Table 4. The APC of childhood cancer mortality rates (girls)

Country	Trend 1		Trend 2		Trend 3		Trend 4		AAPC	
	Years	APC	Years	APC	Years	APC	Years	APC	Last 10 observations	Last 6 observations
Total malignant tumors										
Japan	1970–1972	3.24	1972–1995	−3.21*	1995–1999	−6.46*	1999–2006	−0.57	−1.9*	−0.6
Canada	1970–2004	−3.42*							−3.4*	−3.4*
United States	1970–1977	−4.46*	1977–1995	−2.72*	1995–2005	−1.07*			−1.1*	−1.1*
Italy	1970–2003	−2.80*							−2.8*	−2.8*
UK	1970–2005	−2.73*							−2.7*	−2.7*
New Zealand	1970–2004	−2.57*							−2.6*	−2.6*
Leukemia										
Japan	1970–2006	−4.53*							−4.5*	−4.5*
Canada	1970–2004	−5.28*							−5.3*	−5.3*
United States	1970–1980	−6.09*	1980–2005	−3.14*					−3.1*	−3.1*
Italy	1970–2003	−4.33*							−4.3*	−4.3*
UK	1970–2005	−3.88*							−3.9*	−3.9*
New Zealand	1970–2004	−3.17*							−3.2*	−3.2*
Lymphomas										
Japan	1970–1991	−1.13	1991–2006	−11.85*					−11.8*	−11.8**
Canada	1970–2004	−4.55*							−4.6*	−4.6*
United States	1980–2005	−4.39*							−4.4*	−4.4*
Italy	1970–2003	−3.93*							−3.9*	−3.9*
UK	1970–2005	−4.56*							−4.6*	−4.6*
New Zealand	1970–2004	−0.35							−0.4	−0.4
Central nervous system tumors										
Japan	1980–2006	0.03							0.0	0.0
Canada	1980–2004	−1.50*							−1.5*	−1.5*
United States	1980–2005	−0.87*							−0.9*	−0.9*
Italy	1980–2003	−2.28*							−2.3*	−2.3*
UK	1980–2005	−1.68*							−1.7*	−1.7*
New Zealand	1980–2004	−2.32*							−2.3*	−2.3*
Malignant kidney tumors										
Japan	1976–2006	−3.98*							−4.0*	−4.0*
Canada	1970–2004	−2.90*							−2.9*	−2.9*
United States	1970–1991	−4.60*	1991–2005	0.16					0.2	0.2
Italy	1970–2003	−4.62*							−4.6*	−4.6*
UK	1970–2005	−3.49*							−3.5*	−3.5*
New Zealand	1970–2004	−2.91*							−2.9*	−2.9*
Malignant bone tumors										
Japan	1980–2006	−1.79*							−1.8*	−1.8*
Canada	1980–2004	−0.24							−0.2	−0.2
United States	1980–2005	−1.59*							−1.6*	−1.6*
Italy	1980–2003	−3.52*							−3.5*	−3.5*
UK	1980–2005	−2.22*							−2.2*	−2.2*
New Zealand	1980–2004	1.52							1.5	1.5

*$P < 0.05$.

APC is the annual per cent change; AAPC is average annual per cent change.

obtained in the current study. Research in Great Britain [9, 10], Italy [11] and Sweden [12] showed increased trends in childhood leukemia. A report from Britain indicated that small peaks in the incidence of ALL in 1976 and 1990 coincided with the years immediately following influenza epidemics [13]. Other explanations of the increased trend were characteristics of the environment, such as population mixing, although the etiology of cancer remains complicated and largely unknown.

The stable trend in mortality for childhood CNS tumor implied a modest increase trend in the incidence rate in Japan because of the survival improvement reported in childhood CNS tumors in developed countries in recent decades, while progress in therapy for brain tumors has not been as great as for leukemia. For CNS tumors, computed tomography, which was introduced in the 1970s, and magnetic resonance imaging, which has been used widely since the 1980s, has become

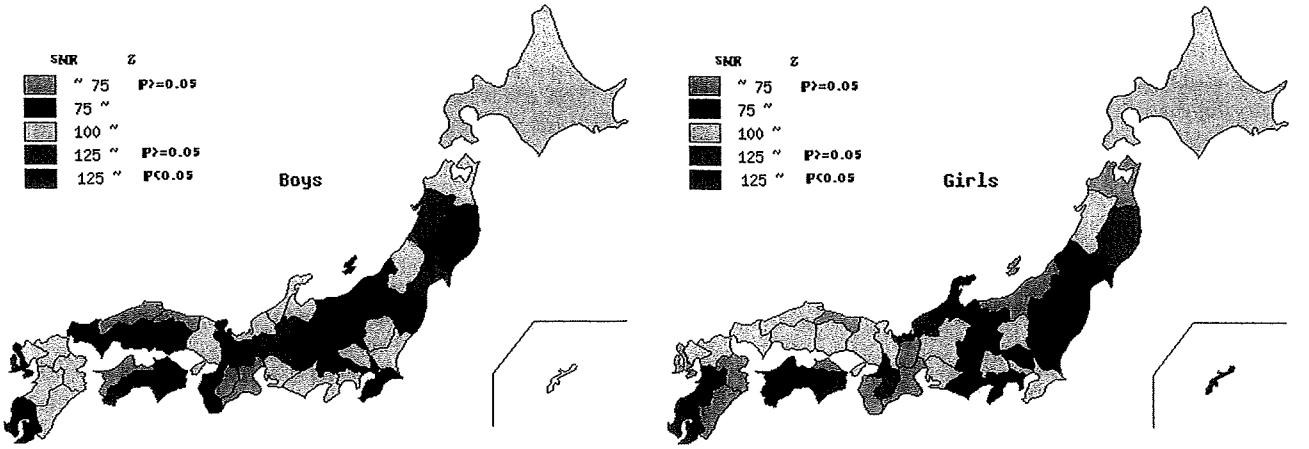

Figure 3. Standardized mortality ratios for childhood cancer in Japan, 2000–2006 by prefecture.

a standard tool for CNS tumor diagnosis and evaluation [14]. Furthermore, improvements in neurosurgical techniques have occurred during the past two decades, including stereotactic surgery, Cavitron Ultrasonic Surgical Aspirator and so on. Childhood cancer survival research from Osaka prefecture in Japan reported a slight increase in 5-year survival [1]. Incidence trends were not evaluated in this study. Data from the population-based cancer registry of Hokkaido prefecture in Japan indicated that the incidence of childhood brain tumors has been increasing, though the cause is unknown [15]. Other studies conducted in developed countries reported a significant increase in childhood CNS tumor incidence [10, 12, 16–21]. This has been explained by changes in detection and/or reports of childhood CNS tumors [22]. Because magnetic resonance imaging became ubiquitous at tertiary pediatric centers in the mid-1980s, it is likely to have increased the rate of detection; however, in the current study, the mortality rate of childhood CNS tumors in Japan was low and constant since the 1980s, and no significant increase in the number of deaths occurred in the middle of the 1980s to support the suggestion that the incidence increase was due to improved diagnostic techniques, if this increase really exists in Japan, and it seems unlikely to explain the long-term continued leveling off of mortality. The etiology of childhood CNS tumors remains largely unknown. Environmental factors are suggested to have a relationship with brain tumors. Further investigation in this field is needed to identify the incidence trends and reasonable explanations for these trends in Japan.

A previous childhood cancer mortality study in Japan presented data up to 1998. Furthermore, trend analysis was according to the correlation coefficient between the mortality rate and death year. Our analysis provides an updated mortality rate and reliable time trend analysis. In general, the mortality trends observed in other developed countries were compatible with Japan, although some differences were apparent. For example, a decrease in mortality during 0–14 years was observed in leukemia in the United States, Canada, Italy, New Zealand and Japan; however, the mortality rate from CNS tumors has decreased in the United States, Canada, UK and Italy in recent two decades. No evidence of decline appeared during 1980-2006 in Japan. For lymphoma, the decline occurred relatively late in Japan, compared with a significant decline without a leveling off period in the United States, Canada, Italy and UK. There is no simple explanation for these trend disparities. It is possible that the distribution of the histology pattern is markedly different among different countries, even in the same diagnostic group. The possible causes for these disparities in the childhood cancer death rate (e.g. late diagnosis, poor treatment quality, lack of health insurance and difficulty in accessing health care) need to be studied further.

A high mortality rate was observed in Kochi prefecture in boys and Tokushima and Kagoshima prefectures in girls. As mentioned above, the geographic disparity might be due to differences in cancer incidence and survival in different regions. Studies of the relationship between social class and childhood cancer have not been consistent. Research from Brazil suggested that higher decreases in the mortality rate were observed in more developed regions, possibly reflecting better health care [23]. We did not perform a similar ecologic study here, because of the small number of death, and we could not even calculate mortality by subtype by prefecture. Further detailed individual-level study is needed to identify a more reasonable explanation for the mortality disparities in childhood cancer.

A few points should be borne in mind when interpreting these findings. Some stable trends in the present study, such as mortality in lymphoma, and malignant bone tumors in New Zealand are more difficult to explain because of the small absolute number and substantial random variation. Other limitations included the wide time span and changes in diagnostic capabilities during the study period, and we were not able to collect any information on social status, employment of individuals and other genetic, environmental factors that would have allowed us to analysis etiological hypotheses.

