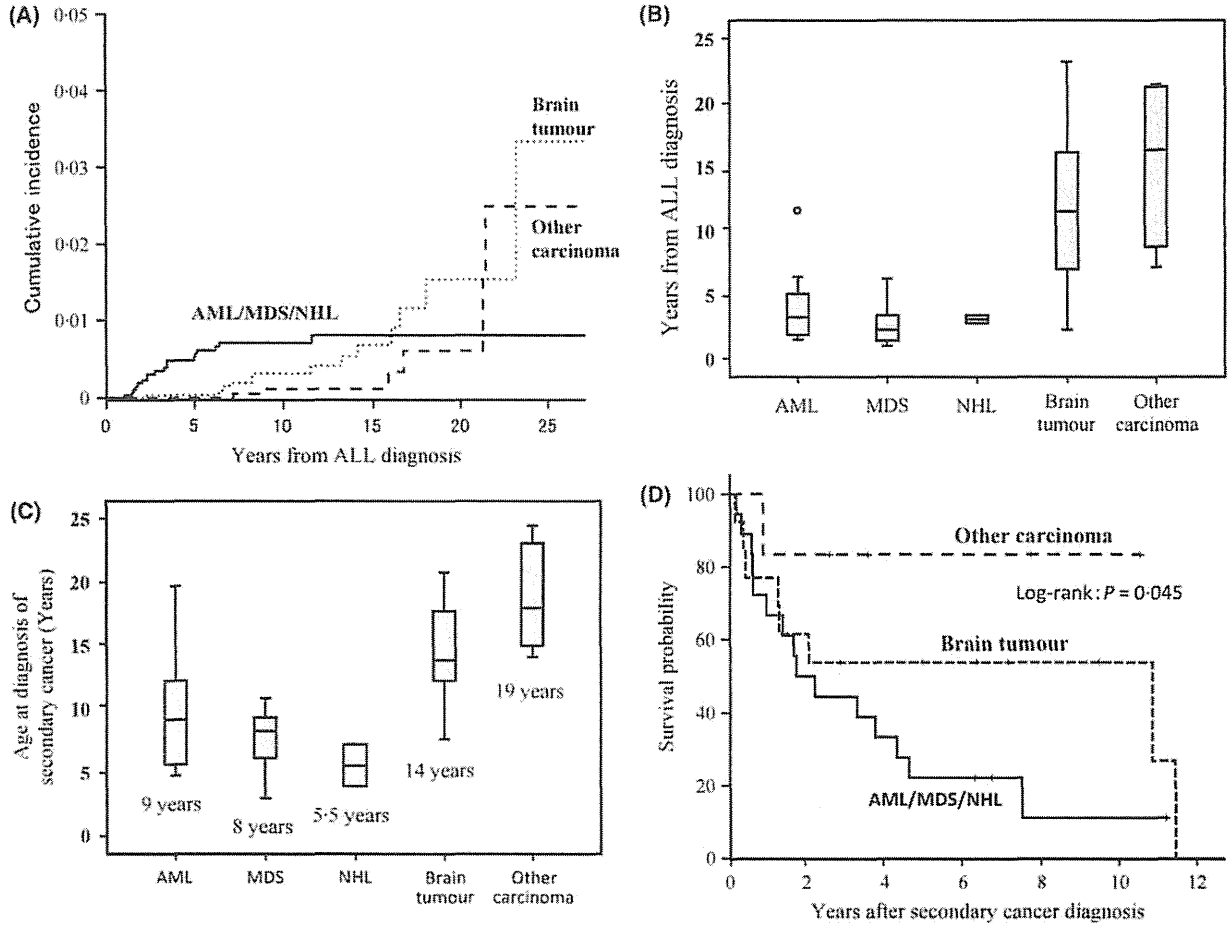

Fig 3. Clinical characteristics according to types of secondary cancer. (A) Cumulative incidence by years since ALL diagnosis of specific secondary cancers including AML/MDS/NHL (solid line), brain tumour (dotted line), and other carcinoma (dashed line). (B) The median latency period from diagnosis of ALL to development of specific secondary cancers. The median time for haematological cancers (AML, MDS and NHL) was shortest, followed by brain tumours and other solid carcinoma. (C) Age at diagnosis of secondary cancers; generally, the median age of haematological cancers was younger compared to brain tumours and other carcinomas. (D) Overall survival of secondary cancer patients are shown using Kaplan–Meier survival curves. Survival probabilities were the lowest for patients with AML/MDS/NHL. Actuarial survival at 4 years from diagnosis of secondary cancers depend on the type; AML/MDS/NHL 33%; brain tumours 54%; other carcinoma 83%. AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; NHL, Non-Hodgkin lymphoma.

initial WBC, immunophenotype, anticancer agents (with the exception of CPM) and maintenance duration of the primary ALL (Table III and Figure S2). Because protocol and anticancer drugs were highly correlated, we were unable to effectively evaluate them in the same multivariate regression analysis. Thus, results using Cox regression adjusting for covariates including treatment protocol (but not anticancer drug) (Table III) showed that CRT was associated with a 6-fold increased risk of secondary cancers compared to patients not receiving CRT (HR = 6·02, 95% CI 1·46–24·8). When CRT was categorized into 3 groups based on dose (i.e. no CRT, 18 Gy, and >24 Gy), similarly increased risks were observed for the moderate and high dose categories (data not shown). Age at ALL diagnosis >7 years (versus 3 years or younger, HR = 3·01, 95% CI 1·14–7·94) and inclusion in the more recent TCCSG L99-15/L04-1502 protocol (versus L84-11, HR = 8·15, 95% CI 1·03–64·7) were independently associated with an increased risk of secondary cancers. The same model, but replacing treatment protocol with the anticancer drugs (i.e. CPM, yes versus no; etoposide, yes versus no; high-dose methotrexate, yes versus no) showed an attenuated risk estimate for CPM (HR = 1·84, 95 CI 0·32–10·4), despite it being statistically significant in the unadjusted analysis (OR = 3·05, 95% CI 1·06–8·76).

Discussion

The risk of secondary cancers in childhood ALL survivors may be influenced by genetic predisposition, but growing evidence shows therapeutic regimen to be another major contributing factor. The risk of developing secondary cancers should be interpreted in the context of the survival

Table III. Cox-regression analysis evaluating the association between select characteristics of the primary ALL diagnosis and risk of developing a secondary cancer.

Intention to treat analysis group (n = 2807)	Patients with Secondary cancer	Patients without Secondary cancer	Crude HR (95%CI)	Adjusted HR (95%CI)	P-value
Protocol					
L84-11	12	476	Reference	Reference	
L89-12	7	392	1·00 (0·37–2·69)	1·35 (0·47–3·84)	0·576
L92-13	4	336	0·78 (0·24–2·56)	3·64 (0·45–29·1)	0·224
L95-14	4	584	0·56 (0·17–1·91)	4·47 (0·46–43·6)	0·198
L99-15/L04-1502	10	982	1·12 (0·42–3·01)	8·15 (1·03–64·7)	0·047
Risk classification					
Standard risk	7	1021	Reference	Reference	
Intermediate risk	20	956	3·42 (1·44–8·08)	2·70 (0·84–8·69)	0·096
High risk	10	771	2·67 (1·02–7·03)	1·01 (0·21–4·84)	0·992
Age at ALL diagnosis					
3 years or younger	8	986	Reference	Reference	
4–7 years	12	965	1·63 (0·67–3·98)	1·76 (0·71–4·40)	0·224
8 years or older	17	888	3·10 (1·34–7·21)	3·01 (1·14–7·94)	0·026
Gender: Male/Female	18/19	1530/1207	1·29 (0·68–2·46)	1·37 (0·71–2·62)	0·347
Attained age ≥20 years: No/Yes	20/17	2054/685	0·89 (0·42–1·90)	0·46 (0·19–1·12)	0·089
Cranial irradiation: No/Yes	8/29	1310/1445	2·57 (1·15–5·75)	6·02 (1·46–24·8)	0·013
Maintenance >1·5 years: No/Yes	15/22	1547/1209	1·16 (0·57–2·36)	3·19 (0·55–18·4)	0·194
Anticancer drugs					
Anthracycline: No/Yes	4/33	182/2574	1·32 (0·45–3·89)	N/A	N/A
Cyclophosphamide: No/Yes	4/33	448/2308	3·05 (1·06–8·76)	N/A	N/A
Etoposide: No/Yes	24/13	1910/846	1·30 (0·65–2·60)	N/A	N/A
High-dose Methotrexate: No/Yes	15/22	793/1963	0·77 (0·23–2·54)	N/A	N/A

ALL, acute lymphoblastic leukaemia; HR, hazard ratio; 95% CI, 95% confidence interval; N/A, not available.
Total number of patients may not equal 2807 for all variables due to missing data.

probability for a given treatment protocol, as low survival will result in fewer secondary cancers. Although the lifetime incidence of secondary cancers has not yet been defined, within the first 20 years of initial diagnosis of childhood ALL, previous studies conducted the U.S. and Europe have estimated it to be between 2% and 5%. To our knowledge, our study is the first conducted among an Asian population to report estimates of the cumulative incidence of secondary cancers in childhood ALL survivors. We found that the cumulative incidence of any secondary cancers in ALL survivors was 1·0% at 10 years and 2·4% at 20 years, respectively.

