表2 貧血と栄養性欠乏症を示唆する指標 (WHO 1972)

貧血が存在すると思われるヘモグロビン (Hb) の濃度

6カ月～6歳の小児	11g/dl 以下
6～14歳の小児	12g/dl 以下
成人男性	13g/dl 以下
成人女性（非妊娠）	12g/dl 以下
成人女性（妊娠）	11g/dl 以下

平均血色素濃度 (MCHC)

31%以下は鉄欠乏を示すものと思われる

血清鉄とトランスフェリン飽和率

血清鉄	50μg/dl 以下
トランスフェリン飽和率*	15%以下

血清葉酸値と血清ビタミン

B_{12} 値

血清葉酸値	3ng/ml 以下
血清ビタミン B_{12} 値	100pg/ml 以下

$$*トランスフェリン飽和率 (\%) = \frac{血清鉄}{総鉄結合能} \times 100$$

表3 赤血球指数の算出方法

$$平均赤血球容積 MCV (fl) = \frac{Ht (\%)}{RBC (\times 10^6)} \times 10$$

$$平均赤血球血色素量 MCH (pg) = \frac{Hb (g/dl)}{RBC (\times 10^6)} \times 10$$

$$平均赤血球血色素濃度 MCHC (\%) = \frac{Hb (g/dl)}{Ht (\%)} \times 100$$

どが軽症型である。サラセミアは，グロビンの α 鎖，β 鎖のいずれかの産生低下により，そのバランスの崩れた状態である。グロビン合成試験などにより，さらに疑いが強まった場合は，ヘモグロビンのアミノ酸組成を調べ，遺伝子解析なども行う。サラセミアでは頭蓋 X 線写真で，hair-standing on end 像とよばれる頭蓋骨髄質の拡大と放射状の骨綾像がみられることがある。

鉄芽球性貧血には先天性と後天性がある。先天性鉄芽球性貧血では，小球性低色素性貧血と正球性正色素性貧血が混在する二相性の末梢赤血球パターンがみられる。後天性の場合は骨髄赤芽球に環状赤芽球をみることがある。鑑別にあたり，血清鉄が上昇しており，総鉄結合能が上昇していないことを確認する必要がある。

正球性貧血には，溶血性貧血や再生不良性貧血（再生不良性貧血は時に大球性である）がある。溶血性貧血はなんらかの原因により赤血球が崩壊し，それに反応して赤血球造血が亢進する病態である。赤血球造血の亢進により網状赤血球が増加し，骨髄では赤芽球の過形成が起こる。網状赤血球は貧血時には骨髄から末梢血中への移動が早くなるため，末梢血液中に増加す

る。これを補正するため，次のような式で網状赤血球（産生）指数を算定する。

網状赤血球（産生）指数（Finch）＝網状赤血球実測値（％）×（患者 Ht 値／正常 Ht 値：
45％）÷網状赤血球成熟期間（日数）

　網状赤血球成熟期間は，Ht 45％のときは1日，35％のときは1.5日，25％のときは2.0日，15％のときは3.0日とする。なお，3以上のときは溶血性貧血が考えられる。溶血性貧血では赤血球の崩壊が亢進し，ヘモグロビンが分解して生じたヘム由来のポルフィリンが増加し，肝におけるグルクロン酸抱合が間に合わず血液中に間接ビリルビンが増加する。また血液中に過剰なビリルビンが存在すると，尿中や糞便中のウロビリノーゲンが高値となる。溶血が血管内溶血であると，血漿中に遊離ヘモグロビンが出現し，これに結合するハプトグロビンが消費されるために，血清ハプトグロビンの低下がみられる。また溶血が起こると赤血球中の諸酵素が血漿中に遊離する。その代表が乳酸脱水素酵素（lactate dehydrogenase；LDH）である。溶血性貧血でLDHが高値となるのはこのためである。とくにLDH1と2の分画が著増する。赤血球塗抹標本での形態学的な検査も鑑別に有用である。小型球状赤血球が多くみられる場合は遺伝性球状赤血球症を疑う。楕円赤血球，有口赤血球のみられた場合はそれぞれ遺伝性のものを考慮する。破壊赤血球が認められ，さらに血清中の尿素窒素やクレアチニンの上昇，血小板減少などがみられたときは溶血性尿毒症症候群が疑われる。便の病原性大腸菌の検査，ベロ毒素の検査も必要である。異常ヘモグロビン症のひとつである不安定ヘモグロビン症でも溶血を起こす。ヘモグロビンの電気泳動やイオン交換高速液体クロマトグラフィー，イソプロパノールによる不安定性試験，アミノ酸分析，遺伝子解析などにより診断に至る[3]。自己免疫性溶血性貧血であれば，赤血球に結合した抗体（免疫グロブリン）を調べる直接Coombs試験，または血清中の抗体（免疫グロブリン）を調べる間接Coombs試験が陽性になる。時に補体結合抗体が原因となっていることがある。発作性夜間血色素尿症は溶血性貧血のなかでも，LDHが異常に高値であることが多い。貧血の他に血小板の減少などが認められた場合，ヘモグロビン尿の有無を検査する。とくに早朝起床時の尿が褐色をしていないかなどを問診で確かめる。Ham試験（酸溶血試験），ショ糖水試験（sugar - water test）が陽性であり，赤血球，顆粒球，リンパ球のCD55，CD59の欠損が認められる。そのほかの溶血性貧血として赤血球の酵素異常であるグルコース6リン酸脱水素酵素欠乏症，ピルビン酸脱水素酵素欠乏症などがある。赤血球のグルコース6リン酸脱水素酵素，ピルビン酸脱水素酵素の測定により確定診断ができる。

