.3	2.4	−7.3
	P	.006	.301	.235	.043	.600	.308	.963	.768	.442
Seizure	Impact	−43.2[c]	−6.3	−4.2	−3.4	−20.6[c]	−7.9	−6.2	28.9[c]	38.7[c]
	P	.000	.312	.297	.619	.001	.158	.177	.000	.000
Ocular/visual impairment	Impact	−29.6[c]	−12.5	−12.3[c]	−7.7	−18.9[c]	5.9	−7.4	16.6	19.2
	P	.000	.022	.003	.233	.001	.315	.127	.028	.027
Endocrine abnormality	Impact	−10.1	−11.1	1.5	6.7	−3.4	12.9	18.7[c]	−2.5	6.3
	P	.088	.044	.741	.350	.561	.020	.001	.727	.453
Higher brain dysfunction	Impact	−18.4	−27.4[c]	−5.4	−14.2	−4.6	15.2[c]	22.3[c]	26.4[c]	2.6
	P	.013	.000	.240	.030	.410	.004	.000	.001	.717

Impact represents the extent to which each late effect influences the scores of each aspect of HRQOL, adjusted for possible confounders: age, gender, age at diagnosis, hydrocephalus at diagnosis, tumor pathology, tumor location, neurosurgery, radiation treatment, chemotherapy, tumor recurrence, and time since completion of antitumor therapy.

[a]A negative impact indicates that the late effect deteriorates the aspect of HRQOL; a positive impact indicates improvement.

[b]A positive impact indicates that the late effect deteriorates the aspects of HRQOL; a negative impact indicates improvement.

[c]$P < .01$.

Table 4 • Impact of Late Effects on Health-Related Quality of Life (HRQOL) in Survivors of Pediatric Brain Tumors Aged 12 to 17 Years (N = 53)

			Physical Functioning	Emotional Functioning	Social Functioning	School Functioning[a]	Cognitive Problems	Movement and Balance	Perceived Physical Appearance[a]	Communication[a]
Motility disturbance of limb(s)	Child report	Impact	−11.0[b]	−2.6	−3.8	3.9	−0.8	−21.6[b]	−27.0[b]	16.8[b]
		P	.008	.397	.463	.269	.887	.000	.000	.000
	Parent report	Impact	−14.4[b]	−1.9	10.5	5.2	0.0	−38.7[b]	−0.3	14.2[b]
		P	.000	.347	.023	.121	.995	.000	.942	.006
Seizure	Child report	Impact	9.1	10.0	12.9	−1.5	−5.7	6.3	−1.8	2.2
		P	.043	.038	.066	.761	.419	.309	.791	.735
	Parent report	Impact	7.0	−4.8	13.7	0.9	3.7	12.1	4.1	−4.0
		P	.111	.175	.043	.847	.640	.076	.537	.598
Ocular/visual impairment	Child report	Impact	−7.8	−5.6	5.3	6.0	6.2	11.0[b]	−15.5[b]	−15.7[b]
		P	.019	.073	.224	.053	.131	.003	.000	.002
	Parent report	Impact	−16.7[b]	3.2	11.1	4.5	18.4[b]	6.3	−38.8[b]	−6.1
		P	.000	.142	.010	.100	.000	.132	.000	.434
Endocrine abnormality	Child report	Impact	0.1	3.8	5.8	−6.6	−11.2	−8.3	−5.3	−11.1
		P	.983	.458	.406	.114	.065	.117	.402	.057
	Parent report	Impact	−5.4	0.4	−9.5	−10.9	−10.8	−7.0	−4.9	−10.4
		P	.142	.878	.121	.005	.109	.215	.393	.126
Higher brain dysfunction	Child report	Impact	−7.8	−1.8	−16.2	−2.1	−13.4	0.9	−0.2	1.2
		P	.067	.687	.029	.648	.033	.885	.979	.825
	Parent report	Impact	−4.7	−6.5	−12.2	−5.9	−11.6	−12.3	4.3	−10.7
		P	.255	.023	.050	.216	.117	.059	.475	.151

Impact represents the extent to which each late effect influences the score of each aspect of HRQOL, adjusted for possible confounders: age, gender, age at diagnosis, hydrocephalus at diagnosis, tumor pathology, tumor location, neurosurgery, radiation treatment, chemotherapy, tumor recurrence, and time since completion of antitumor therapy. A negative impact indicates that the late effect deteriorates the aspect of HRQOL, and a positive impact indicates improvement.

[a] $n = 52$ because a few responses were missing.

[b] $P < .01$ estimated impact on child/parent reporting score after $P < .01$ by multivariate analysis of variance.

ocular/visual impairment deteriorated physical, emotional, and social aspects of HRQOL. This deterioration is similar to adult-onset eye disease, which sometimes causes depression, feelings of frustration, helplessness, anxiety, or anger.[44] Ocular/visual impairment arising from brain tumor differs from ocular/visual impairment arising from other cancers and comprises double vision (17%), blindness (13%), or cataracts (3%).[23] Furthermore, to accommodate visually impaired survivors, we allowed their parents to help them understand and answer the questionnaire. Our study thus identifies special needs for physical, emotional, and social support in survivors with ocular/visual impairment arising from brain tumors.

Younger survivors (aged 12–17 years) with ocular/visual impairment perceived deterioration in their physical appearance and communication but reported relatively few problems in their movement and balance and cognitive functioning. In a previous study of intelligence in children with visual impairment, some children with absolute blindness scored higher in tests than did those with only impaired vision.[45] Taken together, these findings suggest that younger survivors' motor skills and cognitive ability may have developed to compensate for ocular/visual impairment. In addition to vision assistance (eg, enlarged documents or text-to-speech software), it may be important for survivors with ocular/visual impairment to take advantage of their nonvisual senses. Traditionally, in Japan, people with visual impairment are considered to possess enhanced abilities as massage professional, finger pressure therapists, acupuncturists, and as providers of moxa cautery therapy, with visually impaired survivors being said to possess a heightened ability to sense the meridian system and acupuncture points.

Survivors with ocular/visual impairment often experience changes in physical appearance when prescribed glasses or from strabismus. A survivor's physical appearance may also change because of motility disturbance, facial palsy, or hair loss. Perception of physical appearance of survivors who cannot see their own appearance may be easily swayed by their acquaintances. It is important for amelioration of perceived physical appearance of survivors with ocular/visual impairment that nurses, other health professionals, and everyone around the survivors promote supportive behavior.

In contrast to Blaauwbroek et al,[42] we found endocrine abnormalities causing insomnia that led to the deterioration of HRQOL. Because endocrine abnormality is a frequent late effect among survivors,[24] support programs should assess sleep patterns. Although endocrine abnormalities may cause physical and developmental problems, our data found that the abnormalities did not influence other aspects of HRQOL, such as perceived physical appearance or emotional instability. This finding may have arisen because of the fact that we amalgamated endocrine abnormalities (eg, somatotropin, corticosteroid, and vasopressin), thereby blurring the specific impact of each endocrine abnormality. Insomnia was detected as a common issue for survivors with endocrine abnormalities and may coexist with the side effects of corticosteroid or thyroxine therapy and reduction of melatonin secreted from the corpus pineal, a site of predilection for germinoma. Assessment and care for hidden sleep problems should be a support issue for survivors of brain tumors.