The previous reports on secondary cancers in childhood ALL survivors are summarized in Table IV. In 1991, the Children's Cancer Group (CCG) evaluated 9720 cases of ALL diagnosed since 1972 (Neglia *et al*, 1991) with a more recent update reported by Bhatia *et al*(2002) The CCG report showed a cumulative incidence of 1·3% at 10 years after ALL diagnosis, whereas the Berlin-Frankfurt-Munster (BFM) study (Loning *et al*, 2000) observed an overall cumulative incidence of secondary cancers at 15 years of 3·3% and 2·9% (95% CI: 1·6%–4·2%) among patients in first CR. In 1991, a Norwegian study found an overall cumulative incidence of 2·9% by 20 years after diagnosis in a group of 895 patients treated between 1958 and 1985 (Nygaard *et al*, 1991). In the St. Jude study reported by Hijiya *et al* (2007) a comparatively higher cumulative incidence of 4·2% at 15 years and 11% at 30 years was found. Our study of Japanese patients resulted in cumulative incidence and SIR estimates that are consistent with these results reported by the CCG, BFM, and Norwegian studies.

Previous reports from the CCSS and BCCSS (Mody *et al*, 2008; Reulen *et al*, 2011) calculated cumulative incidence and SIR estimates of secondary cancers within cohorts of childhood cancer patients that have survived at least 5 years. The distribution of secondary cancer types reported by those studies appeared to be different compared to ours and other prospective clinical studies (Table IV). As shown previously and in our study, most AML and MDS developed within 5 years after diagnosis of ALL. Thus, studying 5 year childhood cancer survivors probably influenced the comparatively fewer numbers of AML/MDS secondary cancers observed in the CCSS and BCCSS (Table IV).

Our results are also consistent with previous studies with respect to the median latency period by secondary cancer type (shortest for AML/MDS/NHL)(Loning *et al*, 2000; Bhatia *et al*, 2002; Hijiya *et al*, 2007) over-representation of females (Neglia *et al*, 2001; Bhatia *et al*, 2002; Meadows *et al*, 2009) in secondary AML/MDS, and CRT as a strong risk factor for secondary cancer development.(Neglia *et al*, 1991; Nygaard *et al*, 1991; Loning *et al*, 2000; Borgmann *et al*,

Table IV. Previous reports on the incidence of secondary cancers among survivors of childhood ALL.

Authors	Group	Total ALL patients (n)	Treatment Year	Follow-up, years Total person-years (P-Y)	Patients with secondary cancer (n)	Type of secondary cancer	Cumulative incidence	SIR (95%CI)
Neglia *et al* (1991)	CCG	9720	1972–88	4·7 (0·2–16) 43 446 P-Y	43	10 leukaemia/lymphoma, 24 brain tumours, 9 other tumours	0·3% (0·2–0·5) at 5 years 1·5% (1·1–2·1) at 10 years 2·5% (1·7–3·4) at 15 years	42/6·1 = 6·85
Bhatia *et al* (2002)	CCG	8831	1979–95	5·5 (0–16·1) 54 883 P-Y	70	14 AML/MDS, 6 NHL, 2 HL, 19 brain tumours, 4 sarcoma, 4 thyroid cancers, 4 parotid tumours, 4 other tumours	1·3% (0·8–1·5)at 10 years 2·1% (1·4–2·8) at 15 years	7·2 (5·5–9·1)
Nygaard *et al* (1991)	Norway (NOPHO)	895	1958–85	10·5 7·2 (4·3–26·5) 6295 P–Y	8 (6)	3 brain tumours, 2 basal cell carcinoma, 1 thyroid cancer, 2 sarcoma	2·9% (SE 1·4) at 20 years	5·9 (2·2–12·9)
Kimball Dalton *et al* (1998)	DFCI	1597	1972–95	7·6 (0–24·0)	13	3 leukaemia/lymphoma, 5 brain tumours, 5 other solid tumours	2·7% (0·7–4·7)	N/A
Loning *et al* (2000)	BFM	5006	1979–95	5·7 (1·5–18) 28 605 P-Y	52	16 AML, 1 CML, 6 lymphoma, 13 brain tumours, 3 thyroid cancers, 13 other solid tumours	0·5% (0·4–0·6) at 5 years 1·5% (1·3–1·9) at 10 years 3·3% (1·6–5·1) at 15 years	14·1 (11–18)
Hijiya *et al* (2007)	St. Jude	2169	1962–98	18·7 (2·4–41·3) 29 179 P-Y	123	45 AML, 2 CML, 10 MDS, 6 lymphoma, 48 brain tumours, 9 sarcoma, 48 other solid tumours	4·2% (SE 0·5) at 15 years 10·9% (SE 1·3) at 30 years	13·5 (11–17)
Schmiegelow *et al* (2009)	NOPHO	1614	1992–01	10·4 (50% range: 8·0–12·6)	20	8 AML, 8 MDS, 1 brain tumour, 1 oral cancer, 1 LPD after SCT, 1 thyroid cancer	1·6% (SE 0·4) at 12 years	N/A
Mody *et al* (2008)	CCSS	5760	1970–86	21·2 (5–35)	185 (199)	4 AML, 7 NHL, 106 brain tumours, 11 breast cancer, 16 thyroid cancers, 13 sarcomas, 9 skin cancer, 26 others	5·2% (4·3–6·1) at 25 years	5·0 (4·1–6·0)
Reulen *et al* (2011)	BCCSS	No. of leukaemia patients was not available Total 17 981	1940–91	24·3 (50% range: 17·9–32·4) 80 028 P-Y	115 all leukaemias (not limited ALL)	7 leukaemia, 3 lymphoma, 27 brain tumours, 17 thyroid cancers, 61 other solid tumours	N/A	4·3 (3·6–5·2)
This study	TCCSG	2807	1984–05	9·5 (0·2–27) 27 658 P-Y	37	11 AML,5 MDS, 2 lymphoma, 13 brain tumours, 6 other solid tumour	1·0% (0·7–1·4) at 10 years 1·4% (0·9–2·0) at 15 years 2·4% (1·5–3·7) at 20 years	9·3 (6·5–12·8)

CCG, Children's Cancer Group; NOPHO, Nordic Society for Paediatric Haematology and Oncology; DFCI, Dana-Farber Cancer Institute; BFM, Berlin-Frankfürt-Münster; St. Jude, St. Jude Children's Research Hospital, St.Jude; CCSS, Childhood Cancer Survivor Study; BCCSS, British Childhood Cancer Survivor Study; TCCSG, Tokyo Children's Cancer Study Group; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; NHL, Non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CML, chronic myeloid leukaemia; LPD, lymphoproliferative disease; SCT, stem cell transplantation; SE, standard error; SIR, standardized incidence ratio; 95%CI, 95% confidence interval; N/A, not available.

2008; Schmiegelow *et al*, 2009) Another important finding in the present study is that no marked difference was observed in cumulative incidence between the five TCCSG protocols, but the multivariate analysis adjusting for confounders including CRT resulted in a statistically significant increased risk of secondary cancers in patients treated with the recent protocol (Table III). Because of the relatively short follow-up duration for patients included in the recent protocol and potentially complex interplay with treatment, at this point we consider this finding preliminary and it will be followed-up in future studies. Despite considerable reduction in the use of CRT over time, particularly for the more recent treatment protocols, we observed no evidence of a reduction in incidence of secondary cancers among children with ALL (Fig 2D). One explanation may be that CRT is probably linked mainly to secondary brain tumours, which only comprise approximately a third of all the secondary cancers. Furthermore, examination of the data showed that secondary brain tumours were diagnosed in patients enrolled in the earlier treatment protocols, a time when CRT was still commonly administered. Secondary cancers diagnosed in patients enrolled in the more recent treatment protocols were predominantly haematological. Given that the latency for secondary brain tumours is generally longer than that of haematological cancers, it is possible that a longer follow-up period may be needed to observe the effects of the reduction in CRT use. Finally, considering the poor prognosis of secondary AML/MDS (Fig 3D), it is important to identify the associated factors and minimize the development of secondary haematological cancers.

Therapy-related secondary cancers have been identified in patients receiving radiotherapy, chemotherapy, or combined modality therapy for ALL. Our study identified CRT as a strong risk factor, which was also found in the BFM study. (Loning *et al*, 2000; Borgmann *et al*, 2008) The cumulative incidence of secondary cancer for the irradiated group continued to increase with time even after more than 15 years following ALL diagnosis, possibly suggesting a long-term effect of irradiation on the rates of secondary cancers (Fig 2C). Even among the patients treated with more recent non-irradiated protocol, it is currently unknown whether the cumulative risk will remain constant, or whether secondary cancers might arise after a longer latency period. Multi-agent chemotherapy as part of multimodality therapy for cancers has increased the difficulty of assessing which agents might play a causative role in the development of secondary cancers. Alkylating agents, and more recently DNA-topoisomerase II inhibitors, have been linked to the development of secondary AML and MDS.(Hawkins *et al*, 1992; Le Deley *et al*, 2003) In contrast to previous reports, we were not able to demonstrate a clear relationship between the anthracyclines, etoposide or methotrexate and the occurrence of secondary cancers or specific types of secondary cancers.(Relling *et al*, 1999) The crude HR of CPM showed an increased risk of secondary cancers, but adjustment for confounders in multivariate analyses resulted in an attenuated and non-statistically significant finding.