Despite these limitations, when considering the absence of a national cancer registry system in Japan, estimates of incidence may have their own limitations (for example, they may be significantly influenced by errors in diagnosis and classification); evaluation of death may be an alternate effective method to identify more population-based point estimates of

mortality from childhood cancer under these circumstances. Furthermore, the results presented here are based on 100% national coverage and provide an important baseline for monitoring the further progress against childhood cancer in Japan. Analysis of trends in national mortality rates over several decades may provide additional insight into the burden and impact of childhood cancer and suggest more targeted avenues for interventions that further delineate and ultimately reduce mortality from childhood cancer.

conclusions

The present study provides updated figures and trends in childhood cancer mortality in Japan and other developed countries. This will help to estimate care needs and to plan interventions and the quantity of appropriate childhood cancer treatment. Comprehensive efforts designed to identify risk factors for childhood cancer, promote early detection and reduce morbidity and mortality are warranted.

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Trends in cancer mortality in Japanese adolescents and young adults aged 15–29 years, 1970–2006

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Objective: The primary objective of this study is to describe cancer mortality rates and trends among Japanese adolescents and young adults aged 15–29 years for the period 1970–2006.
Materials and methods: Age-standardized mortality rates were calculated by the direct method using age-specific mortality rates at 5-year age intervals and weights based on the age distribution of the standard world population. The joinpoint regression model was used to describe changes in trends.
Results: For all cancers combined, the mortality rate at age 15–29 years during 2000–2006 was 4.41 (per 100 000 population) for males and 3.81 (per 100 000) for females. Trends of mortality from cancer in Japan were similar to that in other developed countries. A notable exception was cervical cancer, for which Japanese young women showed a significant increase, on average 4.0% per year throughout the period.
Conclusion: This report presents updated figures and trends in cancer mortality among adolescents and young adults aged 15–29 years in Japan and other developed countries. We hope this study will raise public awareness on cancer in this age group and provide the impetus for further research to improve the survival and quality of life of the young people in Japan.
Key words: adolescent, cancer, epidemiology, mortality, time trends, young adult

introduction

Cancer is the leading cause of disease-related deaths in adolescents and young adults (AYAs) in Japan. Nearly 7000 adolescents and young adults aged 15–29 died from cancer in Japan in the 7-year period of 2000–2006. Overall cancer patterns reflect cancers that are most prevalent in middle and old age, especially breast, prostate, lung and colorectal. However, the spectrum of malignant diseases among younger ages (childhood, adolescence and young adulthood) differs from patterns at older ages and even among themselves. A prior monograph from the Surveillance, Epidemiology and End Result (SEER) program indicated that malignant disease in persons aged 15–29 years is unique in the distribution of types that occur, with Hodgkin's lymphoma, melanoma, testis cancer, female genital tract malignancies, thyroid cancer, soft tissue sarcomas, and nongonadal germ-cell tumors accounting for 95% of the cancers in this age group. The vast majority of cancers diagnosed before age 30 appears to be spontaneous and unrelated to either carcinogens in the environment or inherited factors [1].

Compared with younger and older age groups, adolescents and young adults have experienced little or no improvement in cancer survival rates in more than two decades. The SEER reports have addressed concerns about the deficit in survival improvement in this population and attributed it to a lack of awareness of the cancer problem in this age group, lack of health-care insurance coverage and access to health care [1–4]. During recent years, more attention has been drawn to the need for further development of treatment services available to adolescents and young adults with cancer. Some developed countries have also reported descriptive epidemiologic results based on population data for AYAs with cancer [5–14]. However, little attention and few resources have been devoted to studying the incidence, risk factors, survival and mortality in this age group in Japan.

To provide a comprehensive picture of the cancer mortality and trend analysis in individuals aged 15–29 years in Japan, we analyzed the occurrence of death from cancer among AYAs at the population level over the period of 1970–2006, using official death certificates, which record 100% of deaths in Japan.

materials and methods

The number of deaths by cause, stratified for sex and by 5-year age group for cancer for the period 1970–2006, was derived from vital statistics compiled by the Ministry of Health, Labor and Welfare of Japan.

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Population figures were obtained from census data and intercensus estimates, by calendar year, age and gender. Population censuses of Japan are conducted every 5 years by the Statistics Bureau, Ministry of Internal Affair and Communications.

For comparison, we also calculated the cancer mortality rate in other developed countries, including Canada (2000–2004), the United States (2000–2005) and UK, England and Wales (2000–2005). Deaths at age 15–19, 20–24 and 25–29 years were derived from the World Health Organization (WHO) mortality database. Estimates of the residential population, based on official censuses, were obtained from the same WHO database.

During 1970–2006, three different revisions of the International Classification of Disease (ICD) were used. In Japan, this included ICD-8 from 1970 to 1978, ICD-9 from 1979 to 1994 and ICD-10 from 1995 onward. Since the differences were minor in various revisions, we recorded cancer sites, including all cancer combined (ICD-10: C00–97), lip, oral and cavity and pharynx (ICD10: C00–14), digestive organs (ICD-10: C15–26), colorectal (ICD-10:C18–21), respiratory and intrathoracic organs (ICD-10: C30–C39), bone and articular cartilage (ICD-10: C40–C41), melanoma of skin (ICD-10: C43–C44), mesothelial and soft tissue (ICD10:C45–C49), genitourinary organs (ICD-10:C51–C68), testis (ICD-10:C62), cervix (ICD-10: C53), ovary (ICD-10:C56), central nervous system (CNS) tumors (ICD-10: C70–C72), thyroid and other endocrine glands (ICD-10:C73–C75), leukemia (ICD10: C91–C95), lymphoid leukemia (ICD-10: C91), myeloid leukemia (ICD-10: C92), lymphomas (ICD-10: C81–85), Hodgkin's disease (ICD-10: C81) and non-Hodgkin's lymphoma (ICD-10: C82–85). Age-standardized mortality rates at age 15–29 years were calculated by the direct method using age-specific mortality rates for 5-year age intervals and weights based on the age distribution of the standard world population.

Joinpoint software 3.3.1 from the Surveillance Research Program of the US National Cancer Institute was used for trend analysis [15, 16]. We allowed up to four joinpoints for each model. Mortality rates and their standard errors were calculated using SAS 9.0. Time trends were assessed by site and sex. Mortality trends for Canada (1970–2004), the United States (1970–2005) and UK, England and Wales (1970–2005) were included for comparison.

The standardized mortality ratio (SMR) by sex was calculated for 47 prefectures in Japan by taking the ratio of the observed to expected deaths. The z value was computed for each SMR, based on the assumption that observed deaths follow a Poisson distribution. The maps were developed using SMR by gender.

results

Table 1 gives age-adjusted 15–29 years mortality rates from all malignant tumors and the main types of cancer in Japan and other developed countries. Age-adjusted mortality rates in Japan for six successive 5-year calendar periods, i.e. 1970–1974, 1975–1979, 1980–1984, 1985–1989, 1990–1994 and 1995–1999, and also for the 7-year period of 2000–2006 were calculated. For all cancers combined, the mortality rate at age 15–29 years during 2000–2006 was 4.41 (per 100 000 population) for males and 3.81 (per 100 000) for females. Trends of age-standardized mortality from cancer are shown in Figures 1 and 2 and Table 2. The mortality for all cancers combined has declined since 1970s for both sexes. The average annual percent change (AAPC) in the last 10 years was -3.1% ($P < 0.05$) for males and -1.6% ($P < 0.05$) for females.

malignant neoplasm of lip, oral cavity and pharynx

Mortality rates from lip, oral cavity and pharynx cancer remained stable at a low level for both genders throughout the period. Death rate was 0.13 (per 100 000) for males and 0.08 (per 100 000) for females during 2000–2006.

colorectal cancer

Since 1970, colorectal cancer mortality has declined among AYA population aged 15–29 years. The reduction during the past 10 years averaged 2.6% per year in males and 3.0% per year in females.

malignant neoplasm of respiratory and intrathoracic organs

Mortality rates from respiratory organs cancer in adolescents and young men increased in the 1970s and fell significantly from 0.20 per 100 000 in 1979 to 0.09 per 100 000 in 2006. For females, the death rates declined throughout the period. The AAPC in the last 10 years was -2.7% for males and -2.1% for females.

malignant neoplasm of bone, connective tissue, skin and breast

Mortality for malignant bone tumors during 2000–2006 was 0.38 (per 100 000) for males and 0.22 (per 100 000) for females. Reduction was observed throughout the period for both sexes (1.4% per year in males and 2.1% per year in females). Figures 1 and 2 show increases in mortality for mesothelial and soft tissue tumors of 3.2% per year in males and 3.0% per year in females in the period 1970–2006. Mortality for melanoma of skin remained low and stable in females from 1970 to 2006. For males, a decline trend has been observed in the last 6 years with an average of 23.8% per year. The rate for both sexes was ~0.05 (per 100 000) during 2000–2006. Female breast cancer mortality rates peaked in 1980 and then fell significantly from 0.35 (per 100 000) to 0.24 (per 100 000) with 1.9% per year during 1980–2006.

genitourinary organ cancer

Mortality rates from testicular cancer increased by 7.1% per year from 1970 to 1977 and fell significantly from 0.54 (per 100 000) in 1977 to 0.16 (per 100 000) in 2006. Relative to cervical cancer, mortality significant increased by an average of 4.0% per year throughout the period. For ovary cancer, the rates have remained stable for the past decade.

CNS tumors

CNS tumors mortality among AYA population was 0.30 (per 100 000) for females and 0.42 (per 100 000) for males from 2000 to 2006. Mortality for males increased significantly by 7.1% per year until 1981 at which point there was a slight and nonsignificant rise. For females, mortality increased by 1.4% per year in the whole period.

malignant neoplasm of thyroid and other endocrine glands

Mortality rates were stable throughout the period for both sexes, with the rate ~0.07 (per 100 000) for males and 0.04 (per 100 000) for females from 2000 to 2006.