Several aspects of HRQOL deteriorated among survivors 18 years or older—but not in younger children—with increased brain dysfunction. Impairment in HRQOL may not become evident until survivors reach the age of pursuing higher education or working age. Furthermore, younger children may be protected at home and during their years of compulsory education. Suzuki[46] noted that adult patients with higher brain dysfunction were coddled by their family, possibly camouflaging functional difficulties. Among children with brain tumors, any possible cognitive difficulties might have been masked by an overprotective family, regardless of whether this was indeed beneficial for their child. Nurses and other health professionals should therefore assess a child's brain dysfunction during their daily lives as well as under standard test conditions, particularly before the child seeks further education or attempts to join the workforce. On the basis of the results of the assessment, nurses could provide support tools and advices (eg, the way to use memory notes) suited for a social situation. We suggest that this testing begin before the survivor experiences any difficulty.

In addition, any disabilities secondary to the higher brain dysfunction, such as intellectual disability, may develop over time. Findings in other studies have indicated that a survivor's intelligence quotient (IQ) may decline gradually.[47] In a strict sense, a survivor's intelligence does increase as the child develops, but not as much as that of children who have never experienced cancer. In effect, the relative IQ of survivors declines. Higher brain dysfunction does not necessarily cause immediate cognitive difficulty. School officials now provide educational support to survivors who request assistance for their cognitive deficit. Furthermore, school officials may have to provide this support for intellectual and social development, even if the survivors do not perceive that they suffer from a cognitive deficit. To initiate support for these children, nurses may have to provide the school officials with a medical assessment that describes in detail the nature of the brain dysfunction and any associated physical symptoms that would hinder the survivor's education.

Several limitations to the present study warrant mention. First, we cannot conclusively confirm that higher brain dysfunction influences HRQOL through IQ because we lack data on the current IQ of participants. Although we planned to obtain IQ for participants from attending physicians, as declining IQ is a strong predictor of poor HRQOL,[20] few departments routinely measure patient IQ. Second, our data were restricted to survivors who visited clinics for follow-up. In Japan, follow-up programs are implemented by attendance at outpatient departments or clinics. Third, we purposefully did not recruit survivors from facilities for the disabled or in hospitals (where life-threatening late effects are treated) because we wished to focus on identifying factors important to a long-term follow-up program. We also made sure to recruit participants from hospitals and clinics that we consider leading centers for treatment and follow-up of patients with pediatric brain tumors. Survivors at these facilities therefore likely receive better support than do those in facilities with fewer patients. As such, the results of this study may not be applicable to all survivors. Fourth, sample size restrictions (primarily the difficulty in recruiting survivors of childhood brain tumors) limited analysis to a subset of late effects. As such, data

on ocular/visual impairment, higher brain dysfunction, and endocrine abnormalities should be interpreted cautiously. Similarly, sample size restricted analysis of multimodal treatments and disease. Disease, treatment, and other factors vary according to differing modalities of neurocognitive and endocrine dysfunction,[48,49] and these differences influence the likelihood of a late effect influencing HRQOL.

However, despite these limitations, this study does clarify the relationship between late effects and HRQOL among survivors of pediatric brain tumors regardless of disease and treatment. We consider our method of weighting data using the inverse of the propensity score to be a study strength, as this enables adjustment for possible confounding effects from disease and treatment background despite the small sample size. Future research should endeavor to identify which factors mediate, buffer, or facilitate the influence of HRQOL under a specific conceptual framework.

Conclusion

Here, we identified 5 late effects influencing different aspects of HRQOL in survivors of pediatric brain tumors (Appendix). All regimens should be designed to avoid these late effects, and treatment should maintain and promote those aspects of HRQOL that are adversely influenced. Nurses and other health professionals should provide specific care designed to support aspects of HRQOL affected by late effects, such as directly explaining seizures to a patient's study or workplace and assessing insomnia coexistent with endocrine abnormalities. Such targeted patient support would help survivors achieve high HRQOL even in the presence of late effects.

ACKNOWLEDGMENTS

We thank all participants and their attending physicians: Kohmei Ida, Kohei Fukuoka, Yasuji Miyakita, Namiko Nishida, Masao Matsutani, Kensuke Kawai, Tomoki Todo, Tsuyoshi Isojima, Jun-ichi Adachi, Kazuhiko Mishima, Tomonari Suzuki, Takamitsu Fujimaki, Kazuyuki Kitamura, Masahiro Shin, Kuniaki Saito, Sachiko Kitanaka, Koji Takano.

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Appendix. Sensitivity Analyses to Test the Robustness of the Result From Propensity Score Analyses

In the present study, we calculated differences in HRQOL scores affected by 5 late effects weighted by the inverse of the propensity score. Propensity score analysis is a new method for adjusting influences from confounders. Previous methods used multiple regression analysis using possible confounders as independent variables. Propensity score analysis is more exact than older methods, particularly when using small samples.[A1] This appendix is a sensitivity analysis of study analyses to test the robustness of the following results:

Among survivors 18 years or older:

1. Motility disturbance of limb(s) had a significant effect on physical functioning.
2. Seizure had a significant effect on physical and social functioning, communication deficit, and drowsiness.
3. Ocular/visual impairment had a significant effect on physical, emotional, and social functioning.
4. Endocrine abnormality had a significant effect on insomnia.
5. Higher brain dysfunction had a significant effect on role functioning, fatigue, insomnia, and communication deficit.

Among survivors aged 12 to 17 years:

1. Motility disturbance of limb(s) had a significant effect on physical functioning, movement and balance, perceived physical appearance (child report), and communication.
2. Ocular/visual impairment had a significant effect on physical functioning (parent report), cognitive problems (parent report), movement and balance (child report), perceived physical appearance, and communication (child report).

We calculated nonstandardized regression coefficients by multiple regression analyses, in which the dependent variables were the scores of each HRQOL scale and the independent variables were each late effect and possible confounders, similar to the variables used by calculating propensity scores, and graphed the inverse probability weighting estimates against the regression coefficients (Figures A1 and A2).

Among survivors 18 years or older, the regression coefficients supported all the results of the main analyses (1–5) (Figure A1). Among survivors aged 12 to 17 years, the regression coefficients supported most of the results of the main analyses (Figure A2). Motility disturbance of the limb(s) affected physical functioning, movement and balance, and communication. Multiple regression analysis showed the following: Motility disturbance of limb(s) had little effect on perceived physical appearance (child report), whereas ocular/visual impairment had a significant effect on perceived physical appearance (child report) and communication (child report) and little effect on physical functioning (parent report), cognitive problems (parent report), and movement and balance (child report).

Findings for this analysis support the results of this study, especially for those effects on survivors 18 years or older. We therefore conclude that each late effect deteriorated some aspect of HRQOL in survivors from pediatric brain tumors.