　再生不良性貧血は，末梢血で汎血球減少が認められる。胎児ヘモグロビンの増加も特徴的検査所見のひとつである。末梢血中の好中球数，血小板数，網状赤血球数の数値により重症度分類を行う（表4）。骨髄の細胞密度の減少をみることも必要である。再生不良性貧血には，前述したように先天的な要因のあるものと後天性のものがある。後天性のものには原因の明確でない特発性，肝炎後に起こる場合，薬剤性のものなどがあり，原因究明のための検査も必要である。

　大球性貧血であれば，ビタミンB$_{12}$，葉酸を測定し，低値であれば，それらの欠乏による巨赤芽球性貧血である。LDHの上昇，好中球，血小板の減少，過分葉好中球が認められるほか，ハプトグロビン低下，間接ビリルビン軽度上昇，尿中ウロビリノーゲンの増加などの溶血所見のみられることがある。骨髄異形成症候群でも大球性貧血がみられ，LDHの上昇，血小板の減少，過分葉好中球などがみられることがあるが，ビタミンB$_{12}$，葉酸の低値がなく，骨髄は

表4 再生不良性貧血の重症度分類

重 症：骨髄が低形成で，少なくとも下記の2項目を満たす		
好中球	$<0.5\times10^9/l$	
	（好中球$<0.2\times10^9/l$最重症）	
血小板	$<20\times10^9/l$	
網状球	$<20\times10^9/l$	
中等症：少なくとも下記の2項目を満たす		
好中球	$<1.0\times10^9/l$	
血小板	$<50\times10^9/l$	
網状球	$<60\times10^9/l$	
軽 症：それ以外のもの		

過形成であることが多い。病型によっては骨髄芽球の出現，環状鉄芽球の増加がみられることがある。

● おもな疾患

鉄欠乏性貧血

貧血の中でもっとも頻度が高いのは鉄欠乏性貧血である。鉄はヘムの構成成分であるため，体内の鉄が不足するとヘモグロビンの合成が低下し，貧血となる。小児期では思春期と乳児期後期など鉄の需要が増す時期に鉄の需要が供給を上まわると生じる病態である。思春期の女子では，数％以上が鉄欠乏性貧血であるといわれている[4]。スポーツによる貧血，ヘリコバクターピロリの感染があると鉄欠乏性貧血の反復をみることが多い[5]ことなどが最近話題になっている。体内の鉄はその2/3がヘモグロビンに結合しているが，そのほか筋肉内のミオグロビンやチトクロームなどの酵素中にも含まれている。そのために鉄欠乏が起きると貧血まで進展した状態でなくても集中力の低下や易刺激性の亢進などさまざまな症状をみることがある[6]。Bruner らは，貧血のない思春期の鉄欠乏の女子を治療群と偽薬による非治療群に分け，認知力に関する検査を行い，治療群で有意に言語の記銘力の改善がみられたことを報告している[7]。鉄欠乏が起きるとまず貯蔵鉄の減少が起こり，これは血清フェリチンの低下としてみることができる。次に血清鉄の低下，鉄結合蛋白であるトランスフェリンの増加を呈し，これが総鉄結合能の上昇という形で表される。その後赤血球プロトポルフィリンが増加し，最終的にヘモグロビンの低下した鉄欠乏性貧血が現れる。