Table 1. Age-adjusted mortality rate (per 100 000) by sex and diagnostic group at age 15–29 years in Japan and other developed countries

Tumor	Japan							Canada	United States	England and Wales
	1970–1974	1975–1979	1980–1984	1985–1989	1990–1994	1995–1999	2000–2006	2000–2004	2000–2005	2000–2005
Males										
Total malignant tumors	8.76	8.39	7.36	6.61	5.92	5.46	4.41	4.91	5.53	5.77
Lip, oral cavity and pharynx	0.12	0.14	0.12	0.09	0.15	0.15	0.13	0.08	0.09	0.13
Digestive organs	2.98	2.39	1.83	1.40	1.12	0.97	0.73	0.43	0.55	0.52
Colorectal	0.78	0.51	0.41	0.37	0.31	0.27	0.24	0.20	0.25	0.20
Respiratory and intrathoracic organs	0.42	0.45	0.41	0.38	0.31	0.27	0.24	0.11	0.17	0.11
Bone and articular cartilage	0.64	0.53	0.46	0.50	0.45	0.44	0.38	0.56	0.51	0.64
Meothelial and soft tissue	0.11	0.15	0.18	0.25	0.22	0.34	0.31	0.29	0.42	0.39
Melanoma of skin	0.06	0.06	0.03	0.04	0.04	0.05	0.05	0.21	0.22	0.28
Genitourinary organs	0.47	0.61	0.51	0.46	0.42	0.28	0.23	0.35	0.35	0.32
Testis	0.38	0.50	0.42	0.35	0.31	0.21	0.16	0.24	0.26	0.21
Central nervous system	0.22	0.29	0.43	0.38	0.39	0.43	0.42	0.72	0.72	0.94
Thyroid and other endocrine glands	0.05	0.10	0.06	0.06	0.06	0.08	0.07	0.06	0.07	0.09
Leukemia	2.56	2.54	2.25	2.12	1.86	1.70	1.23	1.04	1.31	1.18
Lymphoid leukemia	0.25	0.38	0.62	0.74	0.74	0.72	0.53	0.49	0.56	0.59
Myeloid leukemia	1.59	1.46	1.12	1.00	0.84	0.80	0.59	0.36	0.50	0.52
Lymphoma	0.89	0.95	0.85	0.78	0.76	0.58	0.49	0.76	0.76	0.82
Hodgkin's lymphoma	0.13	0.10	0.07	0.06	0.05	0.03	0.04	0.24	0.23	0.26
Non-Hodgkin's lymphoma	0.76	0.85	0.78	0.72	0.71	0.55	0.45	0.51	0.53	0.55
Females										
Total malignant tumors	8.46	7.59	6.74	5.63	4.62	4.32	3.81	4.19	4.45	5.08
Lip, oral cavity and pharynx	0.06	0.07	0.07	0.06	0.06	0.08	0.08	0.08	0.06	0.05
Digestive organs	3.26	2.68	2.10	1.61	1.10	0.90	0.71	0.38	0.42	0.41
Colorectal	0.57	0.39	0.34	0.31	0.25	0.23	0.22	0.10	0.19	0.17
Respiratory and intrathoracic organs	0.28	0.24	0.21	0.20	0.17	0.16	0.14	0.13	0.10	0.10
Bone and articular cartilage	0.33	0.28	0.27	0.24	0.22	0.25	0.22	0.28	0.30	0.46
Meothelial and soft tissue	0.10	0.13	0.20	0.19	0.20	0.29	0.28	0.31	0.32	0.27
Melanoma of skin	0.05	0.06	0.04	0.04	0.03	0.04	0.05	0.12	0.16	0.25
Breast	0.21	0.25	0.31	0.27	0.20	0.21	0.20	0.22	0.28	0.42
Genitourinary organs	1.29	1.02	0.87	0.69	0.59	0.56	0.55	0.54	0.55	0.67
Cervix	0.06	0.05	0.06	0.09	0.13	0.15	0.16	0.26	0.24	0.35
Ovary	0.79	0.71	0.62	0.43	0.31	0.30	0.26	0.19	0.20	0.23
Central nervous system	0.18	0.24	0.22	0.22	0.23	0.30	0.30	0.50	0.51	0.72
Thyroid and other endocrine glands	0.05	0.07	0.07	0.05	0.06	0.04	0.04	0.07	0.07	0.06
Leukemia	2.00	1.90	1.68	1.50	1.28	1.07	0.86	0.78	0.88	0.85
Lymphoid leukemia	0.17	0.24	0.45	0.45	0.48	0.42	0.34	0.18	0.29	0.34
Myeloid leukemia	1.20	1.16	0.84	0.73	0.60	0.53	0.44	0.36	0.43	0.47
Lymphoma	0.40	0.46	0.49	0.41	0.38	0.30	0.27	0.58	0.54	0.59
Hodgkin's lymphoma	0.05	0.06	0.06	0.03	0.02	0.03	0.03	0.25	0.22	0.24
Non-Hodgkin's lymphoma	0.35	0.39	0.44	0.39	0.35	0.27	0.23	0.33	0.32	0.35

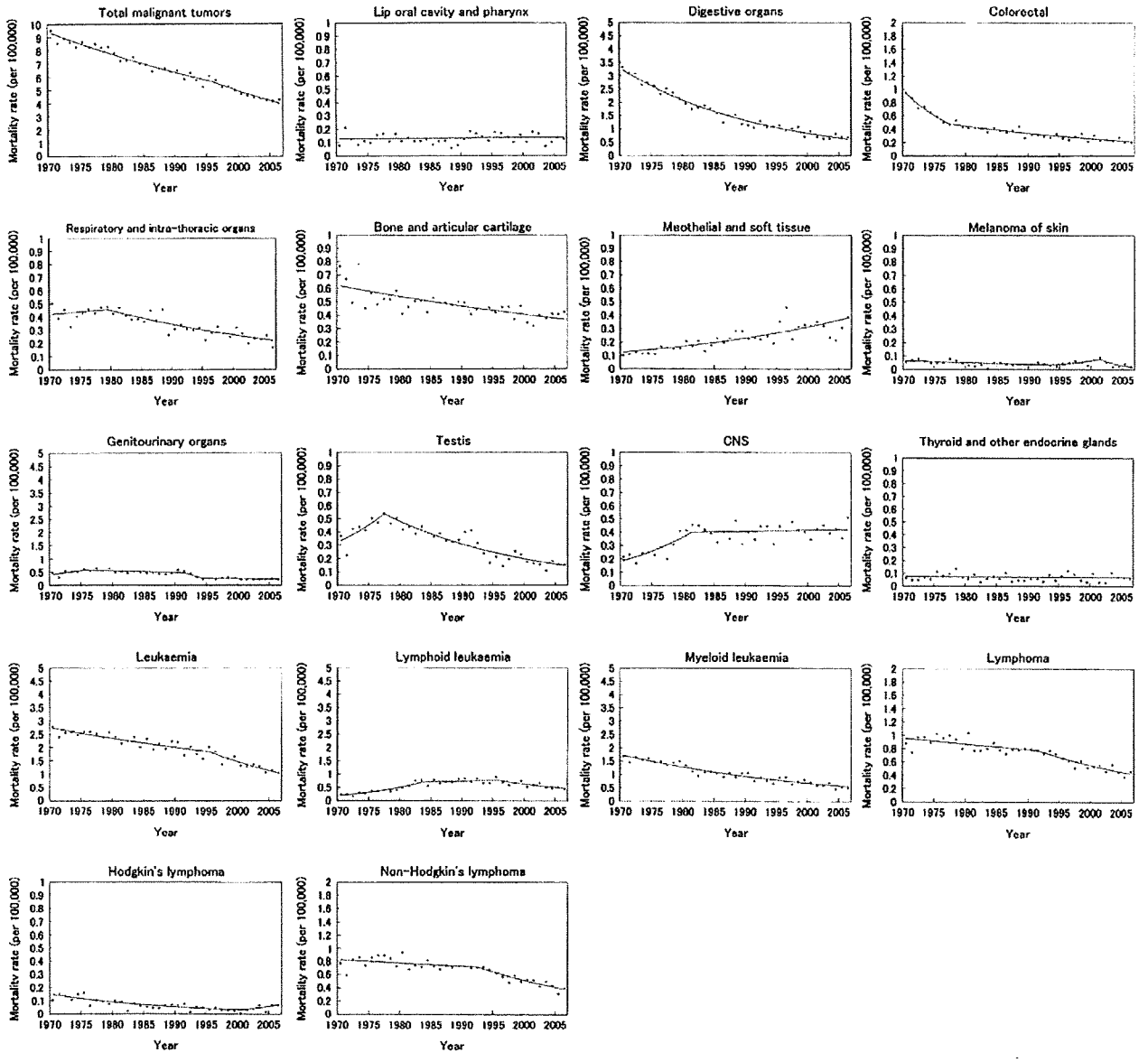

Figure 1. Trends on age-adjusted mortality for cancer among adolescents and young adults aged 15–29 years, Males, Japan, 1970–2006.

malignant neoplasm of lymphoid, hematopoietic and related tissue

Death rate from leukemia during 2000–2006 was 1.23 (per 100 000) for males and 0.86 (per 100 000) for females. Mortality showed continued improvement over time for both sexes. For lymphoma, rate among young people aged 15–29 years was 0.49 (per 100 000) in males and 0.27 (per 100 000) in females during 2000–2006. Significant decline was observed in both sexes (by 3.9% per year in males and 2.8% per year in females in recent decade).

Mortality rates varied among prefectures in Japan. A map of SMR by gender is shown in Figure 3. The SMR was significantly highest among AYAs aged 15–29 years in Hokkaido, Iwate, Akita, Fukushima, Niigata and Miyazaki prefectures for males and Akita, Fukushima, Tochigi, Kochi and Miyazaki prefectures for females.

discussion

This study has presented detailed analysis on the trends of cancer mortality in AYAs aged 15–29 years in Japan. There were 60 959 adolescents and young adults who died from cancer during 1970–2006. Approximately 900 deaths were attributed to cancer in AYAs aged 15–29 years in 2006, which is two times more common than mortality during the first 15 years of life.

