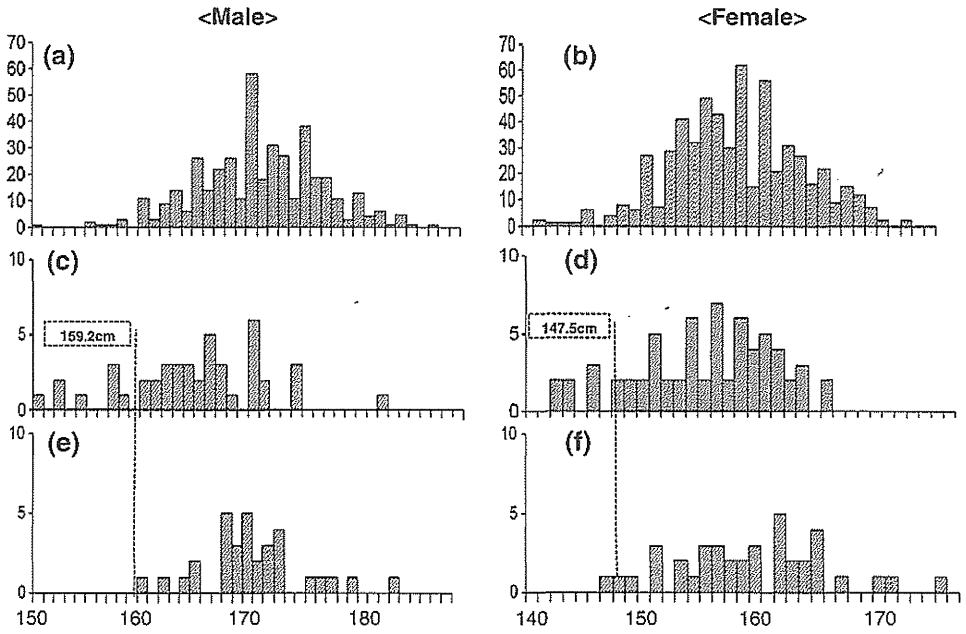

Fig. 1 Height distribution at survey. The height distribution data at survey are presented with respect to gender: **a**, **b** the general population; **c**, **d** CCS treated with RT; **e**, **f** CCS treated without RT. The mean −2 SD height was 159.2 cm for males and 147.5 cm for females in Japanese adults

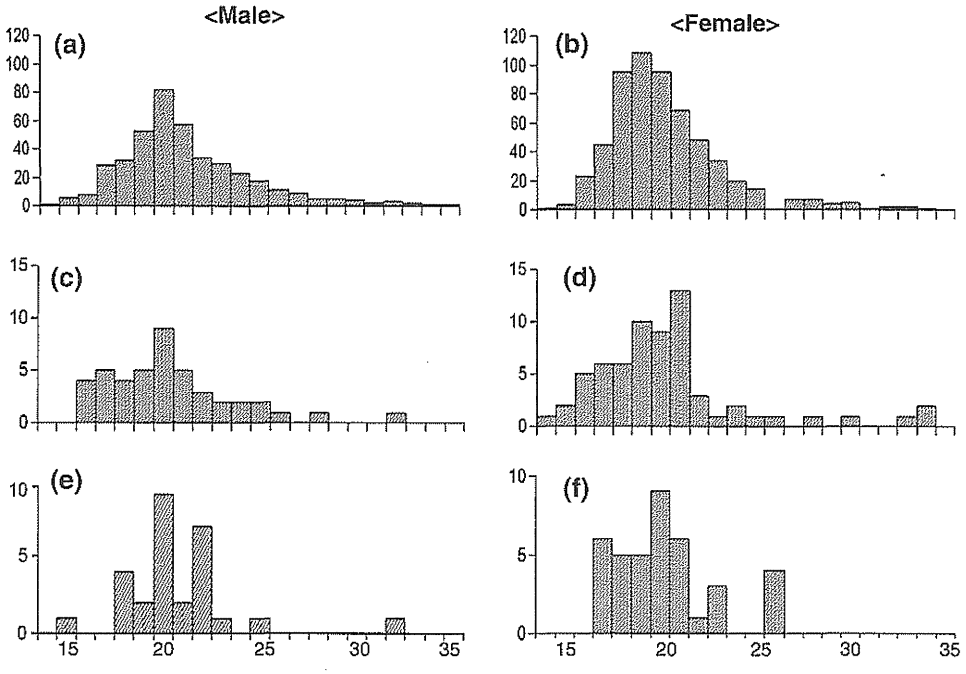

Fig. 2 BMI distribution at survey. The BMI distribution data at survey are presented with respect to gender: **a**, **b** the general population; **c**, **d** CCS treated with RT; **e**, **f** CCS treated without RT. Underweightness (BMI < 18.5) was noted in 27% of males and 26% of females in the CCS with RT group, 9% of males and 26% of females in the CCS without RT group, and 14% of males and 21% of females in the general population group, respectively. Overweightness (BMI > 25) was observed in 11% of both males and females in the CCS with RT group, 22% of males and 8% of females in the CCS without RT group, and 15% of males and 8% of females in the general population group, respectively

QOL in the CCS treated with RT were significantly high for physical dysfunction, difficulty in daily activities, and psychological stress. Each poor QOL factor in the CCS groups was closely associated with the presence of late effects (data not shown).

4 Discussion

We found that late effects and a poor QOL were closely associated with the use of RT in CCS; this finding is important because quality of cure is very critical for CCS because the cure rates have improved markedly. To our knowledge, this report is the first to comprehensively evaluate late effects on CCS after RT in Japan.

In the present survey, a short stature (<−2 SD) and being underweight (BMI < 18.5) were common in the CCS group treated with RT. A short stature was noted in 22 (12%) of 185 CCS participants; it is an important point that 20 (91%) out of 22 CCS with short stature had received RT. Skull irradiation and TBI were closely associated with a short stature, and the adjusted ORs of

Table 3 Risk factors of childhood cancer survivors for short stature

Categories	Factors	Short stature		χ^2 or Fisher (p value)	Logistic regression analysis*	
		Yes ($n = 22$)	No ($n = 161$)		Adjusted odds ratio (95% CI)	p value
Gender	Female	13	93	0.906	1.18 (0.39–3.70)	0.759
	Male	9	68		Ref	
Age at diagnosis (years)	0–5	13	46	<0.001	42.2 (3.69–483)	0.003
	6–10	8	42		26.0 (2.49–271)	0.006
	>10	1	73		Ref	
Years after therapy completion	15 years or more	13	58	0.037	1.68 (0.43–6.52)	0.452
	14 years or less	9	103		Ref	
Primary cancer (1)	Solid tumor	7	49	0.895	2.39 (0.55–10.3)	0.244
	Hematological	15	112		Ref	
Primary cancer (2)	Hematological	15	112	0.693	–	
	Brain tumor	2	8			
	Bone/soft tissue sarcoma	1	17			
	Other solid tumor	4	24			
Radiation sites	Any	20	92	0.002	–	
	Skull	12	55	0.063	4.71 (1.07–20.7)	0.040
	Chest or abdomen	0	12	0.366	–	
	Total body	8	20	0.008	39.9 (2.16–736)	0.013
	Spine	4	4	0.008	6.35 (0.78–51.5)	0.084
	Extremity	0	5	1.000	–	
Stem cell transplantation	Yes	9	37	0.069	0.50 (0.04–6.28)	0.594
Chemotherapy	Anthracycline	18	133	1.000	–	
	Alkylating agents	20	134	0.536		
	Etoposide	9	67	0.950		
Operation	Yes	8	60	0.934	–	
Recurrence	Yes	8	25	0.033	0.72 (0.16–3.31)	0.670

* Hosmer and Lemeshow: $\chi^2 = 66.4$ ($p < 0.001$)

RT for them were significantly high. The adjusted OR of spinal RT was relatively high but not significant because of the small number of CCS with spinal RT in our study. Our results confirmed those of CCSS [13, 14], demonstrating that ORs for a short stature in adulthood among those at 4 years of age or younger at diagnosis, relative to ages of 10–20 years, was 5.67 (95% CI 3.6–8.9) and that hypothalamic-pituitary axis radiation exposure increased the risk of a short stature in adulthood in a dose–response fashion (trend test, $p < 0.0001$). The OR of cranial irradiation with 20 Gy or more was 1.5 (95% CI 0.4–5.1) compared to cranial irradiation with less than 20 Gy; the dose–response was not clear, mostly because of the small number of cases in our study. Growth hormone deficiency due to cranial irradiation is one of the main mechanisms leading to a short stature in CCS; however, the mechanisms behind the association between RT and a short stature remain to be fully elucidated. This study suggests that spinal RT might be one of the independent risk factors for a short stature because the adjusted OR of spinal RT was high, which suggests that direct bone growth failure is one of the mechanisms of a short stature caused by RT in CCS.