Lastly, we found that cumulative incidence of secondary cancers in patients remaining in first CR was significantly higher than the patients who experienced a relapse of their primary ALL, changed treatment regimen, were lost to follow-up or died during first CR unexpectedly (Fig 2B). This finding was unexpected as it could be hypothesized that, because relapsed patients usually receive additional therapeutic exposures, they may potentially be at a higher risk of developing of secondary cancers. Nevertheless, a few studies provide some supportive data for our observations, including Borgmann *et al* (2008) who reported that the cumulative incidence of secondary cancers was unexpectedly low (1·3% at 15 years) despite repeated exposure to intense frontline and relapse treatment using BFM ALL-REZ Study data. In the St. Jude study (Hijiya *et al*, 2007), secondary neoplasms were observed in 123 out of 2,169 (5·7%) patients with continued first CR and in 45 out of 879 patients (5·1%) with relapse. In contrast, however, Bhatia *et al* (2002) demonstrated that the 10-year cumulative incidence of second malignancy was 0·91% in the patients with continued first CR compared with 1·2% in the entire cohort. The interpretation of these inconsistent results is difficult. It could be partially influenced by differences in OS among the patients with continued first CR and patients with relapse across the various studies.

One strength of the current study is that treatment of patients according to TCCSG therapeutic protocols ensured uniform access to standard therapy, giving us the opportunity to explore risk factors associated with secondary cancers in this cohort. Secondly, the follow-up duration was relatively long compared to previous prospective clinical studies and allowed us to describe the incidence of secondary cancers among patients treated on contemporary therapeutic protocols.

The results of this study should be interpreted in the context of acknowledged limitations. One major limitation is that this study was smaller than some previous studies, such as the CCG, CCSS and BCCSS, which may have affected our statistical power for certain analyses. Although all the patients in our cohort were treated according to therapeutic protocols, we do not have detailed information regarding actual cumulative exposures doses after relapse, which potentially could have influenced the development of second cancers. To address this concern, we conducted a sensitivity analysis (per protocol analysis) that included only patients who had completed all planned treatment leading to first CR. These results were largely consistent with the primary analyses (Table S1). Also, we were unable to compare the clonal phenotypes and genotypes between the primary ALL in L84-11/L89-12 and certain secondary ALL candidates. The difficulty in distinguishing between the primary and secondary type of recurrence using current standard techniques is well-recognized. In both of these events, some clonal markers

are maintained between the original diagnosis and recurrence but others can be altered.(Szczepanski *et al*, 2001; Zuna *et al*, 2007) Thus, they were not included in the analysis.

In conclusion, we showed that cumulative incidence of secondary cancer after TCCSG-ALL therapy is relatively low (1·0% at 10 years and 2·4% at 20 years) compared to the previous reports, although it is still 9 times higher than in the general population. We confirm that CRT is a strong risk factor of secondary cancer, but we did not observe evidence for a decrease in incidence despite the marked reduction in CRT treatment in the more recent protocols. In view of the long latency periods and long life expectancy of ALL patients treated in childhood, long and careful follow-up of these patients is warranted. Efforts to identify the causative carcinogenic factors should continue, and future treatment protocols should take these factors into account to maximize the chances of a long and healthy life, while preserving the efficacy of ALL treatment.

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Authorship and Disclosures

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Schemas of the TCCSG (Tokyo Children's Cancer Study Group) protocols.

Fig. S2. Cumulative incidence of secondary cancers according to therapy of primary ALL.

Table S1. Cox- regression analysis limited to per protocol group evaluating the association between select characteristics of the primary ALL diagnosis and risk of developing a secondary cancer.

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General Health Status and Late Effects Among Adolescent and Young Adult Survivors of Childhood Cancer in Japan

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Objective: We sought to investigate general health status and late effects among adolescent and young adult survivors of childhood cancer.
Methods: We conducted a cross-sectional survey, using self-rated questionnaires on current and past health problems. Questionnaires were provided to childhood cancer survivors, a comparison group of siblings and a general population control group that was recruited online. χ^2 tests were used to compare responses to the 72 survey items.
Results: The final sample included 185 childhood cancer survivors (72% response rate), 72 siblings and 1000 general population controls. In the childhood cancer survivors group, the median age of diagnosis was 8 years and the median age at survey was 23 years. According to the physicians' reports, 56% of the childhood cancer survivors experienced at least one late effect. In descending order of prevalence, the current symptoms in the childhood cancer survivors group were (i) impaired visual acuity (45%), (ii) dizziness (36%) and (iii) any allergy (34%). The three most common symptoms had similar prevalence rates in each of the groups. As compared with the control group, the following physical symptoms were significantly more common in the childhood cancer survivors group: mental retardation (odds ratio: 48.6, $P < 0.01$); cataract (odds ratio: 29.7); suspected infertility (odds ratio: 25.1); delayed puberty (odds ratio 24.9); growth hormone deficiency (odds ratio: 23.0); and other audiovisual, urinary, endocrine, infertility, cardiovascular, respiratory, gastrointestinal, spinal, extremity and neuromuscular problems.
Conclusions: Many adolescent/young adult childhood cancer survivors could be suffering from ongoing late effects that stem from cancer and its treatment. Overall health monitoring for childhood cancer survivors can provide indispensable benefits.

Key words: childhood cancer survivors – late effects – general health status

INTRODUCTION

The number of childhood cancer survivors (CCS) has been increasing each year, as a result of advancements in treatment. However, improved outcomes have been accompanied by the emergence of late, treatment-related complications, which include secondary neoplasms, endocrinopathy, organ dysfunction and reproductive problems (1–4). In Japan, it is estimated that ~1 in 700 adults aged between 20 and 39 years are CCS. Additionally, two-thirds of all CCS have one or more late complication, making long-term follow-up of CCS a topic of widely recognized importance (5).

In the Western countries, a number of large cohort studies have examined physical and psychological late effects among CCS (2,6,7). However, few relevant studies have been conducted in Japan. Recently, pediatric oncologists in Japan have become increasingly aware of the importance of long-term follow-up for CCS. As a result of awareness for long-term follow-up, some pediatric oncologists in Japan have started to inform CCS regarding the diagnosis and prognosis of late effects. Ishida conducted the first study on the late effects and quality of life (QOL) among CCS in Japan, based on a cross-sectional nationwide collaborative research program (5,8–10).

CCS who face significant late physical effects can also experience negative psychosocial consequences. However, most CCS do not appear to be impaired by their experience with cancer. Indeed, previous studies on the QOL of CCS indicate that most CCS have good physical and psychological status (11,12). On the one hand, survivorship could increase the CCS' general level of appreciation, potentially making a positive impact on the QOL (10), while on the other hand, several comparison studies have revealed negative impacts of childhood cancer on later QOL (3,13,14). Lack of comparability across these studies is a persistent problem, caused by the wide variation in the areas of focus and designs among various studies.

Web-based questionnaires have become increasingly popular in QOL research (15,16). This type of questionnaire is able to reach a massive population and is less time-consuming and less costly than paper-based questionnaires. Therefore, it presents an attractive alternative to postal surveys, especially when the target population is very large and primarily consists of relatively young respondents (17–19). However, important technical and methodological issues have been raised that should be carefully considered when using web-based questionnaires.

It is evident that many CCS experience advancing physical and mental health problems. However, few studies have investigated how adult and young adult CCS view their daily lives or how their life-perspectives could affect their QOL and health statuses. Therefore, the purpose of this study was to examine the general health status and late effects among CCS who were aged >16 years at the time of the study. We also performed a comparison survey involving the siblings of CCS, as well as age-matched members of the general population that was the control group. To enhance statistical power, we adopted a web-based survey for the general population group to recruit as many participants as possible.

PATIENTS AND METHODS

Study Design and Participants

We performed a cross-sectional survey with self-rated questionnaires on general health status and QOL. The survey was sent to CCS, their siblings (SIB) and the control groups (CONT). The study was conducted between 1 August 2007 and 31 March 2009. The CCS and SIB were recruited from the participant hospitals listed in the Appendix Table A1.

The inclusion criteria for CCS and SIB were as follows: (i) the subjects were aged ≥16 years at the time of the survey; (ii) they were diagnosed with cancer at the age of ≤18 years, and >5 years had passed since the diagnosis of cancer; (iii) the CCS had remained in remission for >1 year without additional need for anticancer therapy; (iv) the CCS were informed about the diagnosis; and (v) informed consent was provided by CCS, SIB and their guardians.

The exclusion criteria were as follows: (i) the attending physicians judged that the survey would be harmful for the participants; (ii) the subjects had an underlying disease besides cancer, affecting their social outcome or QOL; or (iii) the subjects were unable to answer the questionnaires by themselves.