Mortality rates decreased during the study period in both sexes. It is unlikely that the observed time trends in the mortality rate are due to variations in the completeness and accuracy of the population data, because the data we used were provided by official sources, which were founded on the population census. The AAPC was also reported in this study. The AAPC can be used to characterize a short segment based on a joinpoint model fit over a much longer series. This is

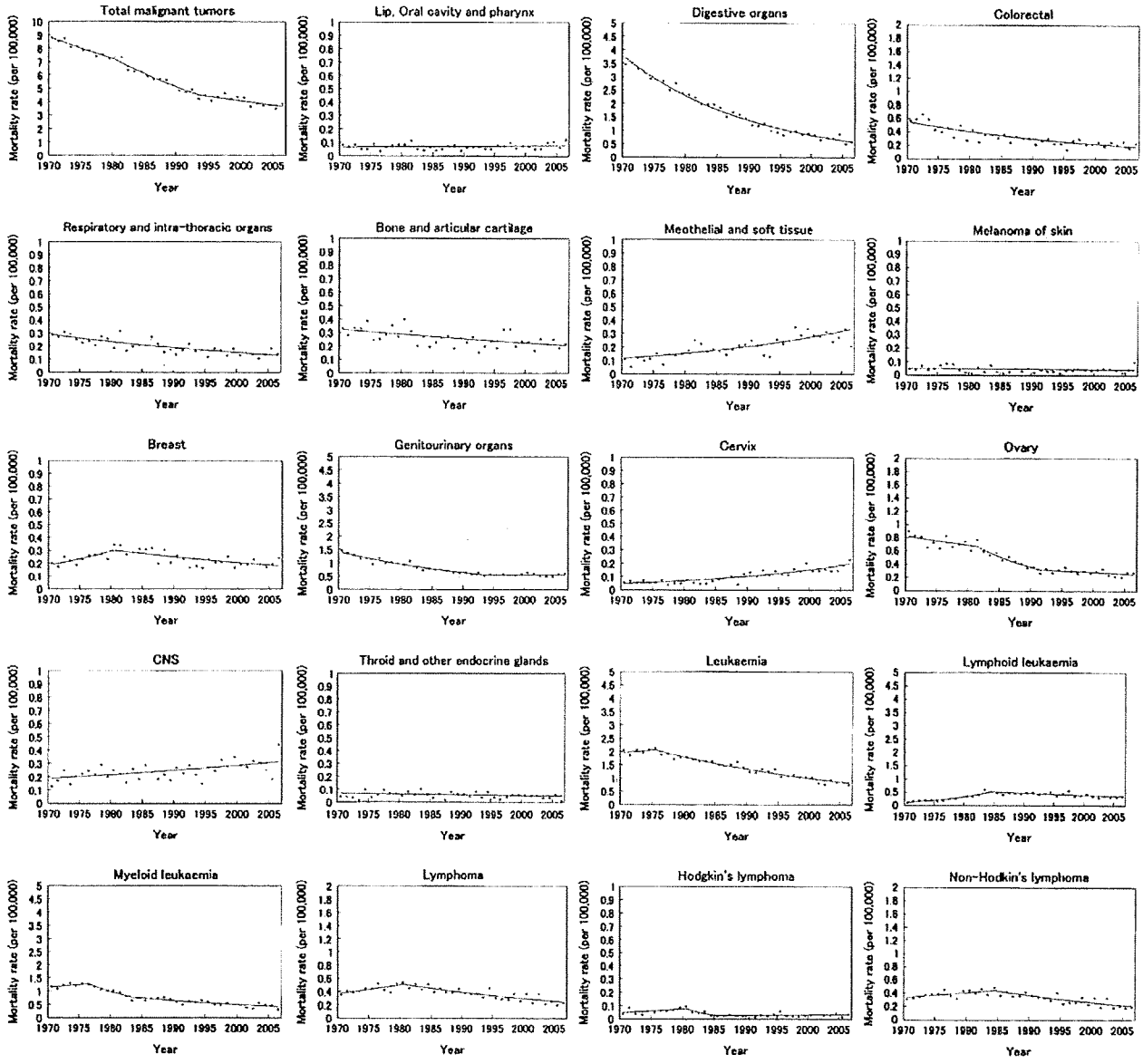

Figure 2. Trends on age-adjusted mortality for cancer among adolescents and young adults aged 15–29 years, Females, Japan, 1970–2006.

especially advantageous when data are sparse (e.g. a rare cancer or data from a small geographic area) [17]. According to trend analysis, marked mortality reductions occurred for cancer of digestive and respiratory organs, testicular cancer, leukemia and lymphoma. Similar decline trends were also observed in the United States, Canada and England and Wales in recent decade. These declines have been attributable to improving treatment for leukemia, lymphoma and testicular cancer.

Compared with the childhood cancers we reported previously [18], the reduction in the cancer mortality rate among AYAs aged 15–29 years has lagged behind the reduction in children. The AAPC in the last 10 years for pediatric cancer were −3.8% per year for boys and −1.9% per year for girls, while comparable declines for AYA population were −3.1% per year for males and −1.6% per years for females in the same period. Similar patterns have also been reported in the United States. A recent monograph published by SEER revealed that cancer mortality rates among this population have mysteriously flattened, while those of children and older adults have steadily improved [19]. The different distribution of cancer type between children and young people might partly explain this lowered reduction in mortality rate among AYA population. Furthermore, survival studies focused on AYAs have also found that some cancers common in adolescents, such as acute myeloid leukemia, acute lymphoblastic leukemia, rhabdomyosarcomam, osteogenic sarcoma and Ewing's sarcoma, are associated with lower 5-year disease-free survival rates in adolescents and young people [12], likely contributing to this deficit in mortality reduction between young adults and children. A report from the United States also attributes this discrepancy in part to the widespread gap in clinical trial participants and health-care insurance coverage between

Table 2. Joinpoint analysis for all cancer combined and selected diagnostic group of cancers, at ages 15–29 years in Japan, 1970–2006

Tumor	Japan								AAPC*			
	Trend 1		Trend 2		Trend 3		Trend 4		Japan	Canada	United States	England and Wales
	Years	APC	Years	APC	Years	APC	Years	APC	1997–2006	1995–2004	1996–2005	1996–2005
Male												
Total malignant tumors	1970–1995	−1.9*	1995–2006	−3.1*					−3.1*	−2.2*	−1.7*	−2.2*
Lip, oral cavity and pharynx	1970–2006	0.2							0.2	−1.0	−1.0*	0.4
Digestive organs	1970–2006	−4.5*							−4.5*	−2.9*	−0.9*	−2.0*
Colorectal	1970–1977	−9.2*	1977–2006	−2.6*					−2.6*	7.5	−0.4	−0.7
Respiratory and intrathoracic organs	1970–1979	0.9	1979–2006	−2.7*					−2.7*	−1.9*	−2.5*	−5.5*
Bone and articular cartilage	1970–2006	−1.4*							−1.4*	−1.6*	1.0*	−0.7*
Meothelial and soft tissue	1970–2006	3.2*							3.2*	−1.7	0.1	1.0*
Melanoma of skin	1970–1994	−2.5*	1994–2001	11.9	2001–2006	−23.8*			−9.6	−1.5*	−3.2*	−0.1
Genitourinary organs	1970–1975	7.0	1975–1991	−1.2	1991–1994	−17.2	1994–2006	−1.4	−1.4	−3.9*	−2.3*	−5.5*
Testis	1970–1977	7.1*	1977–2006	−4.3*					−4.3*	−4.7*	−2.3*	−6.5*
Central nervous system	1970–1981	7.1*	1981–2006	0.2					0.2	−1.3*	−0.9*	−1.4*
Thyroid and other endocrine glands	1970–2006	−0.1							−0.1	0.7	−1.9*	0.4
Leukemia	1970–1995	−1.5*	1995–2006	−5.0*					−5.0*	−2.7*	−1.6*	−3.3*
Lymphoid leukemia	1970–1983	9.8*	1983–1995	0.8	1995–2006	−4.6*			−4.6*	−1.7*	−0.7*	−3.7*
Myeloid leukemia	1970–2006	−3.1*							−3.1*	−2.6*	−3.5*	−2.6*
Lymphoma	1970–1991	−1.0*	1991–2006	−3.9*					−3.9*	−2.8*	−4.8*	−3.3*
Hodgkin's lymphoma	1970–2000	−5.0*	2000–2006	14.0					7.3	−4.2*	−4.5*	−5.2*
Non-Hodgkin's lymphoma	1970–1992	−0.6	1992–2006	−4.4*					−4.4*	−1.1*	−4.7*	−1.5*
Female												
Total malignant tumors	1970–1980	−2.0*	1980–1993	−3.5*	1993–2006	−1.6*			−1.6*	−1.7*	−2.1*	−1.6*
Lip, oral cavity and pharynx	1970–2006	0.5							0.5	−0.1	−0.4	−1.3
Digestive organs	1970–2006	−5.0*							−5.0*	−1.6*	−0.6*	−1.6*
Colorectal	1970–2006	−3.0*							−3.0*	−3.2*	−1.3*	−1.2*
Respiratory and intrathoracic organs	1970–2006	−2.1*							−2.1*	−2.1*	−2.4*	1.6
Bone and articular cartilage	1970–2006	−1.2*							−1.2*	−0.7	0.8	−0.6
Meothelial and soft tissue	1970–2006	3.0*							3.0*	1.3	−0.1	−2.6
Melanoma of skin	1970–2006	−0.6							−0.6	−2.7*	−2.9*	−1.4*
Breast	1970–1980	4.7*	1980–2006	−1.9*					−1.9*	−2.4*	−4.6*	−1.6*
Genitourinary organs	1970–1993	−3.9*	1993–2006	0.1					0.1	−2.2*	−1.6*	−3.8*
Cervix	1970–2006	4.0*							4.0*	−1.1*	−1.2*	−4.5*
Ovary	1970–1981	−1.8*	1981–1991	−7.0*	1991–2006	−1.6			−1.6	−2.7*	0.7	−3.0*
Central nervous system	1970–2006	1.4*							1.4*	−1.6*	−1.1*	−1.5*
Thyroid and other endocrine glands	1970–2006	−0.9							−0.9	0.6	−1.3*	−0.1
Leukemia	1970–1975	1.0	1975–2006	−2.9*					−2.9*	−2.3*	−1.7*	−1.9*
Lymphoid leukemia	1970–1984	10.7*	1984–2006	−1.9*					−1.9*	−6.2*	−0.8*	−0.3