In the CCSS study, adjuvant chemotherapy was not an independent risk factor for a short stature in adulthood [13]. In contrast, Noorda et al. [15] reported that all CCS treatment exposure groups (chemotherapy alone, chemotherapy with cranial or craniospinal radiotherapy) showed a decreased adult height and an increased risk of a short stature in adulthood compared with siblings ($p < 0.001$). They also revealed that the risk of a short stature in survivors treated with chemotherapy alone was elevated (OR 3.4, 95% CI 1.9–6.0) compared with siblings [15]. In our study, no chemotherapeutic agents were associated with the prevalence of a short stature (Table 3, multivariate data not shown).

Table 4 Adjusted odds ratios of radiotherapy for various late effects

Categorical variables	Total (n = 183)	With RT (n = 113)	Without RT (n = 72)	Adjusted odds ratio[a] (95% CI)	p value
Number of late effects					
1 or more	104 (56%)	77 (68%)	26 (36%)	2.74 (1.32–5.69)	0.007
2 or more	42 (23%)	37 (33%)	5 (7%)	5.48 (1.84–16.3)	0.002
3 or more	16 (9%)	14 (12%)	2 (3%)	2.82 (0.54–14.7)	0.219
Content of late effects					
Cardiovascular dysfunction	5 (4%)	5 (4%)	3 (4%)	1.19 (0.24–5.89)	0.835
Pulmonary dysfunction	3 (2%)	2 (2%)	1 (1.4%)	–	0.841[#]
Endocrinological dysfunction	34 (19%)	31 (27%)	3 (4%)	7.27 (1.81–29.3)	0.005
Short stature	25 (13%)	22 (20%)	3 (4%)	2.77 (0.74–10.4)	0.132
Kidney dysfunction	9 (5%)	7 (6%)	2 (3%)	2.26 (0.41–12.4)	0.349
Bone or muscle damage	18 (10%)	12 (11%)	6 (8%)	0.62 (0.42–4.18)	0.623
Skin disorder or hair loss	12 (7%)	10 (9%)	2 (3%)	1.18 (0.20–6.82)	0.854
Neurocognitive dysfunction	8 (4%)	7 (6%)	1 (1%)	6.39 (0.72–56.7)	0.096
Gastrointestinal dysfunction	3 (2%)	2 (2%)	1 (1.4%)	1.28 (0.09–17.5)	0.851
Liver dysfunction	16 (9%)	10 (9%)	6 (8%)	0.58 (0.17–1.97)	0.385
Immunological dysfunction	0	0	0	–	
Second cancer	5 (2.7%)	5 (4%)	0	–	0.070[#]
Chronic infection	0	0	0	–	
Others[b]	23 (12.6%)	19 (7%)	5 (7%)	3.16 (1.05–9.48)	0.004

[#] Non-adjusted p value

[a] Adjusted by cell transplantation, solid tumor, recurrence and duration after Tx completion

[b] Scoliosis, obesity, asymmetric face, poor vision, psychosocial problems, hearing loss, school absence, fatty liver, short bowel syndrome, and hypertension

Table 5 Adjusted odds ratios for various late effects according to radiation sites

Radiation sites	Adjusted odds ratio[a] (95% CI)				
	Skull (n = 67)	Spine (n = 8)	Total body (n = 28)	Chest/abdomen (n = 13)	Extremity (n = 5)
Number of late effects					
1 or more	2.40 (1.11–5.18)	3.06 (0.32–29.0)	3.36 (0.72–15.6)	1.15 (0.25–5.32)	0.91 (0.09–9.13)
2 or more	1.36 (0.57–3.28)	2.06 (0.37–11.4)	2.34 (0.65–8.41)	9.65 (2.34–39.8)	0.23 (0.02–2.76)
3 or more	1.66 (0.44–6.23)	6.42 (0.72–57.1)	2.19 (0.45–10.6)	1.56 (0.23–10.7)	
Content of late effects					
Cardiovascular dysfunction	1.16 (0.24–5.59)	–	–	1.18 (0.11–13.1)	5.09 (0.32–61.5)
Endocrine dysfunction	1.85 (0.68–5.04)	1.12 (0.15–8.11)	12.3 (2.63–57.2)	0.36 (0.06–2.25)	0.24 (0.02–3.36)
Short stature	1.63 (0.56–4.77)	14.1 (2.09–95.6)	1.95 (0.45–8.44)	0.39 (0.04–3.79)	–
Kidney dysfunction	0.81 (0.15–4.54)	–	2.71 (0.18–40.1)	4.47 (0.74–23.9)	–
Bone or muscle damage	0.52 (0.13–1.99)	2.14 (0.33–13.7)	1.39 (0.21–9.34)	4.27 (1.08–16.9)	0.74 (0.07–7.73)
Skin disorder or hair loss	2.26 (0.52–9.87)	–	1.04 (0.21–5.28)	3.91 (0.25–61.3)	–
Neurocognitive dysfunction	16.1 (2.28–114)	11.5 (1.24–106)	–	1.07 (0.11–10.6)	–
Gastrointestinal dysfunction	–	–	–	9.65 (0.72–12.8)	–
Liver dysfunction	0.51 (0.14–1.87)	–	0.44 (0.05–4.32)	2.40 (0.19–30.5))	–
Second cancer	0.19 (0.01–5.71)	–	–	1.81 (0.12–26.6)	23.3 (0.87–622)
Others[b]	1.49 (0.57–3.91)	2.20 (0.37–13.2)	2.62 (0.41–16.7)	1.54 (0.36–6.68)	0.96 (0.09–9.79)

[a] Adjusted by stem cell transplantation solid tumors, recurrence and duration after Tx completion

[b] Scoliosis, obesity, asymmetric face, poor vision, psychosocial problems, hearing loss, school absence, fatty liver, short bowel syndrome, and hypertension

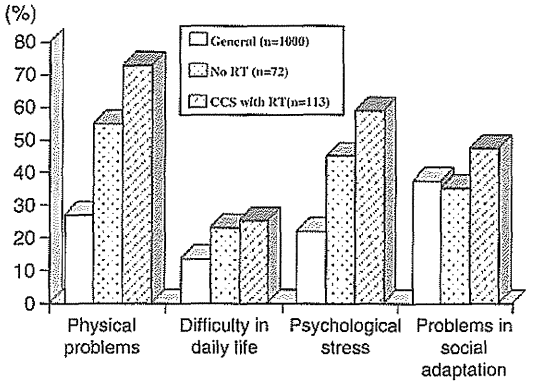

Fig. 3 General QOL of the 3 groups. Physical dysfunction, daily stress, and difficulties with social adaptation were observed in >50% of CCS treated with RT. The general QOL was affected in the CCS treated with compared with the CCS treated without RT and the general population. *Solid bars* the general population; *dotted bars* CCS treated without RT; *hatched bars* CCS treated with RT

Oeffinger et al. [16] reported that 62.3% of CCS exhibit at least 1 late effect and 27.5% exhibit 2 or more late effects. Our results showed similar trends except that late effects were observed in 68% of CCS treated with and 36% of CCS treated without RT. Endocrine system dysfunction is the most frequent complication among the late effects observed in CCS [17–19]. Miyoshi et al. [10] showed that endocrine abnormalities were observed in as many as 67% of 122 CCS in Japan; these data were obtained in cases where endocrinologists were actively involved in the long-term follow-up of CCS. Our results showed that TBI was significantly associated with endocrine dysfunction [11, 18, 20], skull and spinal irradiation with cognitive dysfunction [21], spinal irradiation with a short stature [22], and chest or abdominal irradiation with bone and soft tissue damage [23], respectively.