The control group participants were recruited by a consultancy that performs web-based research (Cross Marketing Inc., Tokyo, Japan), after confirming that none of the participants had a history of childhood cancer.

Methods

After obtaining appropriate informed consent, the CCS and their siblings were provided with a questionnaire by the attending physicians and were asked to return it by post within 1 month. The CCS clinical records were reviewed to analyze cancer-related variables, including diagnosis, birth year and month, age at diagnosis, age at therapy completion, time since diagnosis, treatment variables and late effects observed at the time of the survey among the CCS. To ensure that the data were reliable, the attending physicians were asked to provide medical information about the participants (this medical information was faxed to the research center). Late effects were assessed using the Common Terminology of Clinical Adverse Events version 3.0. To maintain confidentiality of the patients' private information, we employed an encrypted numbering system to dispatch data to the principal investigator.

For the selection of the general population group participants, cross marketing performed online research using ~1.3 million panels, which they referred to as 'research panels.' They recruited respondents from these online panels and conducted quantitative research based on the self-rated questionnaires, using web-based methods. Participants were sampled from the research panel by matching them to the CCS group

in terms of age, gender, residential area and work status. Age was stratified into four categories: 16–19, 20–24, 25–29 and ≥30 years. Residential area was classified into five categories: Kyusyu-Okinawa, Chu-Shikoku, Kinki-Chubu, Kantou-Koushin-etsu and Touhoku-Hokkaido districts.

Measurement of Variables

The questionnaire consisted of 220 items, including 3 items that provided for open-ended responses. We evaluated 7 background items (Q1), 2 items concerning knowledge of disease (Q2), 7 lifestyle-associated items (Q3), 9 items concerning medical visits to the hospital (Q4), 4 items associated with general health-related QOL (Q5), 6 items concerning past operations and history of drug use (Q6), 7 items related to daily habits (Q7), 9 items associated with pregnancy and delivery (Q8), 72 items related to subjective physical dysfunctions (Q9), 36 Short Form (SF-36)-related items (Q10) (20,21), 64 items concerning psychosocial problems (Q11) and 3 items that allowed for open-ended responses (Q12).

For the purposes of the present study, we focused on the items from Groups Q5 and Q9. The Q5 items asked about general QOL, including specific questions on difficulty in daily life, physical problems, psychological stress and difficulty in social adaptation. Participants were asked about the degree of impairment that they faced in daily life, the psychological stress that they experienced and any problems in social adaptation. Response options of 'none', 'mild', 'moderate', 'severe' or 'very severe' were provided.

If the participant presented symptoms at the time of the survey, questions were asked concerning the nature of the underlying problems. The Q9 group consisted of 72 items that belonged to the following 14 subcategories: audiovisual problems, urinary problems, endocrine dysfunction, infertility problems, cardiovascular symptoms, respiratory problems, gastrointestinal dysfunction, tooth diseases, spinal dysfunction, problems in the extremities, neuromuscular problems (including mental retardation), chronic pain, skin and hair problems and allergic diseases. Items from the Q9 group, allowed for responses on a scale of 'never experienced', 'currently experiencing', 'previously experienced' or 'unknown'. Participants who responded that they were currently experiencing the problems were asked about the age at symptom onset, as were participants who reported previously experiencing the problems.

Ethical Issues

The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of the principal investigator's institution (Y.I., Ehime University Graduate School of Medicine, Ehime, Japan and St. Luke's International Hospital, Tokyo, Japan). Before commencement, the study also received approval from the local ethics committees of all the participating hospitals.

Statistical Analysis

We estimated the prevalence of outcomes in the CCS, SIB and CONT groups. For categorical predictors, we performed χ^2-tests or Fisher exact tests (for cells with expected counts <5). Data were analyzed using SPSS software, version 17.0 (SPSS, Inc., Chicago, USA).

We planned a study of independent CCS and siblings, including one sibling per five CCS. This decision was made on the basis of study power calculations. Particularly, prior data indicate that the probability of chronic health conditions among siblings is 0.35 (8,9). If the true probability of chronic health conditions among CCS were 0.60, we would need to study 180 case patients and 36 control patients to be able to reject the null hypothesis that the outcome rates for CCS and siblings were equal, with a power of 0.8 ($\beta = 0.2$) and a Type I error probability (α) of 0.05. In practice, we used an uncorrected χ^2 statistic to evaluate the null hypothesis. We additionally estimated the number of cases that would be required to analyze nine covariates using multivariate logistic regression for identifying risk factors for late effects. The final estimate was 180 cases. We designed our survey to sample independent cases and controls, with five controls per one CCS. Our final target numbers were 200 CCS and 1000 general population participants, with a safety margin to allow for cases excluded on the basis of selection criteria or because of missing data.

RESULTS

Characteristics of the Participants

A total of 189 CCS (response rate: 72%) participated in this study, with a mean age of 23.6 years [standard deviation (SD): 4.6 years] at the time of this survey (Appendix Table A1) and a mean age of 8.3 years at diagnosis [median 7.8 years (range 0.2–17.4)]. Of these, four CCS were excluded from all analyses because they did not meet the study inclusion criteria. The mean follow-up period was 15.3 years (SD: 5.8 years). For the SIB group, the questionnaire was distributed to ~138 individuals; 74 siblings (54%) returned the questionnaire. The mean age of the SIB group was 25.6 years (SD: 5.5 years) for females and 24.3 years (SD: 4.6 years) for males. The general population control group (CONT) included 584 female and 416 male participants, with the mean age being 23.9 years (SD: 5.4 years) for females and 23.8 years (SD: 5.8 years) for males, at the time of the survey. There were no statistically significant differences in the age composition between the CCS, SIB and CONT groups (Table 1). Other socio-demographic data on each group have been reported previously (8).

The distribution of cancer diagnoses in the CCS group was as follows: 44% acute lymphoblastic leukemia, 12% malignant lymphoma, 11% acute myelogenous leukemia, 3% other hematological malignancy, 5% central nervous system (CNS) tumors, 5.4% osteosarcoma or Ewing's sarcoma, 4.3% soft tissue sarcoma and 16% other solid tumors. In the eligible sample, more women (58%, $n = 108$) than men participated

Table 1. Participant demographics

	CCS ($n = 185$)	SIB ($n = 72$)	CONT ($n = 1000$)
Gender			
Male	77	30	416
Female	108	42	584
Age at diagnosis of original cancer			
	8.3 ± 4.8	NA	NA
Age at survey			
	23.6 ± 4.6	25.0 ± 4.2	23.9 ± 5.6
16–19 years	47 (25%)	7 (10%)	248 (25%)
20–24 years	75 (41%)	32 (44%)	415 (42%)
25–29 years	38 (21%)	21 (29%)	203 (20%)
≥30 years	25 (14%)	12 (17%)	134 (13%)

Age is presented as mean value ± standard deviation.
NA, not available; CCS, childhood cancer survivor; SIB, sibling; CONT, general population control.

in the survey. With respect to cancer therapy, 98% of the CCS group underwent chemotherapy, 61% received radiation therapy, 37.8% received operations and 24.9% received hematopoietic stem cell transplantation (Allogenic donor, 72%). A combined therapy involving chemotherapy and radiation was the most common treatment option (39.5%). According to the reports of the attending physicians, 62 CCS (34%) experienced one late effect, 26 (14%) experienced two late effects and 16 (9%) experienced three or more late effects. Therefore, in total, 104 (56%) experienced at least one late effect.

General QOL

Figure 1 presents the prevalence rate of impairment in general QOL, which includes difficulty in daily life, physical problems, psychological stress and problems in social adaptation. In items of psychological stress and problems in social adaptation, the authors defined participant responses of 'mild', 'moderate', 'severe' or 'very severe' as constituting impairment. The prevalence of any problem was 80.5% in the CCS group, 38.6% in the SIB group and 54.5% in the CONT group. All categories of general QOL were significantly worse in the CCS group than in the SIB group, especially physical problems and psychological stress ($P < 0.01$). All categories of general QOL were also significantly worse in the CCS group than in the CONT group ($P < 0.01$), with the exception of problems in social adaptation. The prevalence rates of difficulty in daily life, physical problems and psychological stress were similar in the SIB and CONT groups. However, problems in social adaptation were significantly more common in the CONT group ($P < 0.01$) than the SIB group.

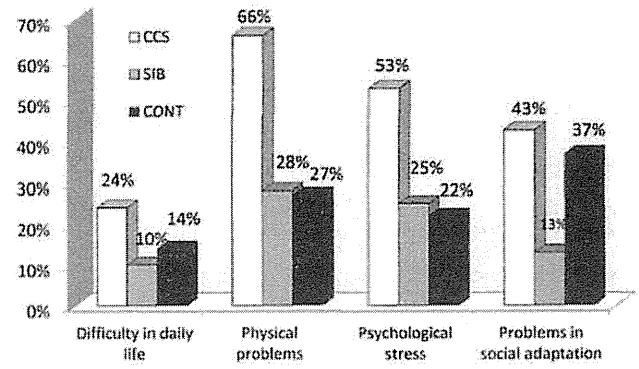

Figure 1. General quality of life (QOL) among the childhood cancer survivors (CCS), siblings (SIB) and general population control (CONT) groups. Solid bars indicate the CCS group; gray bars indicate the SIB group; black bars indicate the CONT group.