治 療

鉄欠乏性貧血の治療は，鉄剤の経口投与が基本である。1日に体重 1kg 当り鉄を 3～6mg 投与する。投与開始後数日で網状赤血球の増加がみられ，その後，ヘモグロビンが回復してくる。ヘモグロビン値が低いほど治療効果が早く現れる。鉄剤の治療は 3～4 カ月は必要で，血清フェリチンが 20ng/ml を超えるまで続けることがのぞましい。鉄欠乏性貧血では，食事療法も重要である。食物中の鉄にはおもに動物性食品に含まれるヘム鉄と植物性食品に多い非ヘム鉄があるが，ヘム鉄は鉄の吸収率がよいのに比し非ヘム鉄からの鉄吸収はあまりよくない。

遺伝性球状赤血球症

溶血性貧血はなんらかの原因により赤血球が崩壊し，それに反応して赤血球造血が亢進するものである。小児の溶血性貧血でもっとも多くみられるのが，遺伝性球状赤血球症である。

溶血性貧血と診断された場合，赤血球塗抹標本上で，小型球状赤血球が多数みられたときは遺伝性球状赤血球症を考え，位走査顕微鏡で観察したり，赤血球浸透圧抵抗が減弱していることを確認する。また家族歴において，溶血性貧血患者の有無，胆石患者の有無も参考になる。

治　療

貧血が強い場合は，摘脾を行う。通常5歳を過ぎてから行うことが多い。脾臓摘出後の肺炎球菌による重篤な感染症を予防するために脾臓摘出前に肺炎球菌ワクチン接種を行うことがすすめられている。また脾臓摘出後しばらくペニシリンなどの抗生物質の投与を継続する。

再生不良性貧血

骨髄低形成と汎血球減少がみられる病態である。約90％は後天性であり，後天性の場合は多くは原因不明の特発性である。二次性の場合は肝炎後，薬剤性もある。骨髄異形成症候群や発作性夜間血色素尿症との鑑別が難しい場合があり，再生不良性貧血からそれらの疾患への移行もある。

治　療

重症型の場合は，血縁者間でHLA一致ドナーがいれば，第一選択は骨髄移植である。HLA一致血縁ドナーがいない場合は，抗胸腺リンパ球グロブリン，シクロスポリンなどによる免疫療法が適応になる。中等症における治療は，免疫療法を選択することが多いが，HLA一致血縁ドナーがいる場合は骨髄移植を選択することもある。軽症型では蛋白同化ホルモンによる治療が選択されることが多い。また貧血に関しては通常ヘモグロビン6.0g/dlを保つように赤血球輸血を行う。この際，鉄過剰に注意が必要である。また血小板減少に関しては10000/μl以下の場合は出血傾向に注意し，5000/μl以下の場合は血小板輸注を行うことが多い。

●治　療

貧血の治療は，原因によって異なる。それぞれの原因に対する治療を行う。鉄欠乏性貧血，遺伝性球状赤血球症，再生不良性貧血については先に述べた。その他，自己免疫性溶血性貧血であれば副腎皮質ステロイド投与，巨赤芽球性貧血であればビタミンB_{12}あるいは葉酸の投与，腎性貧血であればエリスロポエチン投与，骨髄異形成症候群であれば免疫療法あるいは造血幹細胞移植など，慢性炎症に伴う貧血では原因の除去が行われる。また治療はおのおのの状態によっても異なる。例えば，急激に起こった貧血では，ヘモグロビンが6〜7g/dlであっても循環動態の破綻があると考えられるときは輸血を行うが，鉄欠乏性貧血などの慢性的な貧血では，ヘモグロビンが4〜5g/dlであっても輸血は安易に行わない。

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〔前田　美穂〕

Childhood cancer in Japan: focusing on trend in mortality from 1970 to 2006

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Objective: This paper describes the mortality rates and trends from childhood cancer at the population level over a 37-year period in Japan and other developed countries.