The multivariate logistic regression analysis in our previous article [5] revealed that independent significant risk factors besides RT and SCT for late effects were >15 years' duration after therapy completion, solid tumors, and one or more episodes of cancer recurrence. A poor subjective QOL was demonstrated in more than 50% of CCS with RT associated with various late effects, and its prevalence was significantly higher considering high adjusted ORs compared with the general population.

The limitations of our study were as follows: (1) a limited number of subjects was analyzed, (2) patients with solid tumors were underrepresented as compared to those with hematological cancers, (3) a selection bias might have been presented because patients were not recruited by random sampling, (4) incidence and time-to-event data were not available because of the cross-sectional design of the study, (5) thorough medical surveys were not conducted for certain complications such as dental problems and gonadal dysfunction, and (6) standardization of the radiation exposure was not conducted regarding the radiation machine source.

Finally, RT is a well known and the most important risk factor for secondary cancers in CCS. In our study, there were only 5 CCS with secondary cancers, but all cases received RT before the incidence of secondary cancer. Kony et al. [24] reported that both genetic factors and exposure to RT have independent effects on the risk of secondary cancers. The CCSS demonstrated that, in multivariate regression models adjusted for therapeutic radiation exposure, secondary cancers were independently associated with a female sex ($p < 0.001$), younger age at

Table 6 Adjusted odds ratios for poor QOL between RT and no RT group

Question	Group	Yes	No	χ^2 (p value)	Adjusted odds ratio[a] (95% CI)	p value
Physical dysfunction	With RT	81	30	<0.001	7.34 (4.67–11.5)	<0.001
	Non-RT	39	32		3.69 (2.21–6.13)	<0.001
	General	270	730		Ref	–
Difficulty in daily activity	With RT	28	85	0.002	1.92 (1.20–3.09)	0.007
	Non-RT	16	55		2.03 (1.10–3.73)	0.024
	General	136	864		Ref	–
Psychological stress	With RT	67	46	<0.001	5.24 (3.47–7.90)	<0.001
	Non-RT	32	39		2.74 (1.65–4.54)	<0.001
	General	217	783		Ref	–
Problems in social adaptation	With RT	53	59	0.106	1.40 (0.94–2.10)	0.103
	Non-RT	25	46		0.86 (0.51–1.48)	0.586
	General	374	626		Ref	–

[a] Adjusted by gender, age at survey, marital status, and student or not student

diagnosis (p for trend < 0.001), Hodgkin's lymphoma or soft-tissue sarcoma ($p < 0.001$ and $p = 0.01$, respectively), and exposure to alkylating agents (p for trend $= 0.02$) [8, 25]. A cohort study with an extended follow-up period is being conducted now by our research team to analyze the cumulative incidence and risk factors for secondary cancers in Japanese CCS.

5 Conclusions

1. A short stature was frequently observed among CCS treated with RT.
2. Late effects were noted in 68% of CCS treated with RT versus 36% of CCS treated without RT.
3. Skull and spinal RT were significantly associated with neurocognitive dysfunction, spinal RT with a short stature, TBI with endocrine dysfunction, and chest and/or abdominal RT with bone/soft tissue damage.
4. The general QOL was the most markedly affected in CCS treated with RT.

On the basis of these findings, we need to promote a further reduction of RT without a decrease in the survival rates. More studies on the long-term health effects in CCS are needed to improve the therapy in the future [26].

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Conflict of interest statement The authors declare no financial interests.

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REVIEW ARTICLE

Cellular kinetics of neuroblastoma and the role of surgery

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Abstract Neuroblastoma is known for its peculiar cellular kinetics, which has provoked some controversy regarding surgical treatment. Highly sensitive exploration systems using reverse transcription polymerase chain reaction (RT-PCR) methods have been developed to detect neuroblastoma cells. In our series of 49 patients with advanced neuroblastoma, circulating tumor cells (CTC) were detected by this system in 55.6% of the stage 4 patients who were examined, suggesting that the primary lesion may release tumor cells into the peripheral blood. The Kaplan–Meier survival rate was significantly lower among the patients with CTC or chemotherapy-insensitive bone marrow micrometastasis, compared with those without detectable micrometastasis (33.8 vs. 87.5%, $P < 0.05$). In contrast, a stage 3 patient with MYCN amplification exhibited drastic local relapse without systemic dissemination of the disease. Two patients were positive for CTC without an identifiable primary site. These observations indicate that the local growth of the primary tumor and tumor cell dissemination may be regulated by different molecular mechanisms in neuroblastomas. MYCN amplification seemed to be more closely associated with localized tumor growth but was minimally correlated with CTC positivity. High-risk neuroblastoma may include two separate subgroups characterized by different cellular kinetics: a local risk cohort and a systemic risk cohort. Surgical strategies for neuroblastoma should be determined with taking this cellular kinetics into consideration.

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Keywords Neuroblastoma · Cellular kinetics · Circulating tumor cell · Micrometastasis · Surgery

Introduction

Surgical treatment for neuroblastoma has been controversial. Without a doubt, surgery is a major therapeutic tool for macroscopic lesions. However, not only macroscopic tumors, but also the invisible spreading of tumor cells must be considered in cancer treatment strategies. This consideration is especially important for neuroblastomas, because neuroblastoma has peculiar cellular kinetics. Methods for detecting extremely small amounts of neuroblastoma cells have been developed and applied clinically to some extent, providing some suggestions regarding the cellular kinetics of this disease. On the other hand, the prognostic significance of micrometastasis has not been established for neuroblastomas. In the current review, these problems are described and our own experiences are presented.

Cellular kinetics of neuroblastoma

The unique clinical features are well known in neuroblastoma. Classically, a proportion of infantile patients who show massive metastases to the liver, bone marrow, and skin despite the presence of a small primary tumor has been described and is known as "stage IVS" [1]. The spontaneous regression of both the primary tumor and metastases are commonly observed in this unique population. Subsequently, the role of nerve growth factor and its receptor, trk A, has been clarified in the mechanism of the apoptosis of infantile neuroblastoma [2]. Previously, we reported a series of older cases of neuroblastoma that had no

radiologically identifiable primary tumor despite massive systemic metastases [3]. These clinical observations suggest that the local growth of the primary tumor and the systemic spreading of the tumor cells may be controlled by separate molecular mechanisms in neuroblastomas. The respective factors affecting the growth of primary and metastatic neuroblastomas have not been fully identified at present. How the primary tumor and the metastatic tumors grow independently also remains unknown. From the clinical point of view, studies on the mechanism of this peculiar form of cellular kinetics for neuroblastoma are definitely important in relation to the control of tumor growth and spreading.

Detection of neuroblastoma cells

To trace the cellular kinetics, the development of a highly sensitive method is required to detect neuroblastoma cells. Several methods have been developed to detect tumor cells with a very high sensitivity for some cancers. Immunocytochemical methods can detect tumor cells with a sensitivity of 1/10,000, and clinical applications of these methods have often been reported for patients with leukemia [4–6] as well as neuroblastoma [7, 8]. In the 1980s, molecular biological techniques became widespread. Using reverse transcriptase polymerase chain reaction (RT-PCR) method, a selected sequence of tumor-specific genomic mRNA can be amplified and visualized, enabling the detection of tumor cells amidst more than 10^6 mononuclear cells. More recently, nested PCR or a second PCR to increase the sensitivity even further as well as quantitative PCR have become more common. Several researchers have reported that the quantitative evaluation of the minimal residual disease might provide a higher prognostic value in the selected cancers including neuroblastoma [9–11]. These techniques enable the detection of micrometastases that are totally undetectable using conventional radiological imaging tools and microscopic exploration. Several trials, including our own, have explored the presence of extremely low levels of neuroblastoma cells in the peripheral blood and bone marrow [9, 12–17] (Fig. 1).