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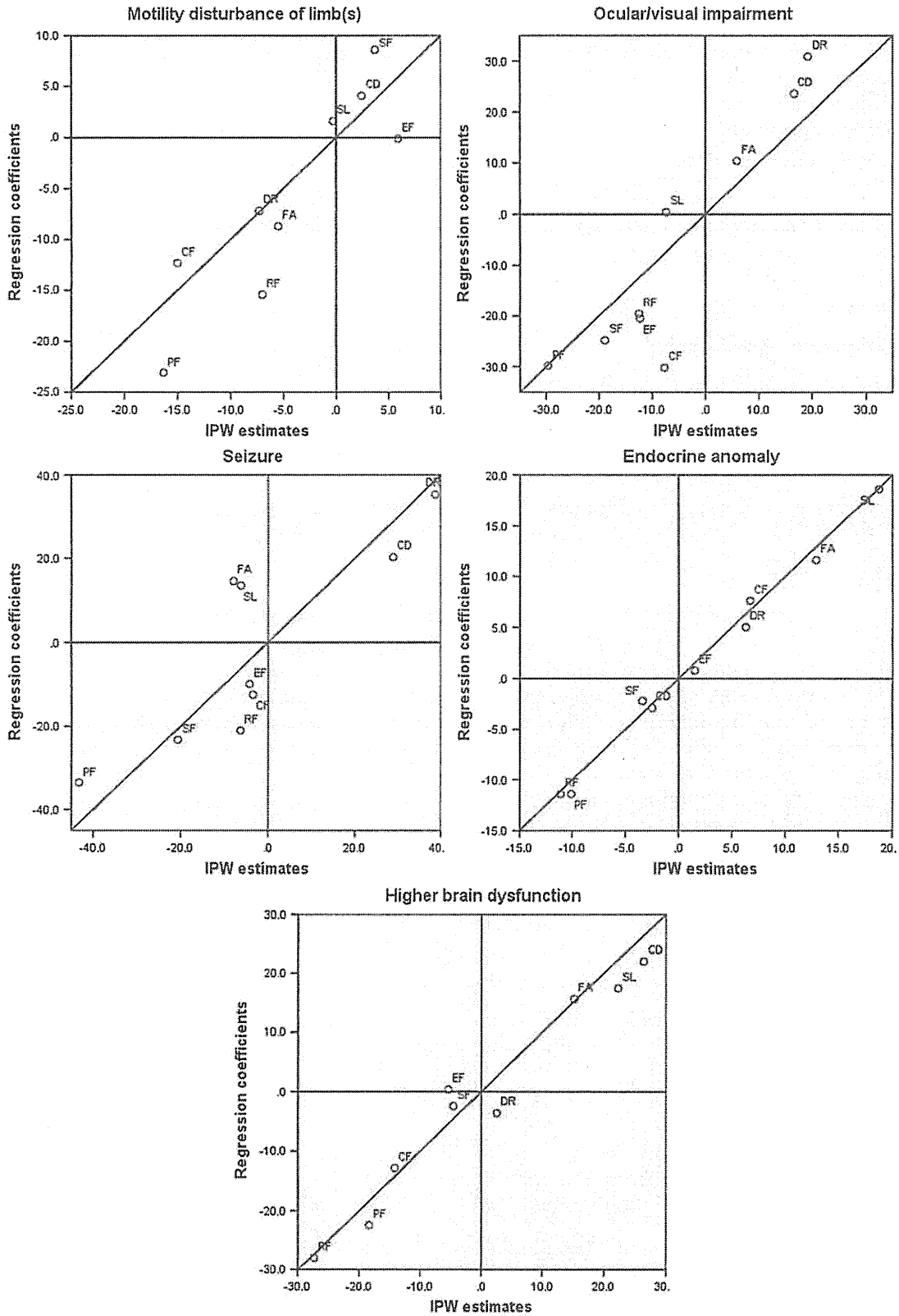

Figure A1 ■ Comparison of 2 kinds of estimates: impact of each late effect of limb(s) on each aspect of health-related quality of life in the survivors 18 years or older. CD indicates communication deficit; CF, cognitive functioning; DR, drowsiness; EF, emotional functioning; FA, fatigue; IPW, inverse probability weighting; PF, physical functioning; RF, role functioning; SF, social functioning; SL, insomnia.

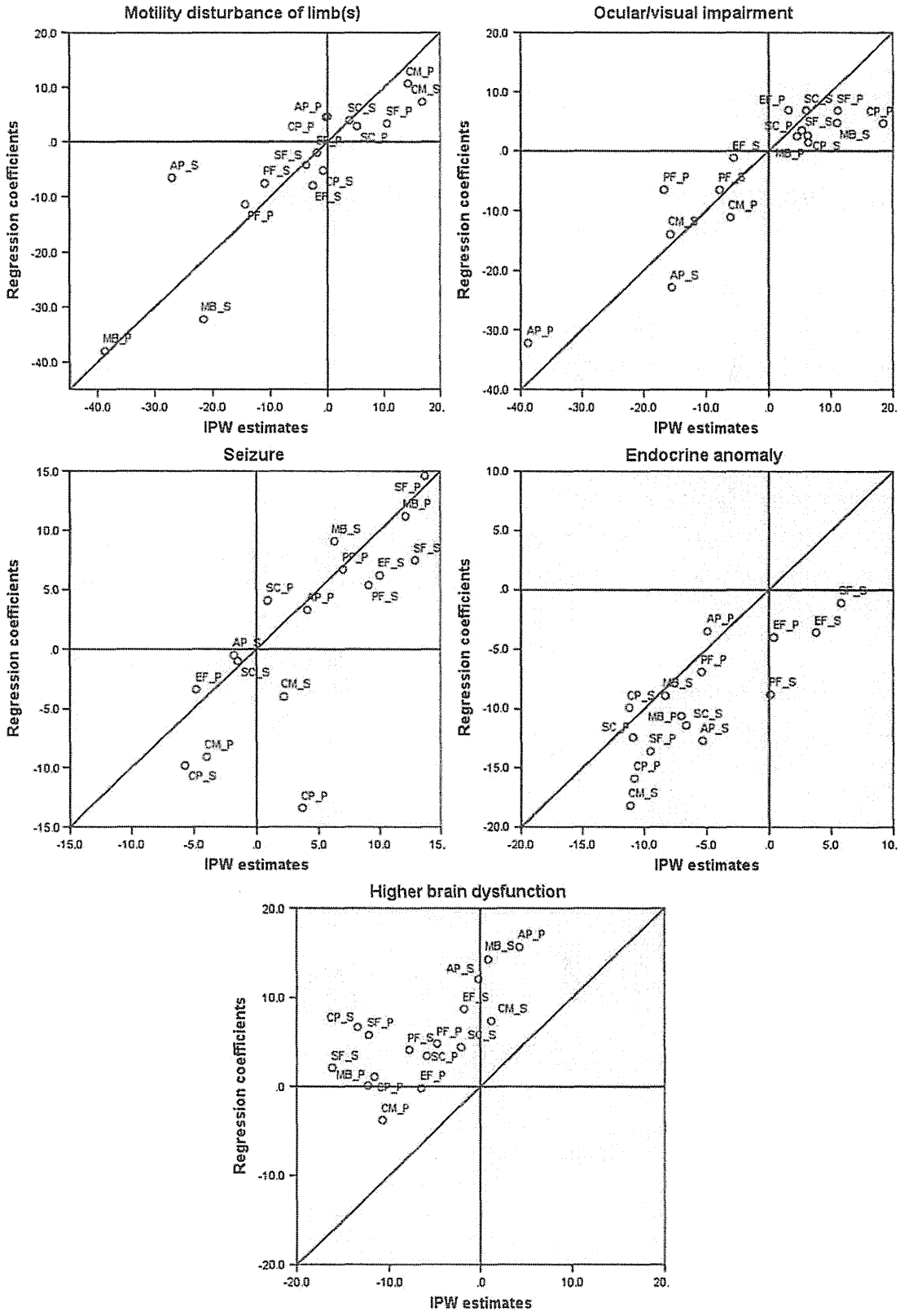

Figure A2 ■ Comparison of 2 kinds of estimates: impact of each late effect on each aspect of health-related quality of life in survivors aged 12 to 17 years. AP_P indicates perceived physical appearance for parent report; AP_S, perceived physical appearance for child report; CM_P, communication for parent report; CM_S, communication for child report; CP_P, cognitive problems for parent report; CP_S, cognitive problems for child report; EF_P, emotional functioning for parent report; EF_S, emotional functioning for child report; IPW, inverse probability weighting; MB_P, movement and balance for parent report; MB_S, movement and balance for child report; PF_P, physical functioning for parent report; PF_S, physical functioning for child report; SC_P, school functioning for parent report; SC_S, school functioning for child report; SF_P, social functioning for parent report; SF_S, social functioning for child report.