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Table 2. *(Continued)*

Tumor	Japan						AAPC*	Canada	United States	England and Wales
	Trend 1		Trend 2		Trend 3		Trend 4							
	Years	APC	Years	APC	Years	APC	Years	APC	Japan 1997–2006	1995–2004	1996–2005	1996–2005
Myeloid leukemia	1970–1976	1.7	1976–1983	−7.0*	1983–2006	−2.6*			−2.6*	−2.1*	−2.3*	−2.4*
Lymphoma	1970–1980	3.2*	1980–2006	−2.8*					−2.8*	−1.6*	−1.3*	−2.4*
Hodgkin's lymphoma	1970–1980	5.2	1980–1985	−19.9	1985–2006	1.3			1.3	−1.7*	−3.2*	−3.6*
Non-Hodgkin's lymphoma	1970–1984	1.9*	1984–2006	−3.3*					−3.3*	−0.1	−5.0*	−1.0*

[a]Last 10 observations.
*$P < 0.05$.
APC, annual percent change; AAPC, average annual percent change.

pediatric and young adults [20]. The proportion of Japanese teenagers with cancer who are included in national and international clinical trials and studies is still unknown. Further studies focused on health-care services and survival outcome among adolescents and young adults in Japan need to be conducted.

There was no decline in mortality from CNS tumors among AYAs in Japan. This implied an unfavorable trend in the incidence of CNS tumors in these populations, although improved diagnosis and certification could not be completely ruled out as contributing factors. The etiology of CNS tumors is complicated and remains largely unknown. Environmental factors are suggested to have a relationship with brain tumors. Increased incidences among children based on local population-based cancer registry data in Japan have been reported previously [21]. Investigations of the incidence of CNS tumors among adolescents and young people are necessary.

The increase in mortality from cervical cancer in AYAs suggests an increased incidence in these populations. This hypothesis can be proved by data from 11 regional population-based cancer registries in Japan [22]. The incidence rate increased from 0.7 (per 100 000) in 1975–1979 to 2.1 (per 100 000) in 2000–2002 among the AYA population aged 15–29 years. The reason for this increase trend among young women is complicated. Some research has attributed it to changes in sexual habits, oral contraceptive use, tobacco smoking, sexually transmitted diseases (papillomavirus) and the extension and distribution of screening among adolescents and young women. The cervical cancer-screening program in Japan was only offered to women aged >30 until 2004, and the coverage rate fell behind that of other developed countries. According to the Organization for Economic Co-operation and Development health data 2008, the coverage of cervical cancer screening was 23% among Japanese women aged 20–69 years, compared with 83.5% in the United States, and 72.4% in Germany [23].

Although Levi et al. [24] reported mortality trends in AYAs aged 15–24 years in Europe, including Japan for comparison previously, they primarily mentioned about seven diagnostic groups (bone sarcoma, soft tissue sarcoma, vary, testis, non-Hodgkin's lymphomas, Hodgkin's disease and leukemia) and only presented data up to 1998. Our report provides updated mortality rates and reliable time trend analysis for AYAs aged 15–29 years in Japan. Trends of mortality from cancer in Japan were generally comparable with other developed countries, but different patterns among countries have been found in this study. For example, the mortality rate from CNS tumors has decreased in the United States, Canada and UK in recent decades; however, no evidence of decline was found in Japan. Unfavorable mortality trends from cervical cancer in young Japanese women throughout the period were not observed in the United States, Canada and UK. Differences in the distribution of the histology pattern among different countries might play a role. Meanwhile, as mentioned above, the lag time in intervention in Japan might contribute to unfavorable trends in cancer mortality.

There are some limitations of this study. The low number of deaths from rare cancers may have biased the result. Some

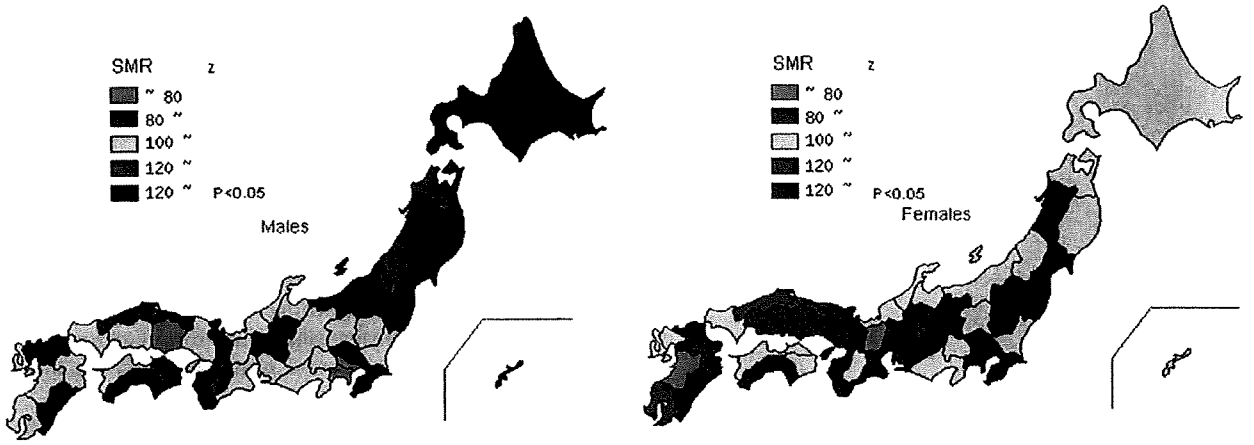

Figure 3. Standardized mortality ratios for cancer among adolescents and young adults aged 15–29 years in Japan, 2000–2006 by prefecture.

stable trends in the present study, such as mortality in thyroid cancer and Hodgkin's lymphoma, are more difficult to explain because of the small absolute number and substantial random variation. On the other hand, mortality rates are not a good substitute for incidence, because treatment for cancers has improved rapidly over time, and survival varies between age groups and populations. Furthermore, deaths occurring in adolescents and young adults relate to cancer diagnosed several years earlier, at younger ages.

Despite these limitations, this report is the first national large-scale study on mortality trends among individuals aged 15–29 years in Japan, which covered 100% AYA deaths from cancer. Moreover, there is no national-level cancer registry system in Japan. Against this background, the analysis of mortality trends over several decades remains an important method to provide additional insight into the cancer burden among AYA population. We believe that these analyses and observations will help to estimate care needs, to plan cancer prevention strategies and to provide reasonable health services for this group of patients.

conclusions

This report presents updated figures and trends in cancer mortality among adolescents and young adults aged 15–29 years in Japan and other developed countries. Mortality has improved for AYAs over the 37-year study period; however, the improvement lags behind that for children. The increased cervical cancer mortality presented here implies an increase in incidence among young Japanese women and draws attention to the need to strengthen 'cervical cancer screening in Japan'. We hope that this study will raise public awareness about cancer in this age group and provide the impetus for further research to improve the survival and quality of life of the young people in Japan.

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LY designed and carried out analyses and drafted the paper; DQ prepared data and created the figure and JF and N.S. edited the paper and commented on the interpretation of the results. All authors read and approved the final draft of the paper.

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SHORT REPORT

Partial hypoxanthine-guanine phosphoribosyltransferase deficiency due to a newly recognized mutation presenting with renal failure in a one-year-old boy

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Abstract We describe the case of a 1-year-old boy with partial hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency. At his first visit to the hospital, he was diagnosed with hyperuricemia and irreversible renal failure. The misssense mutation Asp185Gly (554A>G) was identified in exon 8 of his HPRT gene, and this mutation was inherited from the mother.

Keywords Renal failure · Partial HPRT deficiency · HPRT gene · Hyperuricemia · New mutation

Abbreviations

HPRT	hypoxanthine-guanine phosphoribosyltransferase
APRT	adenine phosphoribosyltransferase
PCR	polymerase chain reaction

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Hypoxanthine-guanine phosphoribosyltransferase (HPRT, OMIM 308000) is a purine salvage enzyme that converts the purine bases hypoxanthine and guanine to their respective mononucleotides using phosphoribosyl-l-pyrophosphate. HPRT deficiency is an inherited disorder, and it develops due to a defect in the HPRT gene, which is located on the long arm of the X-chromosome (Xq26-q27) [3]. The aim of this report is to present the case of a 1-year-old patient with partial HPRT deficiency (without neurological or behavioral abnormalities) suffering from renal failure and to describe a newly recognized point mutation detected in his HPRT gene.