On the other hand, the most suitable molecular marker for specific cancers has not been established for many malignancies. Some markers provide a higher sensitivity, but a lower specificity. Tyrosine hydroxylase, PGP9.5 [18, 19], and, more recently, GD2 synthetase [20], GAGE [21], and cyclin D1 [22] have been named as specific markers of neuroblastoma cells. More than 95% of neuroblastomas exhibit a catecholamine biosynthesis pathway in their tumor cells [23]. Tyrosine hydroxylase is the first and rate-limiting enzyme of this pathway, and specifically expressed in most neuroblastoma cells. Thus, tyrosine hydroxylase

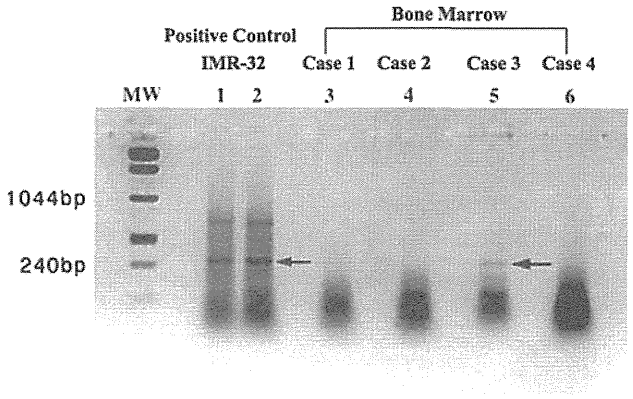

Fig. 1 Exploration of bone marrow micrometastasis of neuroblastoma using a single PCR method. *Lanes 1* and *2* IMR-32 cell line as the positive control. *Lanes 3–6* bone marrow samples harvested from four neuroblastoma patients. *Case 3* (*Lane 5*) showed positive signal for neuroblastoma at 256 bp, as observed in the positive control

mRNA is most commonly used as a molecular marker for neuroblastoma cells. Practically, several types of tyrosine hydroxylase mRNA synthesized using alternate splicing in exons 1 and 2 have been identified [24–26]. Therefore, the primers are usually designed to encode a common sequence region so as to detect all types of tyrosine hydroxylase mRNA [27].

The appropriate sensitivity of the PCR exploration is another problem that remains unsolved. The expression of genomic mRNA by contaminated leucocytes in a very small amount has been described as ectopic RNA. Two-step PCR methods possibly detect these non-specifically expressed mRNA [28]. Future clinical studies may be directed to standardize the methodology employed to detect micrometastatic neuroblastoma. Therefore, at present, all the staging and risk grouping systems are based on light microscopic observation.

Circulating tumor cells

In our own series of 49 patients with advanced neuroblastoma, who were treated between 1991 and 2007, circulating tumor cells (CTC) in the peripheral blood were detected in 55.6% of the stage 4 patients using our previously described single RT-PCR method [29]. The above two patients who exhibited massive metastases without an identifiable primary site also presented CTC positivity regardless of MYCN copy numbers. All the deaths in this cohort of patients with CTC were related to the systemic dissemination of the disease. CTC positivity was not detected in any of the stage 3 patients at this sensitivity level. The detection of CTC was not associated with MYCN amplification. The positive rate was 44.4% among the patients with amplified MYCN and 46.2% among the

patients with a single copy of MYCN [29]. Clinically, 75% of the patients who developed relapse with disseminated metastasis, had a single copy of the MYCN oncogene, whereas all the patients who developed local tumor relapse, showed amplification of MYCN (although the number of patients in this group was not large) [3].

These clinical observations suggest the following hypothetic model explaining the cellular kinetics in neuroblastomas. Tumor cells may grow at the primary site and, simultaneously, translocate into the peripheral blood as CTC to form distant metastases, which may be regulated by molecular mechanisms other than those controlling the local tumor growth (Fig. 2). Potentially, these primary and metastatic lesions may both become sources of CTC. Although the amplification of the MYCN oncogene is closely associated with localized tumor growth, it may be minimally correlated with the systemic dissemination of the disease.

In addition, these observations highlighted the existence of two clinical subgroups exhibiting different cellular kinetics in advanced neuroblastoma patients: a systemic risk cohort with CTC positivity, and a local risk cohort characterized by MYCN amplification but without micrometastasis. These two cohorts may correspond to the two categories in the INRG high-risk group [30].

Prognostic significance of micrometastasis

Although the prognostic significance of micrometastasis or CTC in the peripheral blood is better established for some of the hematological cancers, it remains controversial in neuroblastoma [9, 12–15]. We reported previously that the Kaplan–Meier survival rate was 42.0% in patients with CTC positivity in our series, and was definitely lower than that of 90.0% of the patients with no detectable CTC [29]. In our series, micrometastasis to the bone marrow was detected in 72.2% of the stage 4 patients who were examined. The positive rate was 85.7% in the patients with CTC positivity and 50% in the patients without detectable tumor cells in the peripheral blood. The temporary appearance of bone marrow micrometastasis did not affect the clinical outcome in our series. However, the persistent bone marrow micrometastasis after chemotherapy, which was detected in half of the patients, seemed to be associated with a poor prognosis. Combining these results, the Kaplan–Meier analysis showed a statistically significant difference in the survival rate between patients with CTC positivity and/or persistent bone marrow micrometastasis and those without detectable micrometastasis (33.8 vs. 87.5%; $P < 0.05$). Thus, our observations support a hypothesis that the presence of micrometastasis can be regarded as an independent clinical risk factor other than MYCN amplification, and has strong clinical implication on the determination of treatment strategy in advanced neuroblastoma. Similar observation regarding the bone marrow micrometastasis was also reported from Japan [31]. In addition, since these micrometastases are often chemotherapy resistant, they may include a cancer stem cell-like population of neuroblastoma cells, such as side population cells or tumor-initiating cells. More recently, Hansford et al. [32] succeeded in identifying a highly tumorigenic cell population in the bone marrow of neuroblastoma patients. Future study may be directed to control the proliferation of these cell populations.

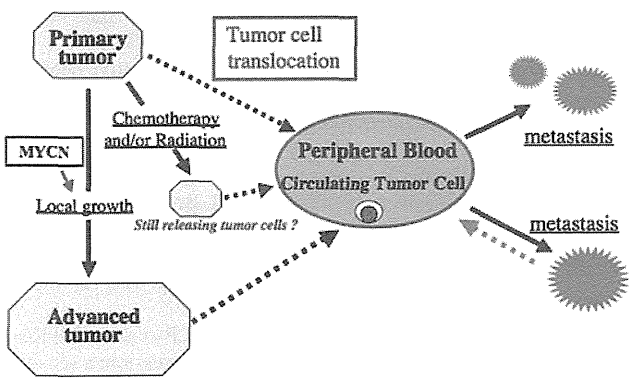

Fig. 2 Hypothetic model for cellular kinetics of neuroblastoma

Optimal local treatment

In recent concepts for neuroblastoma surgery, risk assessment has been emphasized in the design of surgical strategies. Different strategies should be applied according to the risk assessment. Image-defined risk factor (IDRF) is a recently proposed concept used to evaluate image diagnostic findings in a standard manner in relation to the risk groupings of neuroblastoma [33]. In infants with low or intermediate risks who exhibit IDRFs, surgical extirpation may be abandoned. The risk benefit balance of surgical treatment and presumably a benign tumor biology determine the surgical strategy. An analysis of molecular markers provides important information regarding the biological features of tumors, enabling surgical risks to be avoided.

Among the high-risk patients, aggressive surgery would benefit patients in the local risk cohort the most. In contrast, for those in the systemic risk cohort, the clinical impact of intensive surgical treatment remains unestablished [34]. Several studies, including ours, have demonstrated the clinical significance of intensive local treatment for neuroblastoma patients with stage 4 disease, whereas other studies have not [35–37]. We previously observed that no local relapse occurred after completing total resection of the primary tumor, systemic lymph node

dissection, and intraoperative radiation (IOR) [35]. Nevertheless, all the patients with macroscopic residual tumor died within 1 1/2 year after surgery because of systemic metastasis in this series. These observations suggest that surgical eradication may be essential for long-term survival in all patients with high-risk neuroblastomas. The primary tumor might still act as a source of neuroblastoma cells which are released into the peripheral blood, even after chemotherapy and IOR, possibly resulting in systemic relapse. Hypothetically, local control may also play an important role in controlling the systemic dissemination of the disease. If so, reducing the surgical intensity could be considered dangerous also in patients with metastasis. Further studies would be still required to determine if surgical intensity could be reduced even for the cases of the systemic risk cohort.