Breast Cancer (2014) 21:463–471
DOI 10.1007/s12282-012-0414-6

ORIGINAL ARTICLE

Clinicians' perspectives on support for children with a parent who is diagnosed with breast cancer

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Received: 16 April 2012 / Accepted: 18 September 2012 / Published online: 11 October 2012

Abstract
Background There are few data on clinicians' perspectives regarding support for children who have a parent who has been diagnosed with breast cancer. The purpose of this study was to survey the attitudes of physicians and nurses regarding the care of children who had a parent diagnosed with breast cancer.
Methods A survey was mailed to 898 physicians and 135 nurses who were members of the Japanese Breast Cancer Society in 2009. They were asked to answer questions about their attitudes toward and current practice regarding care for children who had a parent with breast cancer.
Results A total of 340 surveys (284 physicians and 56 nurses) were used in this analysis. The mean age of the respondents was 47.2 years, and their mean number of years of practice was 21.7 years. While 69.1 % of them reported that they felt it important for people in their roles to provide support for children, 84.4 % felt they could not provide sufficient support. The results also suggested that female gender in practitioners and nurses as opposed to doctor status seemed to be associated with preference for intervention, current practice of intervention, and recognition of difficulty to support.
Conclusions Physicians and nurses express a variety of opinions with regard to support for children with a parent who has breast cancer. It is important to cooperate with other specialists including physicians, nurses, and psychologists and allocate roles appropriately among them to improve outcomes for these children.

Keywords Parental cancer · Support for children · Physician and nurse preference

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Introduction

The National Cancer Institute estimates that 24 % of adults with cancer are parenting children younger than 18 years of age [1]. Maternal cancer, particularly breast cancer, is most likely to affect families with children, because women in their 30s, 40s, and 50s are at higher risk of developing cancer than men [2]. Of more than 2 million women in the USA currently diagnosed with breast cancer, 35 % are younger than 55 years of age and are likely to have at least one child living in their home [3]. Similarly in Japan, it is expected that the incidence of breast cancer patients who have a child will increase over time [4]. As a

result, women with breast cancer often face the challenge of raising a family while undergoing intense treatment and coping with the psychological ramifications of having cancer, such as the fear of recurrence and/or physical incapacitation. They want to take good care of their children but are often too distressed, symptomatic, or overwhelmed by external pressures to be the parent they want to be [5]. Even though they are often aware of their children's emotional needs, mothers with cancer may knowingly place their children's needs second to their own, because they lack sufficient energy to listen [6]. This will further increase these mothers' levels of distress [7].

Children of a parent with breast cancer have been observed to be at increased risk of having psychosocial problems such as anxiety and depression as well as physical symptoms, such as headache, stomachache, dizziness, sleeping problems, and loss of appetite [7–9]. They may also face many changes in daily family routines because of repeated hospital admissions, hospital visits, and caring for their parent at home [8]. Some studies also indicate that when mothers with breast cancer are distressed, their children may be at risk of adjustment problems [7, 8].

On the other hand, studies have found that better psychological functioning of parents with breast cancer is associated with better psychological functioning of their children [10]. Parents battling cancer are encouraged by watching their children grow up healthy and happy. Therefore, psychosocial support for the children of parents with breast cancer is important from the viewpoint of total care of these parents. Although patients generally want their healthcare team to assist with their family's needs, many physicians do not have direct contact with their patients' children [11]. Little is known about the attitudes of healthcare providers regarding the care of children of parents who have been diagnosed with breast cancer. The purpose of this study was to survey these attitudes among physicians and nurses.

Participants and methods

Participants

Our study was a cross-sectional, anonymous, multicenter, nationwide survey of physicians and nurses in Japan. Questionnaires were mailed to all the medical specialists ($n = 898$) and certified nurses ($n = 135$) who were members of the Japanese Breast Cancer Society in 2009.

Survey instrument

The survey instrument was developed by the investigators (see Appendix). The survey included questions regarding physicians' and nurses' attitudes toward, commitment to, and evaluation of children of parents with breast cancer. The survey also included also demographic information about participants' age, gender, practice environment, and the number of years since they had completed their formal training.

Attitude toward psychosocial support for children whose parent has been diagnosed with breast cancer

Participants were asked about their attitudes toward psychosocial support for children whose parent had been diagnosed with breast cancer, using a 4-point Likert scale with the following options: (1) We should avoid intervening, (2) we should avoid intervening as much as possible, (3) we should try to intervene as much as possible, and (4) we should intervene. They were also asked to freely describe their reasons.

Current practice of psychosocial support for children of parents with breast cancer

Participants were asked about their current support practices for children whose parent had been diagnosed with breast cancer, using a 4-point Likert scale: (1) I do not intervene at all, (2) I hardly intervene, (3) I intervene as much as possible, and (4) I always intervene. They were also asked to freely describe their reasons.

Content of support and its evaluation

We asked only those participants with experience supporting children whose parent had been diagnosed with breast cancer to describe their interventions and successful and unsuccessful experiences. Participants were asked a multiple-choice question regarding intervention content, and were asked to describe their experiences in detail regarding successful and unsuccessful intervention experiences.

The survey was initially piloted on three physicians to examine the clarity and validity of the instrument. It was mailed to the participants after revisions were made following the pilot study. The survey questions were printed on both sides of a cardstock sheet and mailed with a cover letter explaining the study's purpose and how to return it.

Statistical analysis

All the survey data were coded and entered into a database using standard statistical software (SPSS version 17.0 for Windows). The descriptive statistics derived included the following: proportions, means, and standard deviations or medians and ranges. Preference to intervene or not was

entered into the analysis as a dependent variable, and associated factors were assessed by univariate and multivariate analysis. Socio-demographic factors were compared using Fisher's exact test and the t test. Socio-demographic variables that significantly correlated with a dependent variable in the univariate analysis were entered into the logistic regression analysis.

We also conducted descriptive analyses on the content and evaluation of support. Fisher's exact test was used to test group differences in the responses for each category. For comparisons between groups, an absolute value of standardized residual of more than 1.96 indicated statistical significance [12].

Qualitative data were coded and similar codes were grouped together into categories by two psychologists and one physician. These categories were then labeled on the basis of their content.

Results

Demographic data

Of the 933 questionnaires mailed to physicians and nurses, 316 physicians and 67 nurses returned questionnaires, amounting to a physician response rate of 35.2 %, and a nurse response rate of 49.6 %. Of the returned questionnaires, 32 physicians and 11 nurses were excluded because of missing data on the primary points of investigation. Respondent demographic characteristics are listed in Table 1. Physicians accounted for 83.5 % of respondents, and 71.5 % were men. The respondents' mean years in practice were long (physicians 23.0 years, nurses 15.2 years) because we surveyed medical specialists and certified nurses, who require additional time to achieve their professional status.