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 during 2000–2006 was 2.20 per 100 000 population for boys and 1.89 for girls. Mortality for all cancers combined decreased since 1970s in Japan. A stable trend was observed in recent 5 years for girls. For leukemia, a declining trend was observed in the whole period for girls and in 1976–2006 for boys. Mortality rates for childhood central nervous system tumors have remained stable at a low level during 1980–2006.

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 intervention and the quantity of appropriate childhood cancer treatment.

Key words: cancer, childhood, epidemiology, mortality, time trends

introduction

It is estimated that ~3000 Japanese children aged from birth to 18 years will develop cancer. Although childhood cancer is rare compared with adult cancer, it is the fourth most common cause of death among children aged 0–14 years in Japan, according to the report given by the Ministry of Health, Labor and Welfare of Japan in 2005. A population-based study in Osaka prefecture in Japan indicated that death due to childhood cancer declined from 1972 to 1995, while the incidence increased in the same period [1]. In the United States, an estimated 10 400 new cases and 1545 deaths are expected to occur among children aged 0–14 years in 2007 [2]. During recent three decades, the incidence of childhood cancer increased ~0.6% annually. In contrast, mortality from childhood cancer declined by 1.3% per year during 1990–2004 [3]. A population-based study among European children since the 1970s showed that the overall incidence of childhood cancer has increased by 1.0% per year, while mortality has declined by 3.6% per year in the past three decades [4, 5].

The decrease in mortality from childhood cancer has been suggested to be due to the effects of improvements in diagnosis and therapy. For all childhood cancers combined, 5-year relative survival has improved markedly over the past three decades, from <50% before the 1970s to ~80% today [2].

There is no national childhood cancer registry system in Japan, and recent childhood cancer mortality has not been well characterized in terms of temporal and geographic trends. This paper describes the occurrence of death from childhood cancer at the population level over a 37-year period in Japan using official death certification data, which record 100% of deaths in Japan. The aim of this study was to ascertain the general mortality trend for each sex and to study the moment at which a shift in the trend occurred.

materials and methods

The number of death 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. 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 (1970–2004), the United States (1970–2005), Italy (1970–2003), UK (1970–2005) and New Zealand (1970–2004). Deaths at age 0–4, 5–9 and 10–14 years were derived from the World Health Organization (WHO)

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mortality database. Estimates of the population, generally based on official censuses, were based on the same WHO database.

During the study period, three different revisions of the International Classification of Disease were used. In Japan, this included International Classification of Diseases (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 six cancer sites, including all cancer combined (ICD-8: 140–209; ICD-9: 140–208; ICD-10: C00–97), leukemia (ICD-8: 204–207; ICD-9: 204–208; ICD10: C91–C95), lymphomas (ICD-8: 200–202; ICD-9: 200–202; ICD-10: C81–85), central nervous

system (CNS) tumors (ICD-9: 191–192; ICD–10: C70–C72), malignant kidney tumors (ICD-8: 189; ICD-9: 189; ICD-10: C64–C68) and malignant bone tumors (ICD-9: 170; ICD-10: C40–C41). In order to avoid possible bias due to changed ICD, the analysis of CNS tumors, malignant bone tumors and lymphomas (United States only) was restricted to data from 1980 onwards.

Age-standardized mortality rates 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. All rates are expressed per 100 000 children-years.

Table 1. Childhood cancer mortality rate (per 100 000) in Japan and other selected countries (boys)