Patient report

A one-year-old boy was referred to our hospital because of bad temper, fever, tachypnea, and passage of renal stones. He was the only child of nonconsanguineous parents (33-year-old father and 23-year-old mother). The infant had no prenatal or birth problems, but he suffered from failure to thrive since 6 months of age. On admission, physical examination revealed that the toddler was drowsy and inactive with tachypnea (55/min) and a pale face. His height was 70.4 cm (−2.4 SD), his weight was 6.9 kg (−2.7 SD), blood pressure was 114/54 mmHg, body temperature was 38.2 C, pulse rate was 180/min, and neurological evaluations were normal. There was no evidence of gouty arthritis.

He presented with prominent acidosis (pH, 7.089; BE, −25.6 mmol/l) caused by renal failure (BUN, 84 mg/dl; creatinine, 2.1 mg/dl) and hyperuricemia (25.3 mg/dl) with renal stones, but there were no signs of gout or

neurological and behavioral abnormalities. Complete blood cell count revealed mild anemia. Urinalysis showed moderate hematuria and proteinuria in diluted urine (<1,005). The clearance of uric acid (C_{UA}) was 5.16 ml/min and that of creatinine (C_{Cr}) was 17.1 ml/min. The uric acid excretion ratio (C_{UA}/C_{Cr}) was 30% (normal, 4–14%). Renal CT showed one small calculus in each kidney.

The patient was treated with continuous ambulatory peritoneal dialysis, allopurinol, adequate hydration with urinary alkalization, and erythropoietin. Due to these treatments, the serum and the urine uric acid levels were restored to normal. After a 24-month follow-up, his physical was found to be normal at the age of 3 years with height of 88.5 cm (−1.2 SD), body weight of 12.8 kg (−0.5 SD), head circumference of 47.3 cm (−1.5SD), and his neuropsychological status developmental score was 106.

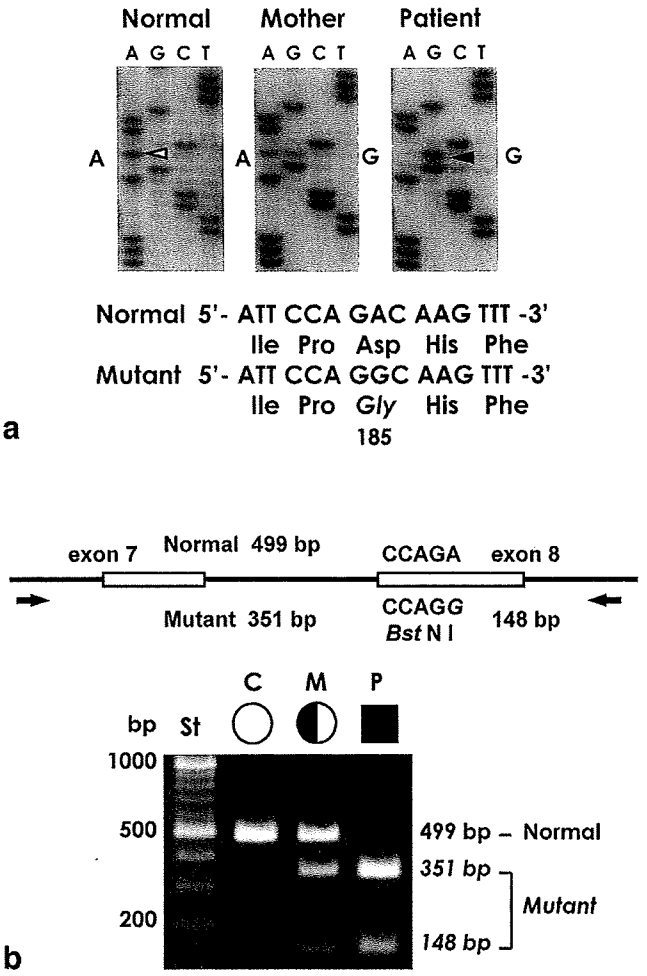

Fig. 1 Molecular genetic analysis of the HPRT gene. **a** Direct sequencing analysis of the DNA fragment including exons 7 and 8. DNA segments containing exons 7 and 8 were amplified from genomic DNA of the patient, his mother, and normal control by PCR described previously. The fragment was sequenced directly by the specific primer (HE8A: 5′-AGA GAG GCA CAT TTG CCA GT-3′). A misssense mutation Asp185Gly (554A>G) in exon 8 of the patient's HPRT gene was identified and his mother was the heterozygous carrier of the mutation showing both A and G bands at the mutation site. **b** Detection of the mutant HPRT gene using PCR-RFLP methods. DNA segments containing exons 7 and 8 were amplified from genomic DNAs of the patient (*P*), his mother (*M*), and normal control (*C*). Utilizing restriction enzyme *Bst* NI the site of CC (A/T)GG was recognized, mutant fragments including the mutation (554A>G) digested to 351 bp and 148 bp were separated from the normal one (499 bp) using 1.5% agarose gel electrophoresis. The mother showed both normal and mutant fragments, indicating a heterozygous carrier

Enzyme activity of RBC

The HPRT activity in the patient's RBC was 0.56± 0.28 nmol/min/mg Hb, which decreased to 30% of that in normal RBC (1.76±0.28 described previously [8]). The HPRT activity in his mother (heterozygous carrier) was normal (1.63±0.07). The adenine phosphoribosyltransferase (APRT) activity in the patient's RBC (0.77±0.08 nmol/min/mg Hb) increased to 1.8 times that in the normal RBC (0.42± 0.10) and that of his mother (0.44±0.02), as is typically described in HPRT deficiency.

Gene analysis

We examined the molecular and genetic basis of the patient's condition according to previously described procedures [8]. By direct sequencing of the fragments, including exon 8, a transition of 554A>G that resulted in a missense mutation of Asp185Gly in the HPRT gene was observed in the patient and his mother who was a heterozygous carrier of the mutation (Fig. 1a). No other abnormalities were detected in the coding exons of HPRT, and the same substitution was found in the reverse transcribed mRNA (cDNA) obtained from the patient (data not shown). The mutation (554A>G) was easy to detect by PCR-RFLP analysis utilizing the *Bst* NI created in the mutant gene (Fig. 1b).

Discussion

To date, more than 300 different HPRT gene mutations have been reported in the Lesch-Nyhan syndrome (OMIM 300322) [4, 5]. A missense mutation of Asp185Gly (554A>G) in exon 8 of the HPRT gene was identified in our patient. The alteration in the patient's enzyme activity (30% of normal) resulted in the overproduction of uric acid,

hyperuricemia, and nephrolithiasis. The patient's mother was heterozygous for the mutation. To the best of our knowledge from previous reports [4, 5] and the database in the website of the Lesch-Nyhan disease international study group (http://www.lesch-nyhan.org/), the identified mutation has not been previously reported, but some mutations in exon 8 associated with partial HPRT deficiency were identified previously.

To the best of our knowledge [1, 2, 6, 7], renal failure has been rarely reported in the case of partial HPRT deficiency during infancy. Infant cases present with failure to thrive, hyperuricemia, and renal insufficiency, which are identical to our patient's symptoms. Partial HPRT deficiency is considered to be rare (one fifth to one tenth of the incidence of Lesch-Nyhan syndrome); however, its renal involvement appeared to be frequent. It is important to increase awareness about partial HPRT deficiency as a cause of renal failure particularly in infants or toddlers because renal failure can be controlled with early allopurinol intervention in most cases.

In conclusion, the prognosis of partial HPRT deficiency in children and adolescents was considered to be good when treated with allopurinol, but renal failure in childhood is one of the life-threatening complications in the case of partial HPRT deficiency.

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総　説

小児がんに対する造血幹細胞移植後の晩期合併症

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要　旨

小児がんの造血幹細胞移植後に認められる主な晩期合併症についてレビューした．移植後の晩期合併症は，全身照射と大量化学療法のいわゆる前処置に伴うものと慢性 Graft versus Host Disease（GVHD）によるものと大きく二つの機序に分けられる．肺障害は，移植後の晩期合併症として生命予後に関わる重要な合併症である．移植後には内分泌系の問題が生じることが多いが，成長障害・甲状腺機能障害が主なものである．骨髄破壊的な通常移植後の小児がん経験者の不妊率は98～99％にも及ぶ．移植後は二次的な免疫不全となるため移植を受けた患者へのワクチンの再接種は不可欠であり，再接種の基準を示した．二次がんとしては，移植後15年の固形腫瘍累積発症率は11％と推定されており，発症には慢性 GVHD と放射線治療が関わっている．

これらの結果は移植後の小児がん経験者の長期フォローアップの重要性を示している．欧米の主な移植グループ合同（EBMT/CIBMTR/ASBMT）で作成された移植後長期フォローアップのスクリーニングと予防に関する推奨ガイドラインを示した．

キーワード：造血幹細胞移植，小児がん，晩期障害（晩期合併症），二次がん，長期フォロー

はじめに

小児がん治療の進歩は著しく5年生存率が70％を超えるようになり，本邦にも数万人以上の小児がんの長期生存者が存在し，成人期を迎えた小児がん克服者の数は若年成人の400～1,000人に1人といわれている．小児がんは身体的・精神的に成長途上に発病するため，成人のがんとは違い疾患のみの影響だけではなく治療の影響を強く受けることが予想される．また治療終了後にも40～50年にわたる長期の生命予後が期待され，復学・社会復帰・就労・結婚・出産などを含めた数多くのイベントを迎えるため自立支援を含めた長期経過観察の重要性が高まっている[1]．