Table 1 Demographic data ($n = 340$)

	Physician ($n = 284$)	Nurse ($n = 56$)
Age		
Mean (SD)	49.1 (8.0)	37.6 (5.0)
Range	33–75	27–53
Years in practice		
Mean (SD)	23.0 (7.9)	15.2 (4.8)
Range	9–46	6–30
Gender		
Male	243	0
Female	41	56
Practice environment		
Cancer unit hospital	108	35
Usual hospital	68	3
University hospital	76	17
Clinic	29	1
Others	3	0

Physicians' and nurses' attitudes towards supporting children

Physicians and nurses were asked to choose one of the four responses that best summarized their attitudes towards supporting children who had a parent diagnosed with breast cancer. As depicted in Fig. 1, 69.1 % preferred to intervene and 30.9 % preferred not to intervene. The results of the univariate analysis of demographic characteristics for preference with regard to intervention are shown in Table 2. The variables that were significantly associated with preference for intervention were age ($p = 0.019$), occupation ($p < 0.001$), and gender ($p < 0.001$). Using these significant factors in univariate analysis, we conducted a logistic regression analysis to identify independent factors for preference for avoiding intervention (Table 2). The results revealed gender to be significantly associated ($p < 0.001$) with preference for avoiding intervention. Occupation showed borderline significance ($p = 0.065$) in multivariate analysis.

The reasons why these professionals prefer to intervene or not intervene were examined through their free descriptions. We could only extract and categorize physicians' descriptions, because we did not receive any replies from nurses in this area. The categories are listed in Table 3. Physicians who preferred not to intervene cited problems such as medical system issues, positional constraints, and the lack of appropriate knowledge. On the other hand, physicians and nurses who preferred to intervene indicated the importance and benefit of support for children and their parents.

Current practice of support

Regarding actual intervention, 84.4 % of all respondents reported that they did not or hardly ever intervened, and only a few physicians or nurses always intervened with children of breast cancer patients (Fig. 1).

Physicians and nurses who wanted to intervene but could not do so were queried on the reasons why they could not; they replied using free descriptions. The answers were as follows: "lack of opportunity to meet children," "support system issues," "anxiety of intervention," "low-priority category in daily context," "family issues," and "few requests for support from patients" (Table 4).

Content and evaluation of support

Physicians and nurses who were trying to intervene but could not were queried about their methods of support using multiple-choice questions. The results are shown in Table 5. Male physicians were less likely to give

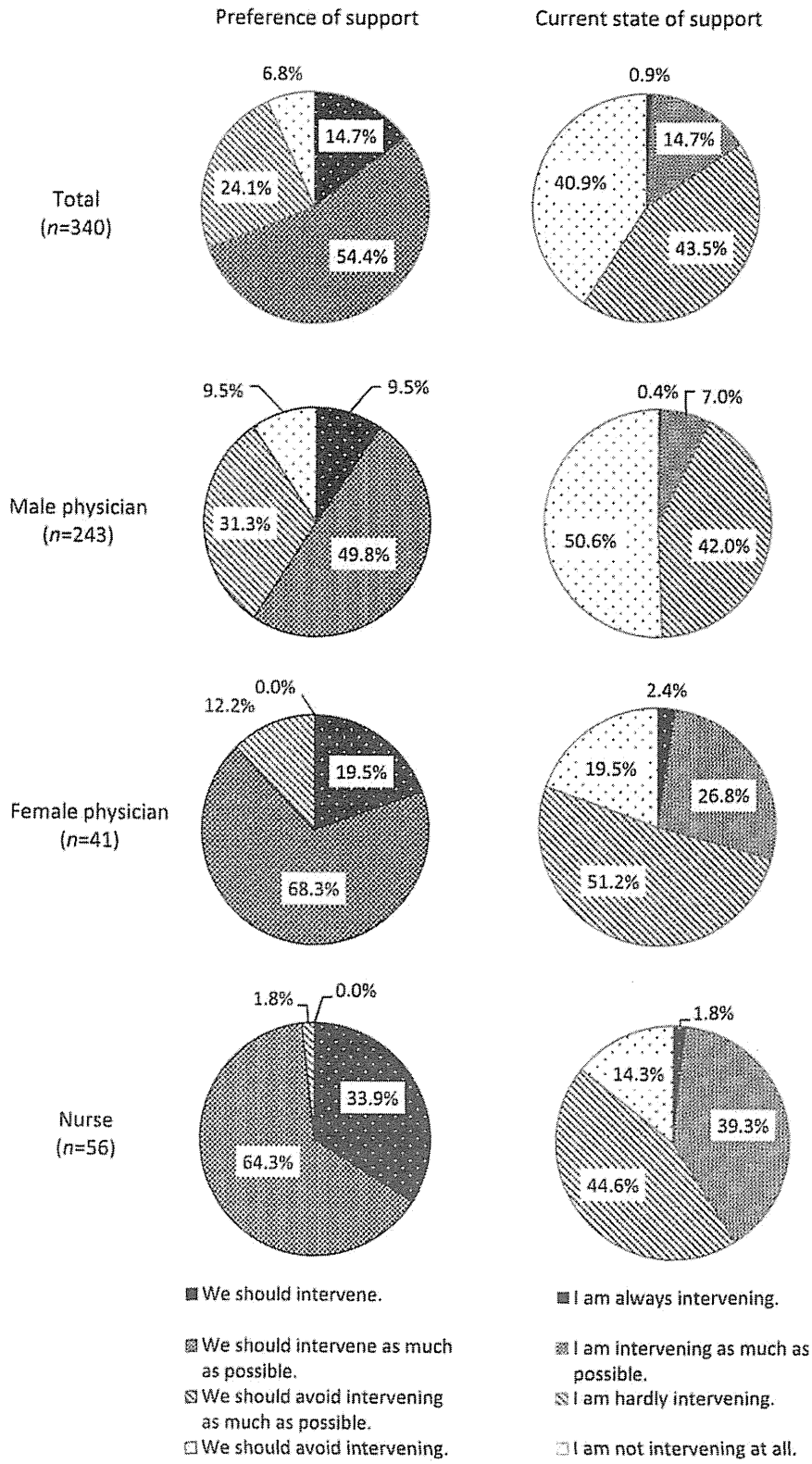

Fig. 1 Attitude toward (*left column*) and current practice (*right column*) of psychosocial support for children who have a parent diagnosed with breast cancer. Many of the physicians and nurses reported that they felt it preferable to support children of breast cancer patients, but in practice they could not provide sufficient support

counseling to their patients ($p < 0.001$), whereas nurses were more likely to give counseling ($p < 0.001$) and/or provide brochures on support ($p = 0.010$).