Period of death	Japan	Canada	United States	Italy	UK	New Zealand
Total malignant tumors						
1970–1974	6.19	7.69	6.47	8.72	7.20	8.45
1975–1979	5.86	6.10	5.25	7.96	6.53	7.59
1980–1984	4.99	5.34	4.60	6.96	5.06	7.04
1985–1989	4.13	4.52	3.74	5.50	4.13	7.17
1990–1994	3.37	3.43	3.33	5.40	3.96	4.94
1995–1999	2.90	2.82	2.87	4.53	3.42	4.83
2000–	2.20	2.65	2.68	3.64	3.00	3.58
Leukemia						
1970–1974	3.39	3.58	2.90	3.94	3.02	3.44
1975–1979	3.10	2.81	2.23	3.50	2.79	3.07
1980–1984	2.46	2.06	1.76	2.85	2.11	2.89
1985–1989	1.91	1.79	1.41	2.20	1.52	2.76
1990–1994	1.54	1.17	1.20	1.99	1.41	1.69
1995–1999	1.21	0.90	0.97	1.64	1.18	1.99
2000–	0.84	0.85	0.85	1.25	0.91	0.78
Lymphomas						
1970–1974	0.61	0.76	–	1.14	0.73	0.77
1975–1979	0.66	0.62	–	0.86	0.65	0.75
1980–1984	0.65	0.49	0.39	0.62	0.40	0.51
1985–1989	0.55	0.32	0.31	0.51	0.29	0.58
1990–1994	0.36	0.21	0.23	0.47	0.25	0.15
1995–1999	0.18	0.16	0.16	0.41	0.20	0.23
2000–	0.14	0.12	0.12	0.27	0.20	0.12
Central nervous system tumors						
1980–1984	0.40	1.17	0.95	1.41	1.12	1.50
1985–1989	0.40	1.18	0.86	1.05	1.10	1.66
1990–1994	0.46	0.97	0.86	1.19	1.10	1.79
1995–1999	0.49	0.83	0.79	0.93	0.94	1.35
2000–	0.43	0.81	0.75	0.87	0.85	1.43
Malignant kidney tumors						
1970–1974	0.18	0.35	0.24	0.45	0.33	0.34
1975–1979	0.16	0.20	0.17	0.34	0.26	0.33
1980–1984	0.12	0.13	0.14	0.23	0.20	0.24
1985–1989	0.09	0.10	0.10	0.19	0.09	0.22
1990–1994	0.07	0.06	0.09	0.13	0.12	0.26
1995–1999	0.06	0.05	0.08	0.13	0.13	0.09
2000–	0.05	0.12	0.08	0.09	0.09	0.08
Malignant bone tumors						
1980–1984	0.15	0.18	0.16	0.33	0.26	0.12
1985–1989	0.15	0.16	0.12	0.24	0.18	0.30
1990–1994	0.14	0.11	0.11	0.19	0.14	0.04
1995–1999	0.13	0.12	0.11	0.14	0.13	0.17
2000–	0.09	0.12	0.13	0.15	0.15	0.24

The joinpoint regression model was used to describe changes in trends [6]. We allowed for up to four joinpoints for each model. The computation of mortality rates and their standard errors was implemented in SAS 9.0. Joinpoint analyses were carried out using Joinpoint software 3.3.1 from the Surveillance Research Program of the US National Cancer Institute. Time trends were assessed for all childhood cancer combined and for six major categories, including leukemia, lymphoma, malignant brain tumor, malignant kidney tumor and malignant bone tumor.

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, on the basis of the assumption that observed deaths follow a Poisson distribution. The maps were developed using adjusted SMR by gender.

results

mortality

Tables 1 and 2 give age-adjusted mortality rates in Japan and five other developed countries for all malignant tumors and for

Table 2. Childhood cancer mortality rate (per 100 000) in Japan and other selected countries (girls)