Prevalence of Physical Symptoms

Physical symptoms that presented after the onset of disease or at the time of the survey are summarized in Table 2 for each of the study groups. Although the exact ranking varied by group, the three symptoms 'impaired vision activity', dizziness' and 'any allergy' were common in each group. 'Impaired vision activity' and 'dizziness' were more common in the CCS group than in the other groups. Other audiovisual problems, neurological problems, infertility, dental problems and orthopedic symptoms were also most common in the CCS group. Because 'suspected infertility' was not among the 20 most common physical symptoms in the SIB or CONT groups, we suggest that those symptoms are related to cancer therapy for CCS. With respect to the age of symptom onset, 'dry eye', 'migraine' and 'faintness' presented at significantly earlier ages in the CCS group than in the SIB group. Although it was only for women's problem, the prevalence of 'irregular menstruation' was the highest among CCS.

Comparative Analysis: CCS versus CONT and CCS versus SIB

Table 3 presents odds ratios (ORs) and 95% confidence intervals (CIs) for participant-reported current or past physical symptoms. Odds ratios compare the experience of the CCS group with the CONT and SIB groups. All 32 symptoms that are listed were significantly more common in the CCS group than in the CONT and SIB groups, according to the χ^2 tests. Several categories of problems (such as audiovisual, urinary, endocrine and extremities) were significantly more common in the CCS group than in the CONT and SIB groups. Moreover, all symptoms in the neuromuscular, cardiovascular, respiratory, gastrointestinal and spinal categories were significantly more common in the CCS group than in the CONT group. In the CCS, CONT and SIB groups, several symptoms in the audiovisual (glaucoma), urinary, endocrine [growth hormone (GH) therapy], cardiovascular, respiratory, gastrointestinal and neuromuscular

Table 2. The prevalence of previous and or current experience of physical symptoms among the CCS, SIB and CONT groups

Physical problem	CCS				SIB				CONT			
	Rank	Prevalence (%)	Onset age	SD	Rank	Prevalence (%)	Onset age	SD	Rank	Prevalence (%)	Onset age	SD
Impaired visual acuity	1	45	13.2	5.0	2	31	15.1	5.7	1	42	12.9	4.6
Dizziness	2	36[a]	16.1	4.6	3	29[a]	18.5	8.3	2	35[a]	17.7	6.0
Any allergy	3	34	11.3	7.8	1	40	9.7	7.5	3	30	12.1	7.5
Tinnitus	4	26	15.2	6.2	13	11[a]	16.3	15.7	4	17[a]	18.5	6.5
Dry eye	5	22	16.8	3.2[b]	4	25	21.4	5.4	7	15	19.9	5.1
Migraine	6	22	15.0	4.9[b]	5	19	21.5	7.7	5	17	18.3	6.3
Impaired hearing	7	18	14.4	8.3	14	8[a]	15.8	9.4	9	13[a]	16.7	7.7
Suspected infertility	8	17	17.9	5.8	43	0	–	–	44	1	22.6	2.5
Dental problems (teeth)	9	17	11.4	8.0	6	18	9.1	4.0	6	15	12.6	6.6
Faintness	10	17	15.4	3.4[b]	6	18	23.2	5.9	14	7	19.2	5.2
Diplopia	11	16	16.2	6.3	8	17	15.0	5.0	10	11	16.7	6.5
Abnormal urinalysis	12	15	15.1	5.7	18	4	14.0	4.2	15	6	18.1	6.4
Chronic constipation	13	14	12.9	6.0	12	14	20.0	0.0	19	4	12.6	5.6
Osteoporosis	14	14	16.2	5.9	28	1	23.0	–	34	1	23.6	5.4
Skin problem	15	13	12.1	7.1	8	17	10.9	7.3	8	14	13.0	8.9
Asthma	16	12	9.4	9.7	11	14	6.7	4.5	12	9	8.5	7.4
Delayed puberty	17	12	13.7	1.6	43	0	–	–	46	0.5	16.3	2.1
Extremity dysfunction	18	12	14.6	4.3	28	1	22.0	–	22	2.4	16.0	9.3
Growth hormone deficiency	19	9[a]	12.1	4.3	43	0	–	–	49	0.4	14.0	1.4
Scoliosis	20	9	12.7	4.0	15	7	15.8	8.5	18	4	16.3	5.3
Only female												
Irregular menstruation	–	57	17.3	4.6	–	43	17.9	3.8	–	39	16.1	4.7

Physical symptoms are presented in the descending order based on their prevalence in the CCS group.
[a]Previous experience of symptoms was more common than current experience of symptoms.
[b]Significant difference between CCS and CONT ($P < 0.05$) according to a Bonferroni multiple comparison test of the symptom onset age.

(mental retardation) categories were more commonly reported as previous experiences than as current experiences. Diabetes, GH deficiency, spinal disease and muscle weakness were most common in the past in the CCS group, while audiovisual (tinnitus, cataract and dry eye), endocrine (osteoporosis, delayed puberty, suspected infertility, infertility examination and irregular menstruation), spinal disease (scoliosis), problems in the extremities (extremity dysfunction, limb length discrepancy and joint disease) and neuromuscular problems (paralysis, faintness, chronic pain and sensory impairment) were most common at the time of the survey in the CCS group. We found that the ORs for mental retardation, cataract, suspected infertility, delayed puberty, GH deficiency, GH therapy, osteoporosis, muscle weakness and paralysis were each >10. Although the associated ORs were lower, the prevalence of tinnitus, impaired visual acuity, dry eye, suspected infertility and irregular menstruation were significantly elevated in the CCS group, according to the χ^2 tests.

DISCUSSION

We have presented the results of a nationwide, Japanese study on long-term general QOL involving young adult CCS. Our principal finding is that a history of childhood cancer has a negative impact on the QOL of young adults, and was specifically associated with physical, psychological, social and daily life issues. Based on a large comparison survey, we also found that CCS were likely to experience endocrine, infertility, extremities, audiovisual, urinary, cardiovascular, respiratory, gastrointestinal and neuromuscular problems. These findings significantly contribute to the published literature because, in Japan, few studies have investigated general QOL among CCS using a suitably large population comparison study (5,8–10).

In a previous study on long-term general QOL, Hudson determined that compared with their siblings, the CCS were significantly more likely to report adverse general health (OR = 2.5), mental health (OR = 1.8), activity limitations (OR = 2.7) and functional impairment (OR = 5.2) (13). Our

Table 3. Odds ratios for reported current or past physical symptoms in the CCS group, as compared with the SIB and CONT groups

Category	Content of physical symptom	CCS versus CONT			CCS versus SIB		
		Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Audiovisual problems	Tinnitus	1.5	1.1–2.0	<0.01	2.3	1.1–4.6	0.01[a]
	Impaired visual acuity	1.1	0.9–1.3	NS	1.5	1.0–2.1	0.04
	Cataract	29.7	6.6–133.0	<0.01[b]	1.1	1.0–1.1	0.04
	Glaucoma	8.1	1.4–48.2	<0.01[b,c]	1.0	0.99–1.0	NS
	Dry eye	1.5	1.1–2.1	0.01	0.84	0.44–1.6	NS
Urinary problems	Abnormal kidney function	9.7	3.3–20.9	<0.01[b,c]	3.6	0.45–28.9	NS
	Abnormal urinalysis	2.6	1.7–4.1	<0.01[b,c]	3.9	1.1–13.4	0.02[a]
Endocrine dysfunction	Diabetes	6.8	1.8–24.9	<0.01[c]	1.02	1.00–1.05	NS
	GH deficiency	23.0	7.8–67.5	<0.01[c]	1.1	1.1–1.2	<0.01
	GH therapy	19.1	6.4–57.5	<0.01[b,c]	1.1	1.0–1.1	0.02
	Osteoporosis	13.7	6.7–28.0	<0.01[b]	10.9	1.5–82.2	<0.01
	Delayed puberty	24.9	9.6–64.6	<0.01[b]	1.1	1.1–1.2	<0.01
Infertility problems	Suspected infertility	25.1	11.3–56.0	<0.01[b]	1.2	1.1–1.3	<0.01
	Infertility examination	6.9	2.8–17.3	<0.01[b]	4.0	0.51–32.1	NS
	Irregular menstruation	1.5	1.2–1.8	<0.01	1.8	0.87–3.7	NS
Cardiovascular symptoms	Any heart disease	5.4	2.2–13.5	<0.01[b,c]	3.5	0.44–29.5	NS
Respiratory problems	Chronic bronchitis	3.2	1.2–8.9	0.02[b,c]	1.1	0.23–5.8	NS
	Other respiratory disease	2.7	1.1–6.6	0.02[b,c]	1.3	0.27–6.6	NS
Gastrointestinal dysfunction	Hepatitis	8.5	3.7–19.3	<0.01[b,c]	2.8	0.62–12.7	NS
	Jaundice	6.3	2.2–18.7	<0.01[b,c]	1.04	1.01–1.07	NS
	Any bowel disease	3.8	1.6–8.3	<0.01[b,c]	1.7	0.37–8.3	NS
Spinal disease	Scoliosis	2.3	1.3–4.0	<0.01	1.3	0.47–3.7	NS
	Spinal disease	4.8	1.8–12.3	<0.01[c]	1.05	1.01–1.09	NS
Problems in the extremities	Extremity dysfunction	5.0	2.8–8.6	<0.01	9.3	1.2–70.5	<0.01
	Limb length discrepancy	2.8	1.5–5.4	<0.01	1.2	0.40–4.0	NS
	Joint disease	2.8	1.3–6.0	<0.01	1.06	1.02–1.09	<0.05
Neuromuscular problems	Paralysis	10.8	2.0–58.6	<0.01[b]	1.5	0.17–13.9	NS
	Mental retardation	48.6	6.2–381.7	<0.01[b,c]	3.5	0.44–28.4	NS
	Faintness	2.6	1.7–3.8	<0.01	0.88	0.43–1.8	NS
	Muscle weakness	11.9	4.2–37.8	<0.01[c]	4.4	0.55–34.4	NS
	Chronic pain	3.9	1.9–7.8	<0.01	2.6	0.57–11.7	NS
	Sensory impairment	7.2	1.6–31.9	<0.01	1.5	0.17–13.9	NS