Participants were also asked to evaluate the methods of support they provided and describe their experiences in detail. In terms of effectiveness, 52.4 % of all respondents

Table 2 Factors associated with preference of avoiding intervention ($n = 340$)

Characteristic	Univariate analysis			Multivariate analysis		
	Prefer to intervene ($n = 235$)	Not prefer to intervene ($n = 105$)	p	Odds ratio	95 % CI	p
Age	45.8 ± 8.9	50.5 ± 7.3	0.019	1.0	0.9–1.1	0.356
Years in practice	20.7 ± 8.2	24.2 ± 7.3		–	–	–
Occupation						
Nurse	55 (98.0 %)	1 (1.8 %)	<0.001	1	0.9–72.2	0.65
Physician	180 (63.0 %)	104 (36.6 %)		7.9		
Gender						
Female	91 (93.8 %)	6 (6.2 %)	<0.001	1	1.6–11.5	<0.001
Male	144 (59.3 %)	99 (40.7 %)		4.2		
Practice environment						
Cancer unit hospital	102 (71.3 %)	41 (28.7 %)	0.066	1		
Usual hospital	50 (70.4 %)	21 (29.6 %)		0.8	0.4–1.5	0.407
University hospital	60 (64.5 %)	33 (35.5 %)		1.3	0.7–2.4	0.417
Clinic	23 (77.0 %)	7 (23.3 %)		0.6	0.2–1.5	0.257

Logistic regression analysis used the respondents who prefer not to intervene as the dependent variable

Table 3 Reasons why physicians and nurses prefer to intervene or avoid intervening to support children who have a parent diagnosed with breast cancer

Reasons to avoid intervening	Reasons to intervene
Intervention is not necessary	On an empirical basis
Uncertain about supporting children	The patients requested that I do so
I cannot determine whether intervention is suitable	I met many children who were worried
I do not know whether a physician/nurse should intervene	I felt that intervention was necessary
It may become excessive meddling	Scientifically proven
Depends on circumstances	Impact of cancer on patients
It changes with the patient's condition	Treatment is stressful for patients
It changes with their family	It takes a long time to treat their disease
Responsibility issues	Many patients who have a child are young and are women
We cannot have responsibility in a result of intervention	To improve the patient's quality of life
It is necessary to obtain parents' permission to intervene	To assess the needs
Support system issues	Impact of cancer on the patient's children
There is no medical treatment fee	Children feel anxiety, fear, and loneliness
It is difficult to find sufficient time to support children	Parental cancer will affect their child's development
The system for intervention is insufficient	There are few opportunities for children to express their fears
We should leave it to a specialist.	Children should be mentally prepared for their parent's death
Lack of knowledge about supporting children	Importance of support as a family
Family issues	The child is a member of a family
It is too private to intervene	Family issues have an impact on the patient's condition
We should leave it to the family	We should treat the entire family as a patient
Parents prefer not to tell their children the truth	Supporting children aids patient's medical treatment effectively
Intervention may have adverse effects on the children	

rated their support as effective, in that it positively impacted the patient, child, and family; 9.7 % ranked their intervention as ineffective, because nothing had changed; and 37.9 % replied "neither," because it was difficult to evaluate the interventional effect on the children or they did not have much experience in that area. There was no statistical difference among the responses of male physicians, female physicians, and nurses (Table 6). Regarding

difficulty, 24.3 % of respondents thought that support was difficult, in that it strayed from family policy, the child refused help, the provider lacked knowledge on how to support children of sick parents, or the provider had no opportunity to meet the patient's children; 36.9 % ranked their intervention as easy, because the child support provider offered their services at the parent's request; and 38.8 % replied "neither," because they did not have much experience in that area or it depended on the case. The results of Fisher's exact test (Table 6) show that male physicians were least likely to consider intervention difficult ($p < 0.05$) and nurses were most likely to consider it difficult ($p < 0.01$).

Table 4 Reasons why physicians and nurses who prefer to support these children cannot intervene sufficiently

Items
Lack of opportunity to meet children
Support system issues
It is difficult for me to find sufficient time to support children
The child-support system is limited
There are few specialists
Lack of understanding within the medical community
Anxiety of intervention
I am concerned about intervening in a half-hearted manner
I cannot take sufficient responsibility for intervention
Lack of knowledge about child support
Low-priority category in daily matters
Family issues
Parents prefer not to tell the truth to their children
I should leave it to the family
Few requests for support from patients

Discussion

Breast cancer has been the most frequently diagnosed form of cancer among Japanese women since the mid-1990s [13]. A rapid increase in the incidence rate of breast cancer was seen among middle and old age groups, especially 45- to 64-year-olds. In 2006, a clear peak in the incidence rate was seen in this age group [14]. Therefore, the incidence of breast cancer patients who have a child at the time of diagnosis will increase over time [4]. Studies show that parental cancer is associated with significant risk of developing various psychosocial problems in both patient and children [8, 15]. Our survey may be the first to examine physicians' and nurses' attitudes toward supporting children who have a parent diagnosed with breast cancer in Japan.

The data from this study include several notable findings. First, 69.1 % of the physicians and nurses in this study reported that they felt it preferable to support children of breast cancer patients, but many of them felt they could not provide sufficient support. These data indicate several difficult issues in the area of psychosocial support for children of sick parents. First are medical system issues such as shortage of people and resources, lack of understanding, and cost of medical care. In North America and Europe, there are some systematic programs of support for children of sick parents, such as the children of somatically ill parents (COSIP) project [16–18], and an adequate number of specialists in many hospitals in areas related to psychosocial support for children, such as CLSs and psychologists. However, in Japan there are few systematic programs or specialists in support for children, so that it is left to each physician's or nurse's discretion. It could lead to the introduction of a comprehensive care service in

Table 5 Responses to survey question about content of child support ($n = 111$)

	Physician						Nurse ($n = 41$)			p^a
	Male ($n = 50$)			Female ($n = 20$)						
	N	%	Standardized residual	N	%	Standardized residual	N	%	Standardized residual	
Provide counseling to their patients	29	58.0	−3.9**	16	76.2	0.5	39	95.1	3.7**	<0.001
Provide brochures on child support	20	40.0	−1.8	7	33.3	−1.4	28	68.3	3.0**	0.10
Counseling to the children	19	38.0	0.8	5	23.8	−1.0	14	34.1	0.0	0.585
Cooperate with specialists[b]	12	24.0	−1.4	10	47.6	2.1	12	29.3	−0.2	0.100
Have a seminar on support for children of cancer patients	4	8.0	−0.9	2	9.5	−0.1	6	14.6	1.0	0.593
Other	4	8.0	2.2	0	0.0	−1.0	0	0.0	−1.6	0.080

Multiple answers were allowed in response to questions. There were 90 missing responses

*$p < 0.05$, **$p < 0.01$

[a] Fisher's exact test was used to test group differences in the responses for each category

[b] Specialists include doctors, nurses, child life specialists (CLS), medical social workers (MSW), and clinical psychologist (CP)

Table 6 Evaluation of support ($n = 103$)

	Physician						Nurse ($n = 38$)			p^a
	Male ($n = 44$)			Female ($n = 21$)						
	N	%	Standardized residual	*N*	%	Standardized residual	*N*	%	Standardized residual	
Effectiveness										
I think it is *effective*	20	45.5	−1.2	12	57.1	0.5	22	57.9	0.8	
I think it is *ineffective*	5	11.4	0.5	2	9.5	0.0	3	7.9	−0.5	0.819
I think it is *neither*	19	43.2	1	7	33.3	−0.5	13	34.2	−0.6	
Difficulty										
I think it is difficult	6	13.6	−2.2*	6	28.6	0.5	13	34.2	1.8	
I *do not* think it is difficult	24	54.5	3.2**	7	33.3	−0.4	7	18.4	−3.0**	0.015
I think it is *neither*	14	31.8	−1.3	8	38.1	−0.1	18	47.4	1.4	

Survey question was as follows: please choose a single response that best summarizes your evaluation of support for children and describe the reasons. There were 98 missing responses

*$p < 0.05$, **$p < 0.01$

[a] Fisher's exact test was used to test group differences in the responses for category

which child care is part of the medical service provided to patients. Therefore, it is necessary to involve children when it comes to providing support for patients in medical institutions. In addition, not only hospital service, but also social welfare might be helpful in providing support for children. It is also necessary to develop an improved consulting system in local governments and community groups. The positional constraints of healthcare providers are also obstructive. Some physicians and nurses are concerned about their lack of knowledge or competence regarding support for children. A lack of appropriate knowledge and procedures to support children of cancer patients may increase work-related stress and exhaustion among healthcare workers [19]. Furthermore, we have to be aware of family issues. Many patients are conflicted about telling their children about their disease or condition. Given these issues, it is important to increase awareness of the importance of support for children of sick parents, and investigate what is necessary for the patient, the children, and families. In addition, we should organize a support system (i.e., a support program as well as brochures and other efforts to increase awareness of it) and support-training program, and improve communication between the patient, the patient's family, and healthcare providers.