On the other hand, an interesting clinical trial is now in progress in Japan. This novel trial is characterized by non-stop chemotherapy until mega-therapy with stem cell transplantation, combined with delayed local therapy, including surgery, until the end of the treatment course [38]. The most beneficial aspect of this new protocol is the avoidance of delays in chemotherapy because of surgical complications.

Consideration of quality of life during the distant post-therapeutic period

Another aspect that should be considered when deciding on the surgical strategy is the securement of a satisfying post-therapeutic quality of life. A high incidence of morbidity has been associated with intensive local treatment [39, 40]. IOR can be used to control the primary site completely; however, the morbidity rate after intensive surgery with IOR was as high as 33.3% in our series. Renal vascular problems were seen in 15.2% of the patients, representing the most common complication after IOR [41]. Thus, modern surgical guidelines for advanced neuroblastoma recommend less harmful surgery and lymph node sampling instead of systemic dissection, and direct to avoid resection of surrounding organs.

Conclusions

In summary, both local and systemic risk must be considered when deciding on a surgical strategy. Some of the clinical observations presented above suggest that local control and systemic control therapies for neuroblastoma may interfere with each other. Therefore, a suitable balance between local and systemic therapy is extremely important for the treatment of neuroblastoma. The suitability of surgical therapy for neuroblastoma should be discussed also based on the observations of the cellular kinetics. Molecular biological tools may help pediatric surgeons to make appropriate decisions by providing a more detailed risk assessment in relation to the cellular kinetics.

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Factors Affecting Health Care Utilization for Children in Japan

Yasushi Ishida, Sachiko Ohde, Osamu Takahashi, Gautam A. Deshpande, Takuro Shimbo, Shigeaki Hinohara and Tsuguya Fukui

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Factors Affecting Health Care Utilization for Children in Japan

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KEY WORDS
ecology, medical care, physician visit, primary care, health diary

ABBREVIATION
OR—odds ratio

Dr Ishida participated in the conception and design of the study, analysis and interpretation of data, statistical analysis, and drafting the article; Drs Ohde and Takahashi participated in the conception and design of the study, acquisition of data, analysis and interpretation of data; Dr Deshpande participated in the interpretation of data and drafting the article; Drs Shimbo and Hinohara participated in the interpretation of data and critical revision of the article; Dr Fukui participated in the conception and design of the study, analysis and interpretation of data, and critical revision of the article. Final approval was made by all coauthors.

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WHAT'S KNOWN ON THIS SUBJECT: In the United States, the ecology of children's medical care is similar to that of adults. Health care utilization for children varies significantly by age, race, ethnicity, income, and health insurance status.

WHAT THIS STUDY ADDS: Compared with data from the United States, children in Japan more frequently visit both community physicians and hospital-based outpatient clinics. Pediatric health care utilization is influenced significantly by age but not affected by income or residence location in Japan.

abstract

BACKGROUND AND OBJECTIVE: Studies on the ecology of medical care for children have been reported only from the United States. Our objective was to describe proportions of children receiving care in 6 types of health care utilization seeking behaviors in Japan on a monthly basis and to identify care characteristics.

METHODS: A population-weighted random sample from a nationally representative panel of households was used to estimate the number of health-related symptoms, over-the-counter medicine doses, and health care utilizations per 1000 Japanese children per month. Variations in terms of age, gender, socioeconomic status, and residence location were also examined.

RESULTS: Based on 1286 households (3477 persons including 1024 children) surveyed, on average per 1000 children, 872 had at least 1 symptom, 335 visited a physician's office, 82 a hospital-based outpatient clinic, 21 a hospital emergency department, and 2 a university-based outpatient clinic. Two were hospitalized, and 4 received professional health care in their home. Children had 2 times more physician visits and 3 times more emergency visits than adults in Japan, and Japanese children had 2.5 times more physician visits and 11 times more hospital-based outpatient clinic visits than US children. Pediatric health care utilization is influenced significantly by age but not affected by income or residence location in Japan.

CONCLUSIONS: Compared with the data from the United States, more children in Japan visit community physicians and hospital-based outpatient clinics. Results of this study would be useful for further delineation of health care utilization of children in the context of a health care system unique to Japan. *Pediatrics* 2012;129:e113–e119

White et al[1] reported the first study on the ecology of medical care based on the population of the United States and the United Kingdom ~50 years ago. They showed that the main bulk of health service utilization occurred at physician visits (250 out of 1000 per month) with hospitalization comprising only 9 incidences out of 1000. Fukui et al[2] previously revealed that, compared with data in the United States, people in Japan visited community physicians and hospital-based outpatient clinics more frequently. This ecology model has been replicated over several decades,[3–6] including from our group,[2,7,8] with findings that were consistent with those of White et al.[1] This model has subsequently been widely used by both policy makers and educators.[9,10]

Unlike the medical system in the United States, Japan has a universal health care system, which allows virtually free health care access to everyone including children. Per recent Organization for Economic Co-operation and Development data,[11] Japan spent considerably less money, compared with the United States, on health care in terms of total health spending per capita (US$ 2729 vs 7538 in 2008) and percent of gross domestic product (8.1% vs 16.0% in 2008). Thus, it is speculated that health care–seeking behavior and health service utilization in Japan may be substantially different from that in the United States. However, no well-designed studies on patients' health care–seeking behavior for health-related symptoms have been conducted, although there are reports of limited sample size.[7,12]

To date, studies on the ecology of medical care for children have been reported only from the United States.[13,14] No similar investigation has been made for the Japanese population. The medical ecology of Japanese children's health care may be different from not only that of Japanese adults but also that of children in the United States. Our objective for this study was to assess health care–seeking behavior of children in Japan by using a nationally representative panel of households.

METHODS

Study Design

A prospective cohort design was employed.

Sample

A nationally representative panel belonging to Japan Statistics and Research Co Ltd that comprised 210 000 households was used (Fig 1). Taking into consideration the size of the cities, towns, and villages, a population weighted random sample of 5387 households was chosen and each household was sent an offer letter with a return envelope. Of the total, 1857 agreed to participate. The sample size was readjusted demographically to 1464 households to make it nationally representative.

Data Collection

Questionnaires and diaries were used for data collection. The questionnaires were scripted to note children's baseline characteristics including family information. The diary was designed to keep a record of any health-related events, symptoms, health care–seeking behavior, and actual use of health services, along with other variables of interest. Parents or other eligible persons were asked to fill out the questionnaires and diaries for children younger than 13 years and those who could not write on their own. The advantage of health diaries includes the ability to keep a record of events continuously and consistently while minimizing recall bias.

Definitions of Variables

1. Age: 4 age groups were identified: <2 years, 2 to 5 years, 6 to 12 years, and 13 to 17 years.
2. Gender
3. Education: 3 categories were defined by the highest degree attained by the head of the household in which a child resided: high school or lower, college/vocational school, and university/graduate school.
4. Economic status: family annual income was divided into 3 categories: <5 million Japanese yen, 5 million to 7 million Japanese yen, and >7 million Japanese yen.
5. Residence location: a large city was defined as a city with a population >1 million, a medium-sized city was identified as 100 000 to 1 million, and a small city/town as <100 000 inhabitants. Residents living outside a city or town were defined as rural.
6. Number of children: the number of children in a family was divided into 3 groups: 1 child, 2 children, and ≥3 children.
7. Single-parent households were defined as family units in which a child's mother or father served as the sole caretaker; responses were classified as "yes" or "no."