NS, not significant; GH, growth hormone.
[a]SIB reported more 'previously experienced' than 'currently experiencing'.
[b]CONT reported more 'previously experienced' than 'currently experiencing'.
[c]CCS reported more 'previously experienced' than 'currently experiencing'.

comparison of CCS and sibling groups showed similar results. However, another study by the British Childhood Cancer Survivor Study (BCCSS) (7) reported that physical and mental QOL among the CCS were comparable with those of the general population. The discrepancy between these results and our own could arise from methodological difference between the studies. Particularly, the results obtained by BCCSS could be a product of relatively small study sample size and the use of a blunt questionnaire. Other studies have shown that CCS report psychological distress, educational and employment problems or low marriage rates (5,22,23).

In the present study, the attending physicians reported that 56% of the CCS experienced at least one late effect. Previous studies have reported various incidences of late effects, some

of which were based on physicians' reports, while others, on the responses of CCS themselves. Additionally, the estimated prevalence rate of any late effect among CCS varied from 44–75%, depending on the study (3,11–13,24). Interestingly, based on a review of oncologists' charts, a study from Korea reported an incidence (more than one late effect: 59.8%) similar to our own findings (24). This similarity may be explained by the comparable number of participants in the Korean study ($n = 241$) or the Asian ethnicity of both study populations. Noteworthy, a recent study by Hudson revealed that the estimated cumulative prevalence of any chronic health condition at the age of 45 years was 95.5% (95% CI, 94.8–98.6%) (25). This finding strongly suggested the importance of ongoing health monitoring for adult CCS.

Although the prevalence of the three most common symptoms was similar across the CCS, SIB and CONT groups, impaired visual acuity was significantly more common in the CCS group than in the SIB group, as revealed by our comparative analysis in Table 3. Indeed, our analysis indicated that cancer treatment could place patients at an elevated risk of several common symptoms that healthy adults often experience.

In the present study, we additionally found that dry eye, migraine and faintness presented at earlier ages among the CCS than in the SIB. Hudson showed that the risks of neurological, gonadal and certain other late effects are correlated with the patient's age at cancer diagnosis and treatment (26). Although the present study did not show an association between the age at cancer onset and late effects (because it is a cross-sectional survey), a similar analysis contributed additional findings on the topic of early onset of minor symptoms, which had not been described previously. These findings help distinguish between the symptoms that are specifically caused by cancer and those caused by its treatment, and this insight is necessary to determine a method of optimally delivering treatments that does not predispose the patient to late effects.

According to a recent study by the Childhood Cancer Survivor Study (CCSS) conducted in the USA, survivors were found to be eight times more likely than their siblings to have severe or life-threatening chronic health conditions, including myocardial infarction, congestive heart failure, premature gonadal failure, second cancers and severe cognitive dysfunction (2). The results of our study are consistent with these previous findings, in terms of the variety of chronic late effects that was observed among the CCS. While we adopted similar questionnaires, the severity of late effects that was observed in the CCSS study was generally greater in that study than it was in our own study. This discrepancy may be explained by methodological differences between CCSS and the present study. First, CCSS enrolled a much larger number of CCS. Second, CNS tumors, bone tumors and Hodgkin's disease were more common in CCSS than in our own study (12.7 versus 5%, 10.9 versus 5.4% and 18.0 versus 0.5%, respectively). Finally, differences in treatment could explain some differences in late effects between CCSS and our study. Indeed, the percentages of patients receiving any radiotherapy were different: 72.9% in the CCSS and 61% in our study. Chemotherapy was provided to 79.0% of patients in the CCSS and to 98% of survivors in our study.

To obtain suitable statistical power, we adopted a web-based recruitment strategy for the general population controls. Indeed, the comparison of CCS and CONT groups offered particularly important details on the various physical and psychosocial QOL issues that are faced by survivors of childhood cancers. However, social adaptation and impaired visual acuity were observed to be similar in the CCS and CONT groups but significantly lower in the SIB group. One explanation for this limitation is that, while general young adult participants are avid Internet users, some of these participants may have lost contact with society or may be overtaxing their eyes. The authors found that the lack of a known denominator can hinder the external validity of the findings of web-based survey studies. Additionally, Klovning et al. (17) has reported that for investigations involving older populations, web-based approaches are less appropriate than postal methods. Consequently, web-based questionnaires present a mixture of benefits and risks (including selection bias) that should be carefully considered when adopting web-based methodologies.

Limitations

This study has several limitations. First, the number of subjects was limited. Moreover, the number of participants and participation rates varied substantially between institutes (30–100%). Approximately one-half of the Japanese institutions have a limited number of pediatric hemato-oncologists (1 or 2), and we have been focusing on improving institutional commitments to long-term follow-up (27). Selection bias may have arisen from the study enrollment design because it was not randomized. Second, the design of the study was cross-sectional, and, therefore, we cannot draw conclusions regarding causality. Third, in-depth medical surveys were not conducted for all aspects of dental problems and gonadal dysfunction. Finally, when we analyzed participants' physical symptoms, we combined participants who were currently experiencing symptoms with those who had previously experienced symptoms. We recognized that methodological problems might arise from decreasing detection power for late persisting complications that were caused by cancer and its treatment. To address these limitations, we presented additional information on the symptoms, by comparing previous and current experiences.

CONCLUSION

(i) CCS in Japan were more likely to experience physical, psychological, social and daily life issues.
(ii) Endocrine, infertility, extremities, audiovisual, urinary, cardiovascular, respiratory, gastrointestinal and neuromuscular problems were common late effects among CCS.

(iii) Over 80% of the CCS had more than one physical problem. However, attending physicians may underestimate the health problems of CCS.

Our findings add to the understanding of the highly variable late effects among CCS. In conclusion, monitoring the overall health of CCS provides an indispensable benefit. Medical staff should expand the focus of cancer survivorship support to include multidisciplinary team support, even when the initial cancer episode is in long-term remission.

Acknowledgements

The institutions that provided patient data and enabled recruitment of CCS in the investigation are listed in Appendix A1.

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Conflict of interest statement

The authors declare no financial interests.

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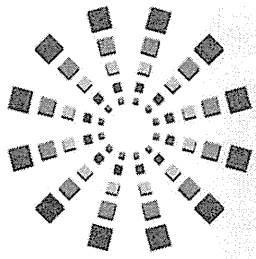
Appendix

Table A1. List of participating institutions and number of participants

Institute	Investigators	Number of distributions	CCS (% of response)
National Kyushu Cancer Center	Jun Okamura	27	19 (70)
Niigata Cancer Center	Keiko Asami	44	28 (64)
Nippon Medical School	Miho Maeda	4	3 (75)
National Center for Child Health and Development	Naoko Kakee Kentaro Aritaki	3	1 (33)
Ehime University	Yasushi Ishida Misato Honda	51	44 (86)
Tohoku University	Masaki Nio Yutaka Hayashi	13	11 (85)
Kagawa Children's Hospital	Tsuyako Iwai	10	10 (100)
National Nagoya Medical Center	Naoko Maeda Keizo Horibe	39	26 (67)
Kurume University	Shuichi Ozono Hiroko Inada	43	30 (70)
International Medical Center in Japan	Hideko Uryu Takeji Matsushita	10	3 (30)
Juntendo University	Kouichi Ishimoto Masahiro Saitou	5	5 (100)
St. Luke's International Hospital	Yasushi Ishida	12	9 (75)
Total		261	189 (72)



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Impact of Late Effects on Health-Related Quality of Life in Survivors of Pediatric Brain Tumors

Motility Disturbance of Limb(s), Seizure, Ocular/Visual Impairment, Endocrine Abnormality, and Higher Brain Dysfunction

KEY WORDS
Adolescent
Brain neoplasms
Child
Multicenter study
Propensity score
Quality of life
Questionnaires
Survivors

Background: Survivors of pediatric brain tumors are often affected by late effects, such as motility disturbance of limb(s), seizure, ocular/visual impairment, endocrine abnormality, and higher brain dysfunction, resulting from the disease and its treatment. Appropriate provision of supportive care will require understanding the effects of these experiences on survivors' health-related quality of life (HRQOL). **Objective:** The aim of this study was to identify the relationships between late effects and specific aspects of the HRQOL of pediatric brain tumor survivors. **Methods:** We distributed questionnaires for measuring HRQOL to 138 survivors and their parents at 8 hospitals and 1 clinic in Japan and simultaneously surveyed late effects using information provided by the survivors' attending physicians. We compared the HRQOL of survivors with and survivors without specific late effects. **Results:** A total of 106 survivors and their parents returned the questionnaires to the researchers. The HRQOL of survivors 18 years or older was negatively affected by all 5 late effects, indicating that their higher impairment was associated with diminished HRQOL. The

HRQOL of survivors aged 12 to 17 years was negatively affected by 2 late effects (ocular/visual impairment and motility disturbance of the limbs). A part of the HRQOL subdomain (motor and cognitive functioning) of survivors aged 12 to 17 years was positively related to ocular/visual impairment. **Conclusions:** Five late effects influenced the HRQOL of pediatric brain tumor survivors. **Implications for Practice:** Nurses and other health professionals should provide specific care designed to support aspects of HRQOL affected by late effects. For example, survivors with ocular/visual impairment may be expected to require additional emotional support, and those with seizures or endocrine abnormalities may be expected to require additional support for sleep disorders.