Second, while 52.4 % of the respondents who said that they make efforts to support children think that their support is effective, 37.9 % think that there is no way to evaluate whether it is effective. This finding might reflect the fact that a good method to measure the effectiveness of support is not yet firmly established. Some studies reported positive changes in children's cancer-related worries and adjustment, and a significant decrease in depression. Parents with cancer also reported positive changes in the level of depression, state of anxiety, and self-efficacy. Although previous intervention studies have reported positive outcome [20, 21], these were experimentally based interventions; the obtained results were based on facilitators' impressions and participants' verbal feedback, elicited by self-constructed, non-validated questionnaires [8]. With the acquisition of more structured and well-grounded knowledge, an instrument that specifically measures the effectiveness of support should be developed. Furthermore, we should examine children's response to support efforts. It is difficult for healthcare providers to evaluate the responses of children, because they do not commonly deal with children who have had a parent diagnosed with cancer. We should gather self-reported information from children to obtain an accurate picture of support needs for children of parents with breast cancer.

Finally, gender and occupation seem to be associated with preference regarding intervention, current practice, and difficulty of support. The results of this study indicate that male gender and the status of physician as opposed to female gender and the status of nurse seem to be associated with the tendency to prefer not to support children. This tendency might be due to professional, cultural, biological features or nurturance or maternal feeling that women and nurses feel in dealing with children of sick parents, or the length of time they are in contact with patients and their children [22]. It is important to decide on a course of support in cooperation with various specialists and allocate roles appropriately. Furthermore, our study showed that the

younger staff preferred intervention more than the older ones. It may reflect differences related to the position. Experienced doctors and nurses, especially those in managerial positions, have multiple functions and responsibilities for managing their ward such as leading a team, coaching subordinates, and attending a hospital staff meeting [23]. Therefore, it may be hard for them to actively promote child support. Further research is needed to verify the effectiveness of child support, and we have to work systematically toward establishing an efficient method of child support.

In consideration of our findings, it is important to remember several limitations. First, we surveyed only physicians and nurses. The results indicate that cooperation with various other specialists is necessary to provide appropriate support to children. Additional studies should be undertaken to explore the attitudes of these other healthcare providers toward supporting the children of their cancer patients. Second, the respondents of this study belong to the Japanese Breast Cancer Society. Some of the experiences and situations they reported might be specific to breast cancer patients. Thus, further research is needed to estimate the current state of support for children of patients among other physicians and nurses who care for patients diagnosed with various cancers.

In conclusion, our study suggests that most physicians and nurses feel the need to support children who have a parent with cancer, but many of them feel that they could not provide sufficient support. Spreading the awareness of the need to care and sufficient specialists and their cooperation are needed for successful intervention or sufficient support for these children, and it should be done as a national project. Our findings should provide a foundation for additional research and possible targeted interventions to improve support systems for children who have a parent with cancer.

Acknowledgments The authors would like to thank the members of the Japanese Breast Cancer Society for participating in this study. This study was supported by a Grant-in-Aid from the Japanese Ministry of Health, Labor and Welfare.

Appendix

(A) What do you think about psychosocial support for children whose parent had been diagnosed with breast cancer? Please choose one answer from the following and describe the reason in your own words:
(1) We should avoid intervening. (2) We should avoid intervening as much as possible. (3) We should try to intervene as much as possible. (4) We should intervene.

(B) How do you support children whose parent had been diagnosed with breast cancer in routine care? Please choose one answer from the following and describe the reason in your own words:
(1) I do not intervene at all. (2) I hardly intervene. (3) I intervene as much as possible. (4) I always intervene.

(C) If you have had some experience in psychosocial support for children whose parent had been diagnosed with breast cancer:
(C-1) What did you do? Please check all that apply.
(1) Provide counseling to their patients. (2) Provide brochures on child support. (3) Counseling to the children. (4) Cooperate with specialists (i.e., Dr, Ns, CLS, MSW, CP). (5) Have a seminar on support for children of cancer patients. (6) Other (What?) ——
(C-2) How effective do you think this support is? Please choose one answer from the following and describe the reason in your own words.
(1) I think it is effective. (2) I think it is ineffective. (3) I think it is neither.

(C-3) How difficult is it to provide this support? Please choose one answer from the following and describe the reason in your own words.
(1) I think it is difficult. (2) I do not think it is difficult. (3) I think it is neither.

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SETBP1 mutations in juvenile myelomonocytic leukaemia and myelodysplastic syndrome but not in paediatric acute myeloid leukaemia

Juvenile myelomonocytic leukaemia (JMML) is a rare myeloproliferative disorder that is characterized by excessive myelomonocytic proliferation (Loh, 2011). Gene mutations in the components of the RAS signalling pathways are a hallmark of JMML and are considered to be central to the pathogenesis of JMML. Mutations in *NRAS*, *KRAS*, *PTPN11*, *NF1*, and *CBL* genes are found in approximately 75–85% of patients with JMML and are implicated in the aberrant RAS signalling (Loh, 2011). These mutations are also associated with congenital abnormalities, such as cardio–facio–cutaneous syndrome (*KRAS*), Noonan syndrome (*PTPN11*), neurofibromatosis (*NF1*), and Noonan-like syndrome (*CBL*). However, no other mutations have been identified in the remaining approximately 20% of patients with JMML.

In this regard, massively parallel sequencing technology has recently identified recurrent somatic mutations in *SETBP1* in atypical chronic myeloid leukaemia (aCML) (Piazza *et al*, 2012). Of the 70 patients with aCML that were examined, 17 (24%) were found to carry *SETBP1* mutations. These mutations clustered between codons 858 and 871, all located in the SKI-homologous region of *SETBP1*. Identical nucleotide alterations have been reported in Schinzel–Giedion syndrome (Hoischen *et al*, 2010), a rare congenital disorder that is characterized by severe mental retardation, distinctive facial features, and higher than normal prevalence of tumours, notably neuroepithelial neoplasia (Schinzel & Giedion, 1978). This report prompted us to search for possible *SETBP1* mutations in JMML or other paediatric haematological malignancies.

To assess the clinical significance of *SETBP1* mutations in paediatric leukaemias, we analysed a total of 414 patients with paediatric leukaemia/myelodysplastic syndrome (MDS) that comprised 42 patients with primary JMML, 24 with MDS, 22 with therapy-related leukaemia, 68 with infant acute lymphoblastic leukaemia (ALL), and 258 with *de novo* acute myeloid leukaemia (AML), including 10 patients with acute promyelocytic leukaemia (APL) and 22 with acute megakaryoblastic leukaemia (AMKL). The median age at diagnosis of JMML was 1 year and 10 months (range, 2 months to 8 years and 4 months), with 27 males and 15 females. MDS included 9 patients with refractory anaemia (RA), 14 with RA with an excess of blasts, and 1 with secondary MDS. The genomic region of the *SETBP1* gene, containing codons 858–871 with the mutation hotspots D868 and G870 in the SKI-homologous region, was amplified using polymerase chain reaction (PCR) with the following primer sequences: forward, 5′-ACCAAAACCCAAAAGGGAAT-3′; reverse, 5′-CGGTTTTGCAGGCTTTTC-3′. Purified PCR products were sequenced using an ABI PRISM 3130 Genetic Analyser (Applied Biosystems, Branchburg, NJ). Mutations in *RAS*, *PTPN11*, and *CBL* have been previously reported in JMML (Shiba *et al*, 2010). The present study adhered to the principles of the Helsinki Declaration and was conducted under the regulations outlined by the Ethics Board of Gunma Children's Medical Centre.