Period of death	Japan	Canada	United States	Italy	UK	New Zealand
Total malignant tumors						
1970–1974	5.10	6.12	5.13	6.90	5.55	6.85
1975–1979	4.61	4.83	4.07	5.90	4.69	6.35
1980–1984	3.88	4.24	3.59	5.48	4.27	4.39
1985–1989	3.30	3.43	3.06	4.36	3.81	5.27
1990–1994	2.75	2.80	2.69	4.19	3.01	3.81
1995–1999	2.23	2.73	2.39	3.29	2.65	3.54
2000–	1.89	2.06	2.28	2.86	2.47	3.06
Leukemia						
1970–1974	2.86	2.80	2.26	3.28	2.43	3.08
1975–1979	2.50	2.34	1.70	2.53	1.82	1.86
1980–1984	1.79	1.71	1.30	2.17	1.59	1.66
1985–1989	1.50	1.37	1.09	1.51	1.26	1.84
1990–1994	1.20	0.89	0.91	1.47	0.89	1.04
1995–1999	0.88	0.87	0.78	1.07	0.91	1.34
2000–	0.68	0.46	0.69	0.82	0.76	0.90
Lymphomas						
1970–1974	0.33	0.39	–	0.54	0.31	0.27
1975–1979	0.35	0.18	–	0.39	0.27	0.41
1980–1984	0.31	0.23	0.16	0.26	0.22	0.21
1985–1989	0.28	0.22	0.13	0.28	0.14	0.25
1990–1994	0.25	0.12	0.09	0.16	0.09	0.10
1995–1999	0.10	0.09	0.08	0.17	0.09	0.20
2000–	0.06	0.39	0.06	0.18	0.09	0.05
Central nervous system tumors						
1980–1984	0.39	1.01	0.84	1.13	0.93	1.43
1985–1989	0.38	0.88	0.77	0.99	0.98	1.37
1990–1994	0.44	0.75	0.77	0.90	0.88	1.26
1995–1999	0.47	0.84	0.71	0.72	0.74	0.88
2000–	0.42	0.69	0.69	0.78	0.71	1.00
Malignant kidney tumors						
1970–1974	0.20	0.32	0.25	0.44	0.37	0.38
1975–1979	0.11	0.23	0.19	0.33	0.26	0.36
1980–1984	0.12	0.13	0.15	0.27	0.18	0.00
1985–1989	0.07	0.11	0.13	0.18	0.18	0.10
1990–1994	0.07	0.10	0.09	0.18	0.15	0.27
1995–1999	0.05	0.14	0.11	0.11	0.12	0.21
2000–	0.06	0.11	0.10	0.10	0.12	0.11
Malignant bone tumors						
1980–1984	0.17	0.20	0.16	0.26	0.29	0.13
1985–1989	0.16	0.14	0.12	0.27	0.26	0.31
1990–1994	0.12	0.13	0.13	0.23	0.14	0.05
1995–1999	0.14	0.12	0.11	0.16	0.13	0.18
2000–	0.11	0.16	0.11	0.12	0.20	0.25

the main types of childhood cancer. A total of 33 059 childhood cancer deaths were reported in Japan during 1970–2006, of which 353 cancer deaths occurred in 2006. For all cancers combined, the mortality rate during 2000–2006 was 2.20 per 100 000 population for boys and 1.89 for girls. Leukemia was the most common diagnosis. Death rates from leukemia were 0.84 for boys and 0.68 for girls. Mortality from childhood CNS tumors was 0.43 for boys and 0.42 for girls. Geographic variations were observed. The rates of childhood CNS tumor and malignant kidney tumor were lower for both genders in Japan than in other countries.

temporal changes in mortality

Trends of age-standardized mortality from childhood cancer are shown in Figures 1 and 2 and Tables 3 and 4. Mortality for all cancers combined decreased since 1970s in Japan. For boys, a declining trend of 1.58% per year ($P < 0.05$) was observed during 1970–1979, followed by an accelerated decline of 3.78% per year ($P < 0.05$) during 1979–2006. For girls, mortality was high in the 1970s and remained stable in 1996–2006 at a low level, after two significant periods of decline (1972–1995 and 1995–1999). The average annual per cent change (AAPC) in recent 10 years was −3.8% ($P < 0.05$%) for boys and −1.9% ($P < 0.05$) for girls. In recent 5 years, declining trend only occurred in boys. The average annual per cent change

during 2002–2006 was −3.8% ($P < 0.05$%) for boys, and for girls a nonsignificant decline was observed from 2002 (AAPC = −0.6%, $P > 0.05$) for girls.

The mortality rate from leukemia in boys remained stable during 1970–1976 (APC = −1.10, $P > 0.05$) and then declined by 4.77% per year ($P < 0.05$) during 1976–2006. For girls, mortality decreased by 4.53% per year ($P < 0.05$) throughout the whole period. The average annual change in recent 10 years was −4.8% ($P < 0.05$%) for boys and −4.5% ($P < 0.05$%) for girls. Similar decline trends were also observed in Canada, the United States, Italy, UK (girls) and New Zealand.

In contrast with the dramatic decline in mortality for childhood leukemia, mortality rates from childhood CNS tumor in Japan remained stable at a low level for both genders during 1980–2006. The average annual change in recent 10 years was 0.5% ($P > 0.05$) for boys and 0.0% ($P > 0.05$) for girls. On the contrary, Canada, the United States, UK and New Zealand (girls) showed significant declining trends in the whole period.