Multidisciplinary treatment[1,2] of pediatric brain tumors has improved treatment outcomes[3,4] and increased survival from pediatric brain tumors. However, patients who survive pediatric brain tumors are known to be at risk of physical, psychological, social, and developmental difficulties.[5–9] A survivor's quality of life (QOL) can be improved by screening, treating, and managing such difficulties at outpatient departments or clinics over the long-term.

The concept of health-related QOL (HRQOL) describes specific health-, disease-, or disability-related aspects of QOL,[10,11] and a high level of HRQOL is a desirable outcome of medical treatment and nursing care. Most survivors of pediatric brain tumors are known to have a lower HRQOL than do children/adolescents/young adults who have never experienced cancer[12] or survivors of other pediatric cancers.[13,14] More specific information is needed regarding the HRQOL of survivors of pediatric brain tumors to provide the most appropriate support and care.

Several factors influence HRQOL, such as current age, age at diagnosis, hydrocephalus at diagnosis, tumor pathology, tumor location, radiation treatment, and tumor recurrence.[12,15–21] Studies of pediatric cancer survivors show that HRQOL may also be influenced by gender, race, surgery, chemotherapy, and time since completion of antitumor therapy.[14,22] Some brain tumor and treatment effects continue after treatment and are called "late effects." Survivors frequently report late effects in neurological, neurosensory, and endocrine functions,[23–25] and several trials of brain tumor clinical protocols have investigated ways to manage such late effects and improve patients' and survivors' HRQOL.[1,26,27] However, the specific influence of each late effect on specific aspects of HRQOL remains unclear. At present, care for survivors with such late effects is implemented individually by specialists such as neurosurgeons, pediatricians, endocrinologists, or ophthalmologists and is adapted to the needs of each survivor and his/her family. In Japan, there is a national project to promote early rehabilitation for patients with higher brain dysfunction caused by stroke or traumatic brain injury, but survivors of pediatric brain tumors have little access to this program. Nurses in Japan are expected to understand the survivors' common and individual needs and coordinate care accordingly. More data on how late effects influence specific aspects of HRQOL could improve nurses' understanding of survivors' needs and, thus, the design of management and support programs specific to survivors of pediatric brain tumors. The purpose of our study was to investigate how 5 common late effects (motility disturbance of limb(s), seizure, ocular/visual impairment, endocrine abnormality, and higher brain dysfunction) in survivors of pediatric brain tumors influence their HRQOL in 2 age groups.

Method

Study Population

Between April 2010 and March 2011, we recruited survivors and their parents from 10 outpatient departments in 8 hospitals and 1 neurosurgery clinic in Japan that provide treatment and follow-up for pediatric brain tumor patients. Families were included in the study if a survivor was diagnosed at 18 years or younger, at least 1 year had passed since completion of antitumor treatment, and the survivor was aged at least 12 years at

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The authors have no conflicts of interest to disclose.

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the time of survey, did not present an active neoplasm, and was not hospitalized. Families were excluded from the study if both the survivor and parent could not understand the purposes of the study (explained in Japanese) or attending physicians determined that the survivor and the parent found the subject of brain tumors too painful to discuss.

Procedure

The criteria stated above matched 139 survivors. Of these 139, only 1 survivor declined to meet the researcher because of time constraints (Figure). Researchers were able to explain the purpose of the study to the remaining 138 survivors when they visited the clinic or hospital. All 138 agreed to participate and provided informed consent so that researchers could obtain their medical histories. Survivors and their parents were given questionnaires, a written explanation of the study, and a stamped, addressed return envelope. Returned questionnaires provided factual informed consent to participation.

Ethical Considerations

The study protocol was approved by the review boards of all participating institutions. In consideration of the Japanese sociocultural environment, we avoided using the terms *cancer* or *tumor* with the children, using the alternate term *disease* in introductory writings and questionnaires. Research objectives were presented to survivors 19 years or younger and their parents simultaneously.

Measurements

Survivors were separated into 2 age groups (aged 12–17 and ≥18 years) because older survivors who may be working or enrolled in higher education were expected to experience different life challenges than those who were still in secondary education, and this difference may affect HRQOL. Survivors 18 years or older at April 1, 2010, were administered the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ) Core Questionnaire 30 (C30) and QLQ Brain Cancer Module 20.[28–30] Those who were 12 to 17 years of age by April 1, 2010, were administered the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales,[31,32] PedsQL Brain Tumor Module,[33,34] and PedsQL Cancer Module.[32,35] Most questionnaires were self-administered, but parents read the instructions, questions, and recorded answers for survivors incapable of self-administration.

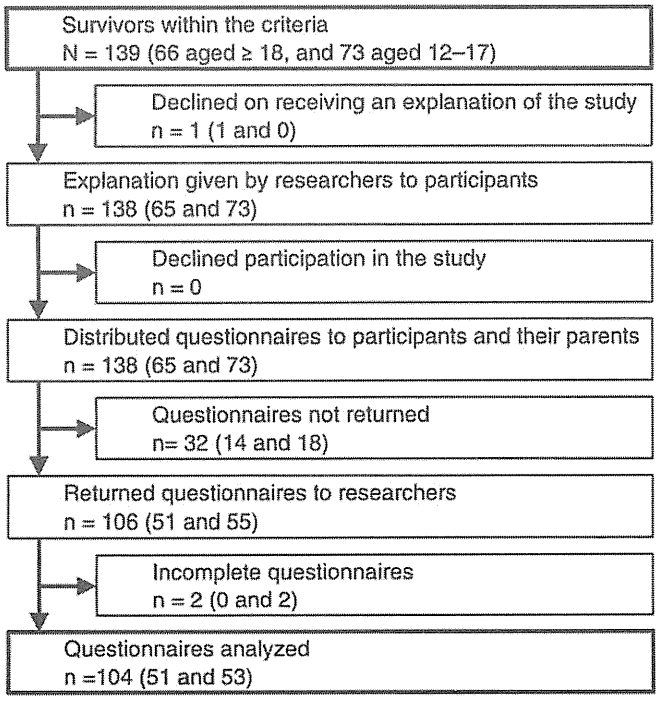

Figure ■ Summary of recruitment procedure and number of participants.

The QLQ C30 has 5 functional scales: physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items), and social functioning (2 items). We selected 4 additional scales to assess symptoms that are important to survivors who have completed treatment: fatigue (3 items) and insomnia (1 item) in C30 communication deficit (3 items) and drowsiness (1 item) in Brain Cancer Module 20.

These questionnaires provide multiple-choice answers on a 4-point Likert response scale (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much), and survivors were asked to identify which answers best applied to them. The score on each scale was calculated from the sum of the items divided by the number of items answered, to account for missing answers. Items in functional scales were reverse scored and linearly transformed on a scale of 0 to 100, with higher scores indicating a better HRQOL. Items in symptom scales were scored and linearly transformed on a scale of 0 to 100, with lower scores indicating a better HRQOL.

The PedsQL Generic Core questionnaire includes 4 scales: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). We selected 2 additional scales from the PedsQL Brain Tumor Module: cognitive problems (7 items) and movement and balance (3 items), as well as 2 additional scales from the PedsQL Cancer Module: physical appearance (3 items) and communication (3 items).

Survivors and parents were asked to identify on a 5-point Likert response scale (0 = never a problem, 1 = almost never, 2 = sometimes, 3 = often, 4 = almost always) the extent to which each item had troubled the survivors over the past 7 days. Items were reverse scored and linearly transformed on a scale of 0 to 100, with higher scores indicating a better HRQOL. The score on each scale was calculated from the sum of the items divided by the number of items answered to account for missing answers.