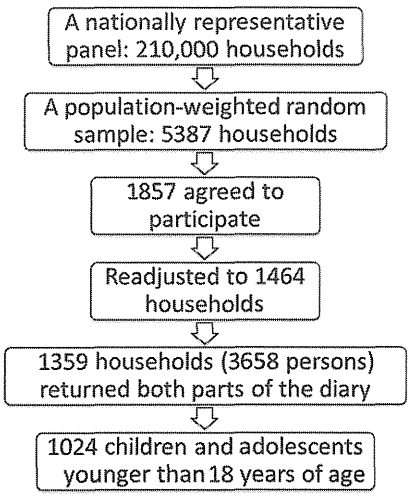

FIGURE 1
Sampling process of this study. Of 1857 households agreeing to participate, the sample size was readjusted to 1464 households to make it nationally representative. Among 3658 persons in 1359 households who returned the diary, we analyzed those of 1024 children and adolescents aged 0 and 17 years.

8. Family living together with grandparents; responses were classified as "yes" or "no".

Ethical Considerations

After obtaining informed consent by post, health diaries (divided into 2 parts, each of 2 weeks duration), questionnaires for recording baseline data, and gift vouchers of 3000 Japanese yen (~30 US$) per person were sent to each member of the 1464 enrolled households in September 2003. The diaries were recorded from October 1, 2003, to October 31, 2003.

A manual accompanied the health diaries to facilitate recording the required information. The diary was in the form of a softbound letter-sized book. Participants were asked to return the first part of the diary after 15 days of entries, whereas the second part was returned after completion of the study period. A weekly phone call to each enrolled family was made as a reminder. Ethical approval was obtained from the research ethics committee of Kyoto University Graduate School of Medicine, Japan.

Statistical Analysis

Descriptive analyses, along with confidence intervals, were performed to estimate the number of different health care–seeking behaviors per 1000 persons per month. We performed χ^2 tests or a Fisher's exact test (for any cells with expected counts <5) within categorical predictors. Dichotomous analyses indicated strong associations between each predictor variable and participation by children in 1 or more health care settings. Too few children used home care services and university hospitals to produce reliable estimates. Therefore, 4 separate logistic regression analyses were performed to derive adjusted odds ratios (ORs) of the independent association of each predictor variable. All data were analyzed by SPSS statistical software, version 19.0 (IBM Japan Ltd, Tokyo, Japan).

RESULTS

Of 1000 children aged 0 to 17 years, on average each month, 872 had at least 1 symptom, 167 visited a physician in the community clinic office setting, 82 visited a hospital-based outpatient clinic, 20 received care in an emergency department, 4 received professional health services in their home, and 2 spent time as an inpatient in a hospital (Fig 2).

Table 1 shows the estimated proportion of children reporting clinical symptoms during a typical month. Most symptoms were significantly dependent on the age of the child. Frequency of symptoms associated with upper respiratory infections (sneezing, cough, fever) or gastrointestinal symptoms (diarrhea and vomiting) was closely correlated with younger age. In contrast, frequency of symptoms associated with pain (sore throat, abdominal pain, headache, leg or toe pain, knee pain, and lumbago) was closely correlated with older age. Children in the older age group (13–17 years) showed similar patterns compared with the adult group; 8 out of the 10 most frequent symptoms were shared between the 2 groups, with the exception of stiff neck and knee pain, which were more common in adults.

Table 2 compares the ecology of medical care for Japanese children in this study with that of adults in Japan[2] and children in the United States.[13] Nearly the same proportion of Japanese children and adults reported at least 1 symptom (OR = 1.14).[2] The ORs of Japanese children visiting a physician's clinic or outpatient hospital clinic were 2.51 and 11.1, respectively, compared with children in the United States.[13] The ORs associated with Japanese children taking over-the-counter medicine, visiting a physician's community clinic, outpatient hospital clinic, or being admitted to hospital were 0.76, 2.15, 3.04, and 0.25, respectively, compared with Japanese adults.[2]

Table 3 demonstrates the estimate for number of children receiving care in different health care settings, stratified by the child/family sociodemographic characteristics. Univariate analysis using χ^2 test or Fisher's exact test revealed that children's age, annual income of the family, education level of

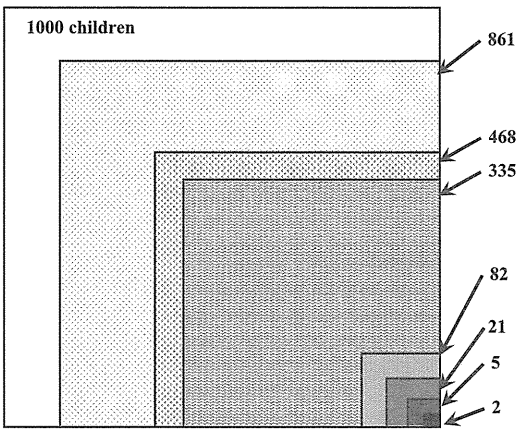

FIGURE 2
Participation in medical care in a typical month for 1000 children and adolescents aged 0 and 17 years. Boxes visually represent proportional participation categorized by type of medical care; smaller boxes do not indicate inclusive subgroups of larger boxes; 861 participants report some clinical symptoms, 468 take some medicine, 335 visit physician's office, 82 visit a hospital outpatient clinic, 21 visit an emergency clinic, 5 visit a university hospital outpatient clinic, and 2 are hospitalized.

TABLE 1 Estimated Proportion of Children Experiencing Clinical Symptoms During a Typical Month, *n* (%)

Symptoms	<2 y (*n* = 89)	2–5 y (*n* = 263)	6–12 y (*n* = 468)	13–17 y (*n* = 204)	χ^2,*P*	Total (*n* = 1024)	Reference (Japanese adults, *n* = 2453)[a]
Sneezing	67 (75.3)	168 (63.9)	184 (39.3)	58 (28.4)	<.0001	477 (48.6)	394 (16.1)
Cough	47 (52.8)	161 (61.2)	150 (32.1)	22 (10.8)	<.0001	380 (37.1)	338 (13.8)
Sore throat	7 (7.9)	33 (12.5)	99 (21.2)	59 (28.9)	<.0001	198 (19.3)	441 (18.0)
Fever	33 (37.1)	71 (27.0)	62 (13.2)	24 (11.8)	<.0001	190 (18.6)	166 (6.8)
Abdominal pain	1 (1.1)	30 (11.4)	73 (15.6)	43 (21.1)	<.0001	147 (14.4)	267 (10.9)
Headache	1 (1.1)	9 (3.4)	67 (14.3)	50 (24.5)	<.0001	127 (12.4)	719 (29.3)
Abrasion	7 (7.9)	30 (11.4)	54 (11.5)	5 (2.5)	.001	96 (9.4)	36 (1.5)
Leg or toe pain	1 (1.1)	6 (2.3)	53 (11.3)	25 (12.3)	<.0001	85 (8.3)	191 (7.8)
Common cold	6 (6.7)	20 (7.6)	29 (6.2)	15 (7.4)	.889	70 (6.8)	202 (8.2)
Muscle pain	0	1 (0.4)	25 (5.3)	38 (8.2)	<.0001	64 (6.3)	171 (7.0)
Bruising	9 (10.1)	11 (4.2)	37 (7.9)	6 (2.9)	.016	63 (6.2)	36 (1.5)
Itching	2 (2.2)	24 (9.1)	26 (5.6)	6 (2.9)	.014	58 (5.7)	75 (3.1)
Diarrhea	12 (13.5)	22 (8.4)	18 (3.8)	5 (2.5)	<.0001	57 (5.6)	121 (4.9)
General fatigue	1 (1.1)	6 (2.3)	25 (5.3)	14 (6.9)	.032	46 (4.5)	443 (18.1)
Dermatitis	9 (10.1)	12 (4.6)	17 (3.6)	6 (2.9)	.032	44 (4.3)	40 (1.6)
Nausea	1 (1.1)	9 (3.4)	24 (5.1)	9 (4.4)	.319	43 (4.2)	112 (4.6)
Knee pain	0	4 (1.5)	24 (5.1)	12 (5.9)	.009	40 (3.9)	206 (8.4)
Tooth pain	0	5 (1.9)	21 (4.5)	5 (2.5)	.056	31 (3.0)	112 (4.6)
Vomiting	7 (7.9)	12 (4.6)	11 (2.4)	1 (0.5)	.002	31 (3.0)	14 (0.6)
Hand or finger pain	1 (1.1)	7 (2.7)	19 (4.1)	3 (1.5)	.194	30 (2.9)	86 (3.5)
Dry skin	2 (2.2)	5 (1.9)	15 (3.2)	7 (3.4)	.696	29 (2.8)	28 (1.1)
Lumbago	0	1 (0.4)	13 (2.8)	14 (6.9)	<.0001	28 (2.7)	650 (26.5)

[a] Other common symptoms in adults, *n* (%): stiff neck, 555 (22.6); stomachache, 188 (7.7); shoulder pain, 149 (6.1); and menstrual pain, 130 (6.1).

the head of household, number of children in the family, and single parenthood were significant factors in the health care–seeking behavior of children.