With reference to the pattern of mortality for lymphomas, death rates for boys were stable during 1970–1985 and declined significant thereafter by 8.56% per year. The trend for girls leveled off during 1970–1991 and showed a declining trend of 11.85% per year during 1991–2006; however, except for New Zealand females, the death rates in other countries for both genders significantly declined throughout the whole period.
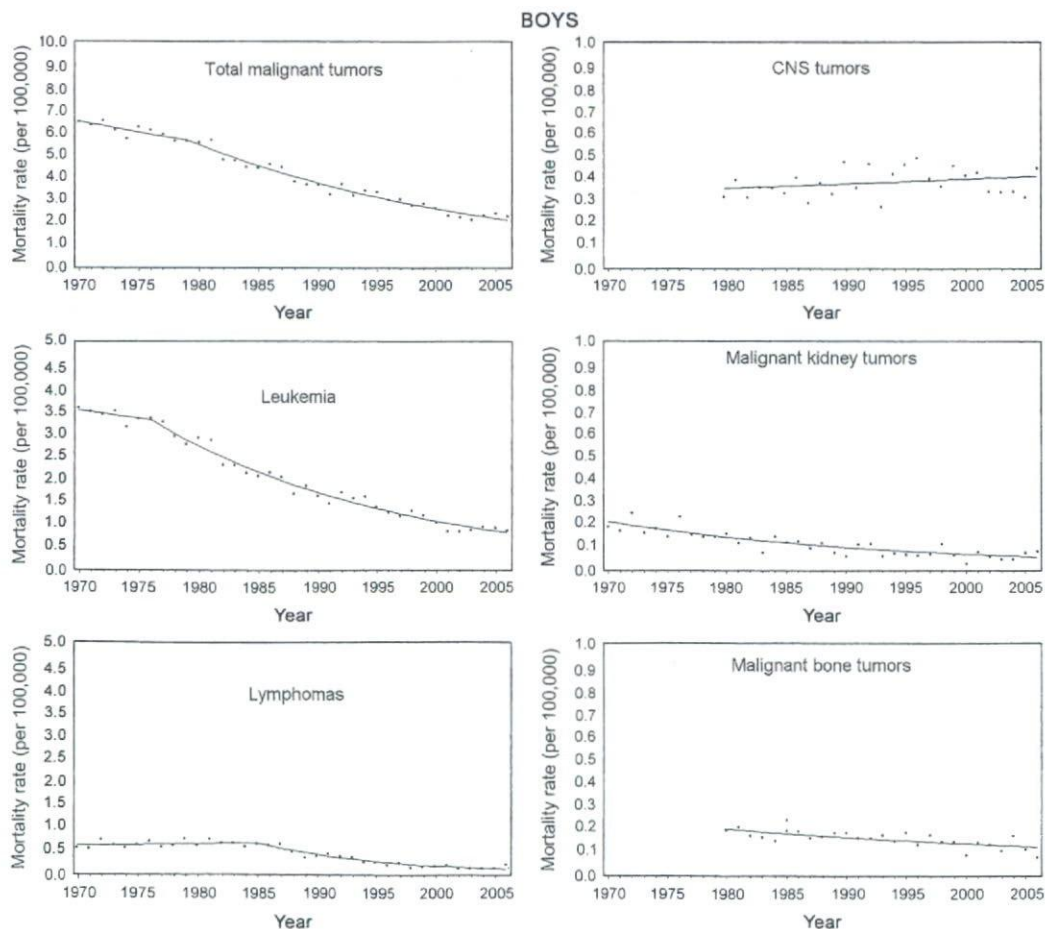
BOYS