治療終了後晩期合併症の最大のリスク因子は原疾患の種類と病期，そして施行された治療法であり，小児がんのうち晩期合併症が特に問題になるのが，原疾患としては脳腫瘍[2]と骨・軟部組織腫瘍，治療法としては放射線治療と特定の抗癌剤（アンスラサイクリン系，アルキル化剤，エトポシドなど）であり，造血細胞移植は最も晩期合併症リスクの高い治療法の1つである．移植後の晩期合併症に関しては，欧米で優れた総説[3)~5)]や成書[6)~9)]が出ているが，本邦では非常に少なくまとまったものがあまりない[10)11)]．そこで晩期合併症のうち造血細胞移植に関連したものを表1にまとめた[7]．その中で慢性 Graft versus Host Disease（GVHD），呼吸器合併症，内分泌障害，不妊・性腺障害，二次性免疫不全と再予防接種，二次がん，生活の質への影響を中心に説明を加え，最後に最近発表された移植後スクリーニングや合併症予防対策の推奨ガイドラインを紹介した．

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移植後の晩期合併症機序と慢性 GVHD

小児の移植後晩期合併症を総合的に解析したデータは少ないが[12]，Pitcher らの骨髄移植後3年以上経過した83例（自家22例，HLA 一致同胞61例）では，平均3.7種類の晩期合併症（Total Body Iraadiation（TBI）群では5.0種類，非 TBI 群では2.3種類）を有していたとされている[7]．

移植後に晩期合併症が生じる機序を，図1にまとめ

表1 移植後の主な晩期合併症[7)]

臓器	治療内容	リスク因子	臨床症状	頻度*	備考
神経	化学療法—MTX 頭蓋照射	遷延する免疫不全による中枢神経感染症	白質脳症 脳血管障害 中枢神経感染症 脳腫瘍—二次がん	白質脳症：7% 感染症：7%	慢性GVHDとの関連があるもの—血管炎，多発筋炎，重症筋無力症，末梢神経炎
心理／認知	化学療法—MTX，Bu 頭蓋照射	頭蓋照射＋TBI 幼少時照射（＜3歳） 女性 フォロー期間	認知障害—記憶，注意力，知能，空間認知，言語力 学業成績 心理学的問題	記憶障害：46% 言語力：50% 特殊教育：36% 頭蓋照射ない場合は大きな問題なし	慢性GVHDが存在すると移植後の心理・社会的適応に強く影響
歯牙・口腔	化学療法 顎部を含む照射	幼少児	歯牙：歯根低形成，矮小歯，歯牙無形成，顔面骨低形成 唾液減少，口腔／唾液腺腫瘍	歯牙：44−94% 唾液減少：43%	局所照射と慢性GVHDが唾液減少と口腔内腫瘍発生に関与
眼	移植前照射 TBI ステロイド 化学療法？	TBI（特に単回照射） ステロイドの長期投与	後嚢下白内障 乾燥性角結膜炎 涙の減少，結膜炎，角膜の欠損，角膜潰瘍，網膜炎	白内障：照射なし5.5% 分割TBI 34%，単回TBI ～100%	乾燥性角結膜炎は慢性GVHDと関連強い
聴力	白金製剤 Aminoglycoside 放射線照射	幼少児では言語獲得に影響	感音性難聴 言語獲得の障害	移植前後に白金製剤を使用した場合 22−82%	
心臓	Anthracycline 大量Cy 胸部照射	移植前大量輸血 敗血症	不整脈 心筋障害 心膜炎（心嚢液） 弁膜症	不整脈：16% 左心不全：25% 運動負荷時異常：74% 心筋症：7%	
腎臓	白金製剤 IFO 腹部照射 腎毒性薬剤	移植時の腎不全 肝中心静脈塞栓症 幼少児？	放射線腎症—慢性腎不全 血栓性微小血管障害 近位尿細管障害 高血圧	GFR低下28% 尿細管障害45% 放射線腎症45% 高血圧16% 慢性腎不全～28% 末期腎不全まれ	蛋白尿やネフローゼが慢性GVHDと関係していることはまれ CyAやFK506が腎不全を増強する
内分泌	放射線照射 化学療法—Bu，Cy	単回TBI	下垂体：成長の項参照他のホルモンは不定 甲状腺：機能低下多い 機能亢進も報告あり 甲状腺腫瘍—2次がん 副腎：不定 膵臓：糖尿病 メタボリック症候群	甲状腺機能低下：単回TBI 58%，分割TBI 25% 甲状腺腫瘍：125倍 糖尿病8%（2型17%） メタボリック症候群39%	自己免疫機序が慢性GVHDと関係している
成長	TBI，TLI 頭蓋照射 ステロイド	移植時6歳未満 高線量放射線 成長ホルモン欠損 低栄養？ 原疾患（サラセミア，Fanconi貧血など）	成長障害—低身長 骨格不均衡 骨塩量減少 成人成長ホルモン欠乏症	低身長21% ＜平均最終身長＞ 男−1.17SD，女−0.56SD 頭蓋＋TBI：−2.07SD TBI＜6歳−3.49SD 6−12歳−1.92SD 12−15歳−0.37SD	慢性GVHDとの関連がある—特にステロイドの使用 成長ホルモン療法の効果は予測しにくい

た[3)]．全身照射と大量化学療法のいわゆる前処置に伴うものと慢性GVHDによるものと大きく二つの機序があげられる．慢性GVHDではステロイドホルモンの長期投与も相乗的に加わり高度の免疫不全がおこり易感

生殖	放射線照射 化学療法—Bu, Cy	移植時年長 女性 高放射線線量—TBI アルキル化剤総量	思春期遅延/停止 不妊 ホルモン補充必要 男:テストステロン低値, LH/FSH上昇 無精子症, 乏精子症 女:無月経, E2低値, LH/FSH上昇 流産, 未熟児の増加 早期閉経	男:TBI例の思春期遅延, ホルモン補充7% 不妊;大量Cy24% Bu+Cy7%, TBI 1% 女:TBI例の無月経44% 卵巣機能回復Cy54% TBI 10%, Bu+Cy1% 妊娠;Cy24%, TBI 1%, Bu+Cy0%	慢性GVHDとの関連なし 長期フォローが必要 不妊対策
骨・筋	化学療法—MTX 頭蓋照射 局所照射 ステロイド	年長児(>16歳) 骨頭壊死は10歳以下ではまれ 成長ホルモン欠損 性腺機能低下	骨頭壊死—股関節 骨軟骨腫—多発性, まれに悪性化 骨塩量減少 骨すべり症, 側弯症	骨頭壊死—0.6% 骨軟骨腫—26% 骨塩量減少—様々	慢性GVHDとの関連がある—特にステロイドの使用 適切なコントロール群を設定した上で, 前向き研究が必要
二次がん	アルキル化剤 VP-16 放射線照射	年少児 頭蓋照射(特に幼少時) 高線量	固形腫瘍(脳腫瘍, 甲状腺腫瘍等)—移植後4-8年(5歳未満多い) AML/MDS—移植後早期約2年—特に5-又は7モノソミー	固形腫瘍:10年で4%, 15年で11% コントロールの60倍 AML/MDSは自家移植で起こりやすく, 小児ではまれ	lymphoproliferative disordersはEBVに関連, 同種移植後の強い免疫抑制下で移植後1年以内に起こることが多い

*頻度はあくまで代表的な論文から引用した数字であり, 絶対的なものではなく頻度が高いものかどうかの目安である.
表で使用した省略語:MTX, methotrexate;Bu, busulfan;TBI, total body irradiation;Cy, cyclophosphamide;IFO, ifosphamide;VP-16, etoposide;LH, lutenizing hormone;FSH, follicle-stimulating hormone;E2, estradiol;AML, acute myloid leukemia;MDS, myelodysplastic syndrome;GFR, gromerular filtlation rate;GVHD, graft versus host disease;CyA, cyclosporine A;FK506, tacrolimus

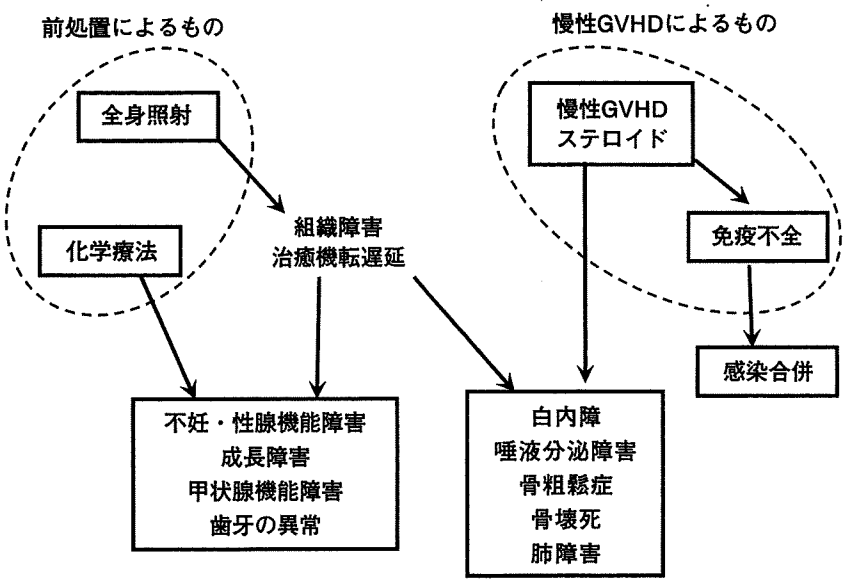

図1　移植に伴う晩期合併症の機序[3)]

染性が問題になり, 晩期合併症だけでなくQuality of Life (QOL) への悪影響が大きい[13)].

慢性GVHDは全移植患者の約半数に発症し, 現疾患死亡を除いた10年生存率は約50%と生命予後に大きな影響を与える[14)]. 最近では, 移植医療技術の向上に伴う生存率の向上, 非血縁者間移植やHLA適合同胞以外の血縁ドナーの増加, 末梢血幹細胞移植例数の増加, ドナーリンパ球輸注といった要因によって, むしろ慢性GVHDは増加しているともいわれている. 慢性GVHDの予後因子としては, 血小板減少, 発症の仕方(急性GVHDに引き続いておこるかどうか), Performance status(PS)の低下, 黄疸などが報告されている.