Table 4 shows the results of multivariate analyses. Receipt of care in physicians' community clinic was the most sensitive to various sociodemographic characteristics in the model (age, education level, number of children, and single parenthood), with the exception of annual income and residence location. Community clinic visits were significantly more likely for younger children compared with children ≥13 years of age (OR = 7.32, $P < .001$ for children aged <2 years; OR = 5.66, $P < .001$ for children aged 2–4 years; OR = 2.41, $P = .001$ for children aged 6–12 years). Conversely, physicians' clinic visits were significantly less likely for children in families where the head of the household had a university or graduate school level of education (OR = 0.55, $P = .008$), 3 or more children in the family (OR = 0.55, $P = .024$), or single parenthood (OR = 0.49, $P = .032$; Table 4, including 95% confidence intervals of ORs).

As for over-the-counter medicines, use of these medications increased with older age. Of note, children living with grandparents took less over-the-counter medicines in the multivariate model (Table 4).

Children's age was also the strongest predictor for seeking care in an emergency department (OR = 6.82) and a hospital-based outpatient clinic (OR = 3.31). Families with higher annual income tended to visit community clinics (OR = 1.19) over hospital outpatient clinics (OR = 0.43). Gender and residence location were not independently associated with variation in proportions of children receiving care in any of the health care settings investigated.

DISCUSSION

This study is the first application of the classic ecology of medical care model to Japanese children. We demonstrate that the same proportion of Japanese children as adults reported at least 1 symptom during the study period[2] and that a substantial proportion of children have an encounter with the health care system in a typical month. Although overall patterns appear generally

TABLE 2 Ecology of Medical Care for Japanese Children Versus Adults in Japan and children in the United States

	This Study (Children <18 y)	OR of Children in Japan Versus the United States	OR of Japanese Children Versus Adults	Children in the United States (Dovey et al[13])	Adults in Japan (Fukui et al[2])	Adults in the United States (Dovey et al[13])
Having at least 1 symptom	872 (850–892)	NA	1.14 (0.88–1.47)	NA	857 (842–871)	NA
Taking an over-the-counter medicine	468 (442–494)	NA	0.76 (0.64–0.91)	NA	536 (510–562)	NA
Visiting a physician's clinic	335 (306–365)	2.51 (2.03–3.11)	2.15 (1.75–2.64)	167 (161–174)	190 (174–206)	235 (229–241)
Visiting an emergency department	20.5 (12.7–31.2)	1.63 (0.81–3.27)	3.04 (1.29–7.19)	12.8 (11.7–13.9)	6.5 (3.4–11.3)	13.0 (12.2–13.8)
Visiting an outpatient clinic in community hospital	82 (66–101)	11.1 (5.33–23.0)	0.86 (0.63–1.17)	8.2 (7.0–9.4)	94 (81–108)	25.8 (24.0–27.6)
Visiting an outpatient clinic in a university hospital	4.9 (1.6–11.4)	NA	0.71 (0.23–2.26)	NA	6.5 (3.4–11.3)	NA
Requiring hospitalization[a]	2.0 (0.2–7.0)	0.50 (0.09–2.73)	0.25 (0.05–1.17)	3.5 (2.7–4.3)	7.6 (4.4–12.7)	13.3 (9.6–11.0)
Requiring home health care	3.9 (1.1–10.0)	2.00 (0.37–11.0)	1.34 (0.30–5.98)	2.2 (1.4–3.0)	3.3 (1.4–6.4)	17.7 (15.6–19.8)

Values are given as number per 1000 (95% confidence interval) unless otherwise stated. NA, not available.
[a] Excluding hospital stays for birth.

TABLE 3 Estimates for Number of Children Per 1000 Participating in Health Care in a Typical Month by Sociodemographic Characteristics and Settings (%)

Demographic Characteristic	Taking an Over-The-Counter Medicine	Visiting a Physician's Clinic	Visiting an Emergency Department	Visiting an Outpatient Clinic in a Community Hospital	Visiting an Outpatient Clinic in a University Hospital	Requiring Hospitalization[a]
Age, y	$P < .0001$	$P < .0001$	$P < .0001$	$P < .0001$	$P = .537$	–
<2 ($n = 89$)	21 (24.7)	52 (59.6)	8 (9.0)	16 (18.0)	1 (1.1)	0
2–5 ($n = 263$)	107 (41.8)	115 (44.9)	8 (3.0)	31 (12.2)	1 (0.4)	0
6–12 ($n = 468$)	229 (50.0)	134 (29.3)	3 (0.6)	25 (5.6)	3 (0.6)	1 (0.2)
13–17 ($n = 204$)	110 (55.4)	34 (17.2)	2 (1.0)	10 (4.9)	0	1 (0.5)
Gender	$P = .992$	$P = .554$	$P = .068$	$P = .565$	$P = .999$	$P = .999$
Boy ($n = 530$)	242 (46.8)	178 (34.3)	15 (2.8)	45 (8.7)	3 (0.6)	1 (0.2)
Girl ($n = 494$)	226 (46.8)	157 (32.6)	6 (1.2)	37 (7.7)	2 (0.4)	1 (0.2)
Annual income, JPY	$P = .597$	$P = .371$	$P = .011$	$P = .020$	$P = .458$	–
<5 million ($n = 342$)	164 (46.2)	125 (35.4)	5 (1.5)	37 (10.5)	1 (0.3)	0
5–7milion ($n = 309$)	161 (50.2)	104 (32.4)	13 (4.2)	30 (9.4)	3 (1.0)	2 (0.6)
≧7 million ($n = 314$)	158 (48.4)	98 (30.3)	3 (1.0)	16 (4.8)	1 (0.3)	0
Education of head of household	$P = .040$	$P = .031$	$P = 0170$	$P = .853$	$P = .801$	$P = .999$
High school or lower ($n = 391$)	197 (40.7)	177 (36.6)	10 (2.0)	37 (7.7)	1 (0.3)	1 (0.3)
College/vocational school ($n = 188$)	114 (48.9)	74 (31.9)	1 (0.5)	17 (7.4)	1 (0.5)	0
University/graduate school ($n = 228$)	141 (50.0)	74 (26.3)	7 (2.6)	25 (8.8)	1 (0.4)	1 (0.4)
Residence location	$P = .416$	$P = .720$	$P = .464$	$P = .665$	–	–
Large city ($n = 94$)	42 (45.7)	33 (36.2)	4 (4.3)	6 (6.4)	1 (1.1)	0
Middle city ($n = 225$)	105 (48.0)	72 (32.9)	4 (1.8)	16 (7.1)	0	0
Small town ($n = 450$)	194 (44.2)	152 (34.7)	8 (1.8)	41 (9.3)	2 (0.4)	0
Rural area ($n = 255$)	126 (50.6)	77 (31.0)	5 (2.0)	20 (7.8)	2 (0.8)	2 (0.8)
Number of children	$P = .147$	$P = .002$	$P = .248$	$P = .087$	$P = .845$	$P = .213$
1 ($n = 165$)	70 (41.2)	67 (39.4)	14 (8.5)	3 (1.8)	0	1 (0.6)
2 ($n = 522$)	266 (49.4)	188 (34.9)	51 (9.4)	16 (3.1)	3 (0.6)	0
≧3 ($n = 283$)	145 (49.8)	72 (24.7)	18 (6.0)	2 (0.7)	2 (0.7)	1 (0.4)
Single parent	$P = .002$	$P = .914$	$P = .096$	$P = .841$	$P = .999$	$P = .999$
Yes ($n = 127$)	42 (33.9)	41 (33.1)	0	11 (8.7)	0	0
No ($n = 897$)	426 (48.6)	294 (33.6)	21 (2.3)	71 (8.1)	5 (0.6)	2 (0.2)
Living with grandparents	$P = .821$	$P = .795$	$P = .152$	$P = .134$	$P = .590$	$P = .999$
Yes ($n = 182$)	92 (48.9)	60 (31.9)	1 (0.5)	10 (5.5)	0	0
No ($n = 788$)	390 (48.0)	267 (32.9)	21 (2.5)	72 (8.9)	5 (0.6)	2 (0.3)

JPY, Japanese yen.