The patients' physicians provided the following disease and treatment information: age at diagnosis, presence of hydrocephalus at diagnosis, tumor pathology, tumor location, neurosurgery, radiation treatment, chemotherapy, tumor recurrence, time since completion of antitumor therapy, and the presence or absence of clinically problematic late effects, namely, motility disturbance of limb(s), seizure, ocular/visual impairment (visual impairment, visual field deficit, disturbance in ocular motility, etc), endocrine abnormality, and higher brain dysfunction (eg, aphasia, agnosia, apraxia, anarithmia).

Statistical Analysis

Statistics were calculated using IBM SPSS software, version 19 (SPSS, Inc, Chicago, Illinois). We excluded questionnaires where more than 50% of the questionnaire items were missing or incomplete. We compared age, gender, and the disease and treatment information of 104 survivors who returned valid, completed questionnaires (respondents) with data obtained for the 34 survivors who did not return questionnaires (nonrespondents).

We estimated the extent to which each late effect influences the HRQOL by comparing HRQOL scores between survivors with and survivors without late effects. These effects may be confounded by other factors, such as age, gender, age at diagnosis, presence of hydrocephalus at diagnosis, tumor pathology, tumor location, neurosurgery, radiation treatment, chemotherapy, tumor recurrence, and time since completion of antitumor therapy. We controlled for imbalances caused by the confounders by calculating a propensity score from a stepwise logistic regression to predict the probability of late effect occurrence, where the late effect is the dependent variable and the possible confounders (Table 1) are independent variables.[36] In this method, the validity of the propensity score analysis is indicated by a high C statistic (the rank-order statistic to quantify the capacity of the model to predict the late effect occurrence; identical to the area under the receiver operating characteristic curve): motility disturbance of limb(s), 0.78; seizure, 0.94; ocular/visual impairment, 0.86; endocrine abnormality, 0.84; and higher brain dysfunction, 0.81. We estimated unbiased differences in the HRQOL scores between the presence and absence of each late effect by calculating the difference weighted by the inverse of the propensity score.[37] We assessed the validity of the estimates by plotting the inverse of the propensity score against a multiple regression analysis using possible confounders as independent variables.

We tested the significance of the unbiased differences in the HRQOL scores at the .01 level of significance. No parent reports were taken for survivors 18 years or older. For survivors aged 12 to 17 years, we tested the correlation between child- and parent-reported scores and the significance of unbiased differences in the PedsQL scores with multivariate analysis of variance.

Results

Sample Characteristics

Of the 138 survivors examined, 106 survivors and their parents returned the questionnaires to researchers (Figure). Two questionnaires were excluded because more than half of the responses were missing or incomplete, and 104 responses were analyzed as valid respondent. We observed no statistically significant differences in the age, gender, disease, and treatment information of respondents compared with nonrespondents (Table 1).

Of 51 survivors 18 years or older, the median age at diagnosis was 14 years, and about 10 years had passed since treatment completion. Of 53 survivors aged 12 to 17 years, the median age at diagnosis was 11 years, and about 5 years had passed since treatment completion. The sample was heterogeneous with respect to tumor pathology, tumor location, and treatment experiences. Nearly half of the respondents were germinoma survivors, which reflects a high incidence of this disease and which has a favorable prognosis in Japan.

HRQOL Scale Descriptions

The average score for survivors 18 years or older on QLQ functioning scales ranged from 79.4 on the cognitive functioning scale to 84.0 on the role functioning scale (Table 2). Drowsiness scored higher (indicating that this was a problem for survivors) than fatigue, communication deficit, and insomnia on the QLQ symptom scale.

For survivors aged 12 to 17 years, the mean child-reported PedsQL scores were similar to the parent-reported scores, except that parents reported a score of emotional functioning higher than their children did, and children reported a score of communication higher than their parents did (Table 2). When individual questionnaire answers were compared, intraclass correlation coefficients between answers on self-report scores and parent-report scores ranged from 0.42 to 0.88, indicating a moderate to high level of agreement between self-reported and parent-reported assessment of HRQOL.

Most of the QLQ scales were internally consistent (Cronbach's α coefficients >.70), except for the social functioning (α = .69) and fatigue (α = .67) scales. For the PedsQL scales, the α coefficients were greater than .70 (Table 2), except for child reports of social functioning (α = .67) and perceived physical appearance (α = .69) and parent reports of emotional functioning (α = .56), school functioning (α = .65), and communication (α = .56).

Impact of Late Effects on HRQOL

For survivors 18 years or older, specific late effects influenced linked aspects of HRQOL (Table 3). Motility disturbance of limb(s) significantly affected physical functioning, and seizure affected physical and social functioning, communication deficit, and drowsiness. Ocular/visual impairment significantly affected physical, emotional, and social functioning. Endocrine abnormality significantly affected insomnia. Higher brain dysfunction significantly affected role functioning, fatigue, insomnia, and communication deficit. All the significant affects indicated deterioration in HRQOL.

Similarly, for survivors aged 12 to 17 years, specific late effects influenced aspects of HRQOL (Table 4). Motility disturbance of limb(s) significantly affected physical functioning, movement and balance, perceived physical appearance (child report), and communication. Ocular/visual impairment significantly affected physical functioning (parent report), cognitive problems (parent report), movement and balance (child report), perceived physical appearance (child report), and communication (child report). The late effects on cognitive problems and movement and balance improved HRQOL. Late-effect seizure, endocrine abnormality, and higher brain dysfunction did not affect HRQOL.

Discussion

We examined how frequent late effects in survivors of pediatric brain tumors influenced HRQOL. We found that several late

Table 1 • Characteristics of Survivors of Pediatric Brain Tumors by Age Group and Comparison With Nonrespondents (N = 104)

	Respondents Aged ≥18 y (n = 51)		Respondents Aged 12–17 y (n = 53)		Nonrespondents (n = 34)		
	Mean (Median)	SD (IQR)	Mean (Median)	SD (IQR)	Mean (Median)	SD (IQR)	P[a]
Age, y	26.8 (24.4)	7.6 (21–31)	15.4 (15.3)	1.8 (14–17)	21.0 (18.2)	7.9 (15–24)	.495
Age at diagnosis, y	13.3 (13.9)	3.5 (11–15)	9.5 (10.5)	4.1 (7–12)	11.4 (12.1)	4.3 (9–14)	.731
Time since completion of antitumor therapy, y	11.1 (8.1)	8.3 (5–16)	4.6 (4.3)	3.3 (2–6)	7.8 (5.2)	7.1 (2.9–9.7)	.894

	Respondents Aged ≥18 y (n = 51)		Respondents Aged 12–17 y (n = 53)		Nonrespondents (n = 34)		
	n	%	n	%	n	%	P[b]
Gender							
Male	37	73	40	75	26	76	1.000
Female	14	27	13	25	8	24	
Tumor pathology							
Germinoma	23	45	21	40	14	41	.871
Other germ cell tumor	5	10	6	11	4	12	
Medulloblastoma/PNET	5	10	6	11	4	12	
Low-grade glioma	9	18	11	21	8	24	
High-grade glioma	4	8	1	2	0	0	
Others	5	10	8	15	4	12	
Tumor location							
Cerebral hemisphere	12	24	11	21	8	24	.751
Periventricular	30	59	32	60	20	59	
Infratentorial	6	12	9	17	6	18	
Multiple locus	3	6	1	2	0	0	
Hydrocephalus at diagnosis							
Experienced	17	33	20	38	16	47	.335
Not experienced	30	59	32	60	15	44	
Not recorded	4	8	1	2	3	9	
Neurosurgery	47	92	45	85	29	85	.764
Radiation treatment	44	86	42	79	23	68	.088
Chemotherapy	34	67	40	75	21	62	.394
Tumor recurrence	10	20	6	11	4	12	.781
Late effects							
Motility disturbance of limb(s)	12	24	6	11	2	6	.158
Seizure	10	20	4	8	3	9	.564
Ocular/visual impairment	11	22	4	8	7	21	.423
Endocrine abnormality	17	33	25	47	12	35	.687
Higher brain dysfunction	7	14	7	13	1	3	.116

Abbreviations: IQR, interquartile range (lower quartile-higher quartile); PNET, primitive neuroectodermal tumor.
[a]Mann-Whitney *U* test for comparison between 104 respondents and 34 nonrespondents.
[b]Fisher exact test for comparison between 104 respondents and 34 nonrespondents.

effects influenced specific aspects of HRQOL, irrespective of disease and treatment background.

These late-effect influences are both statistically significant and exceed minimal clinically important differences (MCIDs). Minimal clinically important differences are used to benchmark the impact of an intervention or exposure (late effect here) on outcome scale score (HRQOL here). Maringwa et al[38] reported MCIDs for deteriorating physical functioning (−9 points), role functioning (−12), fatigue (+9), and a communication deficit (+7) for patients treated for brain tumor and social functioning (−7) in patients with lung cancer.[39] Similarly, Taphoorn et al[40] reported MCIDs for deteriorating drowsiness (+12) in patients with brain tumors, and Varni et al[41] also reported MCIDs for physical functioning (−6.7 for child report and −6.9 for parent report), emotional functioning (−8.9 and −7.8, respectively), social functioning (−8.4 and −9.0, respectively), and school functioning (−9.1 and −9.7, respectively). The late-effect decrements in HRQOL reported here are larger than the MCIDs