表2　Bronchiolitis Obliterans（BO）とBO Organizing Pneumonia（BOOP）比較[22]

	BO	BOOP
頻度	0-48%	＜2%
発症時期	移植後後期（＞1年）	通常100日以内
臨床症状	呼吸困難，咳，喘鳴	呼吸困難，咳，発熱
XP/CT所見	正常，肺気腫，気管支拡張	斑状陰影，すりガラス状結節状陰影
肺機能	閉塞性（PEV1低下）	拘束性（FVC低下）
BAL	好中球優位	リンパ球優位
診断	臨床診断	病理組織
治療	ステロイド/免疫抑制剤	ステロイド
予後	反応不良，致死率高い	反応性良好，可逆的

FEV1：一秒率，FVC：努力性肺活量，BAL：肺胞洗浄液

近年よりよい予後予測モデルとしてJohns Hopkinsスコアが開発されたが，これは血小板数，皮膚病変の程度，progressive発症の3因子のあるなしでスコア化し，低リスク，中間リスク，高リスクの3群に分類するもので，予後との良好な相関がみられている[15]．一方IBMTR（Inter-national Blood and Marrow Transplant Registry）も予後予測スコアを発表しているが，Karnovskyスコア(PS)，慢性下痢，体重減少，皮膚病変，口腔病変を指標にするものである[16]．

このような状況の中でNIH（National Institutes of Health）から慢性GVHDの定義と分類に関してコンセンサス文書が発表された[17]．重症度分類としては，PS，皮膚，口腔，眼，消化管，肝，肺，関節/筋膜，生殖器のそれぞれにつき0点から3点までの4段階スコアを行い，総合的に軽度：1～2臓器に限定され，最大スコア1点以下のもの，中等度：最大スコアが2点以下のもの（肺のみはスコア1点でも中等度と見なす），重度：最大スコアが3点または肺のスコアが2点以上と3段階に分類するものである．難治性の慢性GVHDに関しては，mycophenolate mofetil，thalidomide，hydroxychloroquine，sirolimus，extracorpo-real photochemotherapy(ECP)，各種のモノクローナル抗体製剤（CD20抗体：rituximab，IL-2 receptorα阻害剤：daclizumab，TNFα阻害剤：infliximab）など種々の治療が試みられているが著しい効果は認められないことが多い[14][18]．

呼吸器合併症

呼吸器（肺）障害は，造血細胞移植後の晩期合併症として生命予後に関わる重要な合併症である．一般に，移植後は一過性にDLcoで測定されるガス拡散能が低下するが，合併症がない限り，拘束性障害（努力性肺活量FVC低下）や閉塞性障害（一秒率FEV1低下）などは軽度にとどまると言われている[19][20]．Seattleの215例の解析では閉塞性障害9%，拘束性障害28%，混合型3%とされている[20]．最近移植後小児の肺障害に関して包括的な総説が発表された[21][22]が，非感染性の晩期のものとして重要なのはBronchiolitis Obliterans（BO）とBronchiolitis Obliterans Organizing Pneumonia（BOOP）であるので，この二疾患を比較して表2にまとめた[23]．BOは自家移植での報告はまれであり，BO発症危険因子として確実なのは同種移植であることとprogressive型慢性GVHDであった．また危険性が高くなるのがDe novo/quiescent慢性GVHD，高年齢，移植前閉塞性肺疾患既往，移植早期の呼吸器ウイルス感染症であり，低ガンマグロブリン血症や胃食道逆流なども危険因子となる可能性がある．BOはほとんどの症例で徐々に始まり，発熱を伴うことはまれで，臨床症状としては乾性咳嗽（60～100%），呼吸困難（50～70%），喘鳴・副鼻腔炎などで20%は無症状である．理学的には，肺気腫状・呼吸音減弱・喘鳴・呼気延長などが見られ，通常ラ音は認めず，胸部X線・CT写真でも肺気腫状の所見を示すが浸潤影を欠く．肺機能検査で，FEV1/FVC＜0.7及びFEV1＜75%（予測値）の所見が見られ，感染症が否定され気管支拡張剤の効果が乏しいことで，気管支喘息などとも鑑別される．胸部X線・CT写真で，通常斑状・結節状陰影を示すBOOPは，ステロイド反応性が良好で多くの症例で可逆的なのに対して，BOは治療反応性も極めて不良であり予後不良とされている．

内分泌合併症

造血細胞移植を受けた患者のほとんどに何らかの内分泌系の問題が生じる[24][25]．その障害の程度は移植前に

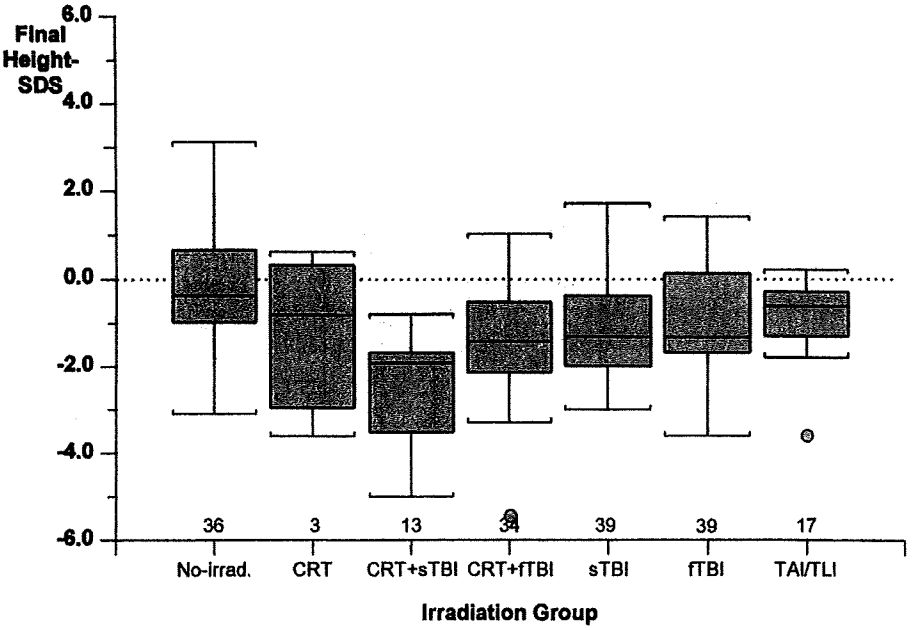

図2 骨髄移植後の成長障害（EBMT）[26]
それぞれのグループ上の数字は症例数を示し，ボックス自体は25パーセンタイルから75パーセンタイルを示しており，ボックスの上下の線は3パーセンタイルから97パーセンタイルを示した．図中の省略語はSDS：standard deviation score, No-irrad.：no irradiation, CRT：cranial radiation therapy, sTBI：single-dose total body irradiation, fTBI：fractionated total body irradiation, TAI：thoraco-abdominal irradiation, TLI：total lymphoid irradiation

原疾患に対して行われた治療に加えて，前処置として施行される抗がん剤大量療法やTBIが大きく関わる[26]．そのため成長，生殖，甲状腺，そして糖・脂質代謝にその影響が出やすい[24)25)]．

1）移植後の成長障害

移植を受けた患者の成長に作用する因子は遺伝的な因子，栄養摂取の状況，ホルモンや治療の影響など様々で，視床下部―下垂体への照射による成長ホルモンの分泌不全または分泌異常が最もよく知られているが[27)~29)]，直接骨の成長が阻害される機序も重要である[30)]．

成長ホルモン欠損症の発症率は研究によって異なり，その範囲は20～70%と大きい[29)31)]．図2に示したEBMT（European Group for Blood and Marrow Transplantation）のデータでは，成長障害に関して頭蓋照射とTBIによる相乗効果が見られ，放射線照射方法によっても影響を受ける[27)]．成長ホルモン補充の効果に関しては一定せず，放射線によって生じた成長の遅れはホルモン補充によって好転するということが知られているものの[29)31)]，そのcatch-up growthは不十分とするものが多く，骨の成長自体が障害されている可能性がある[31)]．分割全身照射後は，座高の減少が著しく，それはホルモン補充によっても改善しないことが最近報告された[32)]．

2）甲状腺機能障害

甲状腺機能障害に関しては単回TBIの場合，甲状腺機能低下症の発症率は最高70%となり，これに対して分割照射の場合では15%～20%と言われている[33)34)]．代償性甲状腺機能低下症の発症時期の中央値は移植後12か月で，おそらく一過性であろうと思われる．石黒らは9歳未満で移植した症例では代償性甲状腺機能低下が有意に多く，移植児年齢がリスク因子であると報告している[35)]．TBIを含まない前処置を受けた患者でも，10～15%には代償性甲状腺機能低下症が認められるという報告がある[36)]が病因は解明されていない．甲状腺ホルモン補充は比較的容易であり，機能低下の疑われる症例では，積極的に補充を考慮する必要がある．

3）糖尿病とメタボリックシンドローム

移植により，耐糖能障害や2型糖尿病発症リスクが高まる可能性があり，リスク因子として肥満，糖尿病家族歴，運動不足，食生活，成長ホルモンの使用，そして人種などが挙げられる[37)]．Bakerらの研究では1,089名の患者を対象に糖尿病・高血圧などの調査を行ったところ，同胞に比べて糖尿病は3.65倍，高血圧は2.06倍発症リスクが高いという結果であった[38)]．Seattleグループで748名の患者を対象に2型糖尿病に関する調査を行ったところ，フォローアップ期間の中央値は11年で34名にその発症が認められ，白血病の