[a] Excluding hospital stays for birth.

similar for children and adults,[2] the proportions of each group differed significantly. Despite the same frequency of clinical symptoms,[2] twice as many children visited a community clinic and 3 times as many children visited emergency rooms, whereas the number requiring hospitalization was 4 times that of adults in Japan.[2] Compared with results from the United States,[13] 2.5 times more Japanese children visited a community physician's office or emergency clinic, and 11 times more Japanese children visited hospital-based outpatient clinics.

As expected, age strongly affected the ecology of medical care for children. Among all children, those <2 years of age were less likely to take over-the-counter medicine and most likely to receive care at least once in a typical month regardless of clinical setting. Children 2 to 5 years of age were more likely than those 13 to 17 years of age to receive care regardless of setting. In contrast, a smaller proportion of children aged 6 to 12 years, compared with those aged 13 to 17 years, received care in emergency departments, whereas the oldest age group comprised the least visits to both outpatient hospital-based and community clinics. These results are consistent with the previous report from the United States.[13]

Recently, pediatric professional organizations in the United States and elsewhere have recommended that over-the-counter medications, including cough and cold remedies, should not be given to infants.[15–18] Our data suggest that Japanese parents restrict use of over-the-counter medications for younger children, especially those younger than 2 years of age. Of note, living with grandparents was associated with significantly reduced over-the-counter medicine use. Several possible interpretations for this association may be considered; grandparents may have a lower threshold taking an ill grandchild to a clinic, or grandparents may be especially adverse to over-the-counter medicine use for children.

Multivariate regression analysis in our study confirmed that children's health care–seeking behavior is affected more substantially by age than by any other socioeconomic characteristics included in our study, a finding also consistent with previous reports from

TABLE 4 Adjusted ORs (95% Confidence Interval) for Children's Health Care Participation by Sociodemographic Characteristics and Setting

Demographic Characteristic	Taking an Over-the-Counter Medicine	Visiting a Physician's Clinic	Visiting an Emergency Department	Visiting an Outpatient Clinic in Any Hospital
Age, y				
<2	0.18 (0.09–0.36)	7.32 (3.64–14.7)	6.82 (1.22–38.1)	3.31 (1.30–8.46)
2–5	0.42 (0.26–0.69)	5.66 (3.21–9.97)	2.52 (0.47–13.4)	1.56 (0.67–3.66)
6–12	0.72 (0.46–1.11)	2.41 (1.41–4.11)	0.23 (0.02–2.58)	0.82 (0.35–1.93)
13–17	Reference	Reference	Reference	Reference
Gender				
Boy	0.82 (0.60–1.13)	0.90 (0.64–1.26)	0.62 (0.20–1.90)	1.04 (0.60–1.79)
Girl	Reference	Reference	Reference	Reference
Annual income of family, JPY				
<5 million	Reference	Reference	Reference	Reference
5–7milion	0.97 (0.65–1.46)	1.05 (0.69–1.61)	2.40 (0.66–8.74)	0.86 (0.45–1.65)
≧7 million	0.81 (0.53–1.25)	1.19 (0.76–1.87)	1.22 (0.24–6.09)	0.43 (0.19–0.96)
Education of head of household				
High school or lower	Reference	Reference	Reference	Reference
College/vocational School	1.40 (0.91–2.13)	0.75 (0.49–1.17)	0.19 (0.02–1.56)	1.11 (0.53–2.32)
University/graduate school	1.17 (0.77–1.77)	0.55 (0.35–0.86)	0.81 (0.25–2.67)	1.80 (0.88–3.68)
Residence location				
Large city	0.72 (0.40–1.28)	0.78 (0.42–1.43)	1.03 (0.21–5.04)	0.64 (0.22–1.88)
Middle city	0.75 (0.47–1.20)	0.85 (0.51–1.40)	0.28 (0.03–2.55)	0.88 (0.39–2.00)
Small town	0.76 (0.51–1.13)	0.89 (0.58–1.36)	0.61 (0.17–2.21)	1.05 (0.54–2.03)
Rural area	Reference	Reference	Reference	Reference
Number of children				
1	Reference	Reference	Reference	Reference
2	1.26 (0.83–1.91)	0.66 (0.42–1.01)	1.95 (0.50–7.68)	1.03 (0.52–2.03)
≧3	1.42 (0.88–2.30)	0.55 (0.35–0.86)	1.06 (0.16–7.19)	0.68 (0.28–1.60)
Single parent				
Yes	0.85 (0.48–1.53)	0.49 (0.25–0.94)	—	1.78 (0.69–4.59)
No	Reference	Reference	Reference	Reference
Living with grandparents				
Yes	0.63 (0.40–0.98)	1.06 (0.66–1.72)	0.57 (0.07–4.98)	1.31 (0.59–2.92)
No	Reference	Reference	Reference	Reference

JPY, Japanese yen.

the United States.[13,14] Of particular interest is the physicians' office setting where, adjusting for other variables, fewer children received care if they had 2 or more siblings, a single parent, or were living with a head of household with a higher level of educational attainment. No association of medical access with either annual family income or residence location was demonstrated, a fact to which the robust Japanese universal health care system might plausibly contribute.[19–21] It is interesting to consider that the United States might also anticipate a trend toward the findings in this study if recent health reforms, in addition to promotion of the medical home concept, provide wider insurance coverage to help ensure that all children have equitable access to appropriate health care resources.[13,22,23]

Although Dovey et al[13] were unable to reproduce estimates of clinical symptoms reported in the original study by White et al,[1] our study produced comparable estimated proportions of reported clinical symptoms for children. Population-based literature on children experiencing clinical symptoms is sparse and outdated. Our nationally representative study provides these estimates for children in Japan according to age group. This study revealed that frequency of symptoms associated with upper respiratory infections or gastrointestinal symptoms was closely correlated with younger age and that frequency of pain symptoms was closely correlated with older age.

This study has important strengths. First, this analysis was based on a nationally representative sample that was large enough to produce reasonably precise estimates of the true proportions of children receiving care. This is particularly helpful to generalize our findings to the Japanese pediatric population at large. Second, data were collected from the surveyed sample by using a medical diary, which minimized recall bias. Shaul et al[24] reported that providing both an adult and child survey to an adult could result in lower response rates. However, the response rate in our study (92.8%) was satisfactory. D'Souza-Vazirani et al[25] showed that mothers are a good source of information regarding children's acute health care use. Third, the summary findings are based on a single cohort.

There are, however, some limitations to our study. First, data were collected during a single month (October). Seasonal variations of disease incidence and prevalence, especially in children, could result in estimates different from the current data. October is soon after school begins in the United States and is a time of relatively high numbers of upper respiratory infections and minor illnesses that may result in a significant increase of health care utilization. In contrast, in Japan, the school year begins in April. As such, October represents a typically uneventful and calm month for children in terms of health status. Second, we did not evaluate the appropriateness of particular health care–seeking behaviors because disease outcome data related to individual children's symptoms were not collected.

CONCLUSIONS

Compared with the data from the United States, more children in Japan visit both community physicians' clinics and hospital-based outpatient clinics. The health care–seeking behavior of

children was influenced significantly by children's age but not affected by income or location of residence in Japan. Results of this study will be useful for further delineation of health care–seeking behavior of children in the context of a health care system unique to Japan.

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Factors Affecting Health Care Utilization for Children in Japan

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