SETBP1 mutations were found in 2 of the 42 patients with JMML (4·8%; Gly870Arg in JMML 2, Ser869Arg in JMML 24) and one of the 24 patients with MDS (4·2%; Ile871Thr in MDS 3) but not in the 22 patients with secondary AML, 68 with infant ALL, or 258 with *de novo* paediatric AML, including 10 patients with APL and 22 with AMKL (Fig 1A). The origin of the mutations was not determined due to the lack of appropriate normal tissue samples. In all 3 patients with *SETBP1* mutations, a chromatogram exclusively showed a mutated sequence, indicating that the mutations were heterozygous (Fig 1A). Although one of the 2 JMML patients with an *SETBP1* mutation survived after unrelated cord blood transplantation, the other died following relapse 4 months after undergoing related peripheral blood stem cell transplantation (Table I). In contrast, the MDS patient who had an *SETBP1* mutation was initially diagnosed with neuroblastoma at the age of 6 years. He was subsequently treated with chemotherapy and autologous bone marrow transplantation and achieved complete remission (CR). However, 3 years after the initial diagnosis, blast cells appeared in his peripheral blood and he was diagnosed with secondary MDS. Chromosomal analysis of the bone marrow cells revealed 45, XY, −15, der(7)t(7;15)(p13;q15), add(18)(q21) and add(20)(p13). He received chemotherapy with etoposide and cytarabine; however, he did not achieve CR. He died of haemorrhagic shock 18 months after being diagnosed with secondary MDS.

Mutations in *NRAS*, *KRAS*, *PTPN11* and *CBL* genes were found in 21%, 4·8%, 38% and 12% of patients with JMML respectively, in our study (Fig 1B) (Shiba *et al*, 2010). Although almost all of the *NRAS*, *KRAS*, *PTPN11* and *CBL* mutations occurred in a mutually exclusive manner, *SETBP1* mutations were found in patients with *PTPN11* or *NRAS* mutations (Table I and Fig 1B). This finding suggests that both gene mutations associated with the *RAS* pathway and *SETBP1* mutations can cooperate in the pathogenesis of JMML.

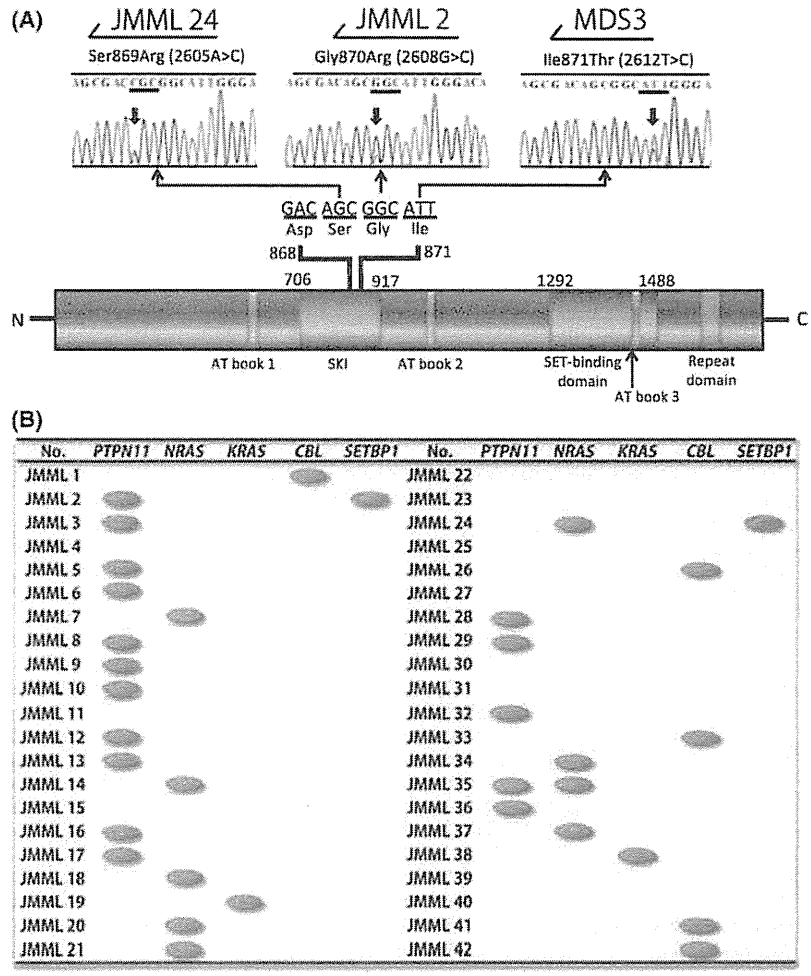

Fig 1. (A) Location and type of *SETBP1* mutations in patients with juvenile myelomonocytic leukaemia (JMML) and myelodysplastic syndrome (MDS). (B) Mutation profile of 42 JMML patients for a panel of 5 genes. Mutations in *PTPN11*, *NRAS*, *KRAS*, *CBL*, and *SETBP1* genes were found in 21%, 4·8%, 38%, 12%, and 4·8% of 42 patients with JMML, respectively.

Table I. Clinical characteristics of the patients with *SETBP1* mutations.

Patient	Sex	Age	WBC ($\times 10^9$/l)	Karyotype	Nucleotide change	Amino acid change	SCT	Relapse	Survival (months)	Other mutations
JMML-2	F	24 months	39·9	46XX	2608A > C	Gly870Arg	U-CBT	–	182+	*PTPN11*
JMML-24	M	26 months	24·5	46XY, −7	2605G > C	Ser869Arg	allo-PBSCT	+	6*	*NRAS*
MDS-3	M	12 years	6·3	45XY, −15, der(7)t(7;15)(p13;q15), add(18)(q21), add(20)(p13)	2612T > C	Ile871Thr	–	–	18†	–

F, female; M, male; Gly, glycine; Arg, arginine; Ser, serine; Ile, isoleucine; Thr, threonine; SCT, stem cell transplantation; U-CBT, unrelated cord blood transplantation; allo-PBSCT, allogeneic peripheral blood stem cell transplantation; +, alive.

*Died of relapse 6 month after initial diagnosis.

†Died of haemorrhage shock 18 months after diagnosed with secondary MDS.

High levels of *SETBP1* expression have been described in elderly patients with AML (Cristobal *et al*, 2010), and *SETBP1* has been identified in a specific paediatric T-cell ALL as a chromosomal translocation partner of *NUP98* (Panagopoulos *et al*, 2001). SETBP1 has been reported to promote the self-renewal of murine myeloid progenitors via activation of HOXA9 and HOXA10 (Oakley *et al*, 2012). The patients with an *SETBP1* mutation had a worse prognosis and presented higher white blood cell counts at diagnosis and also exhibited higher amounts of SETBP1 and SET protein, lower