Figure 1. Mortality rates of childhood cancer deaths, boys, Japan, 1970–2006.
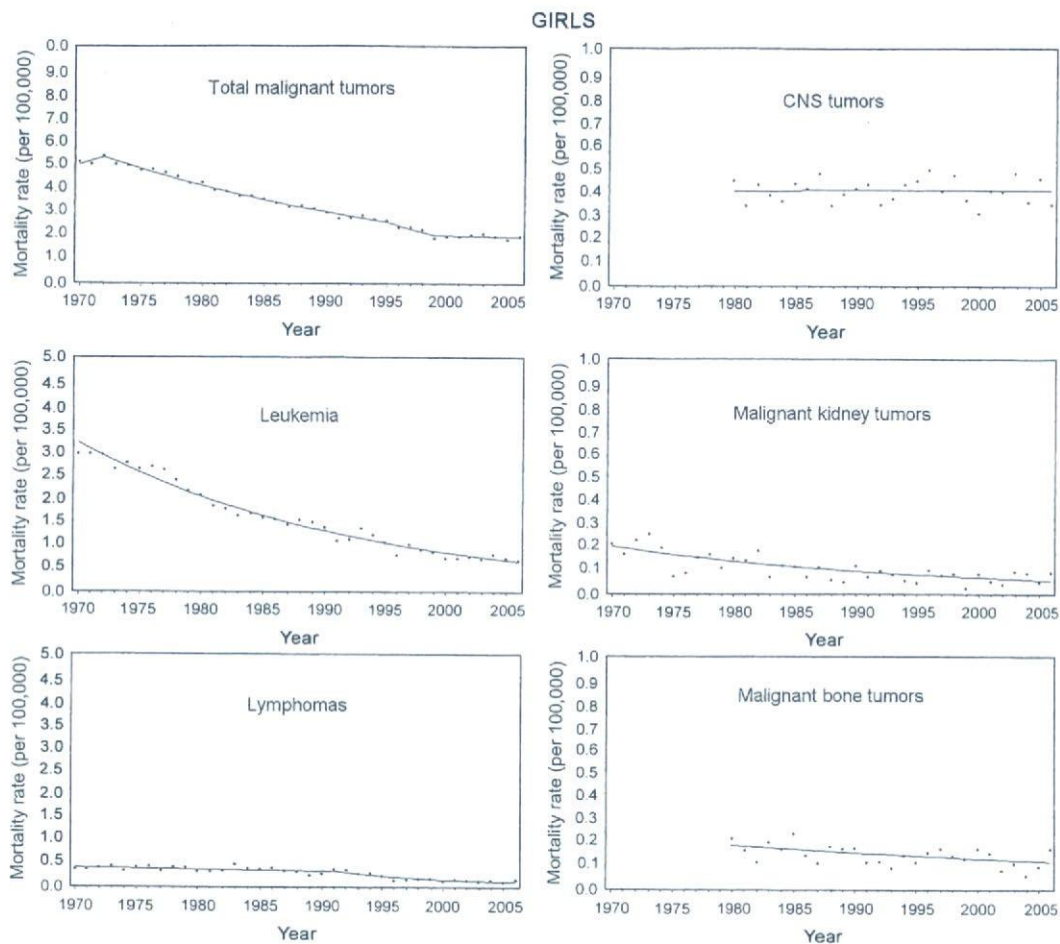
Figure 2. Mortality rates of childhood cancer deaths, girls, Japan, 1970–2006.

Regression analysis also revealed that the death rate for malignant kidney tumors declined by 4.12% per year for boys and 3.98% per year for girls during 1970–2006. Similar trends were observed for malignant bone tumor. Mortality decreased by 2.03% per year for boys and 1.79% per year for girls throughout the whole period.

Mortality rates varied from prefecture to prefecture in Japan. A map of SMR by gender is shown in Figure 3. The SMR was significantly highest among children in Kochi prefecture for boys and Tokushima and Kagoshima prefectures for girls.

discussion

In this study, we quantified the childhood cancer burden in Japan, focusing on mortality, and compared these figures with other developed countries. The results indicated that mortality from childhood cancer in Japan is substantial, while the number of deaths is small. There were 33 059 cases of childhood cancer death over the period 1970–2006 in Japan. Approximately 400 deaths each year were attributed to cancer in children aged 0–14 years. Mortality from all cancers combined in Japan is comparable to that in the European, North American and Oceanic countries included in this study for contrast.

The joinpoint regression method was used in our research to evaluate the trend in childhood cancer deaths. This method has allowed a detailed and accurate description of the pattern of childhood cancer mortality since it identifies the calendar years in which statistically significant changes in trends occurred. This offers a clearer picture of actual trends in mortality over long periods of time rather than using only one trend statistics. We also reported the average annual percentage change 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 especially advantageous for situations when the data are sparse (e.g. a rare cancer or data from a small geographic area) [7]. Our results showed a declining cancer mortality rate for boys in the whole period and a stable trend for girls in recent 5 years. 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 analyzed data were provided by official sources and based on the population census. The significant time trend observed for most tumor types is congruent with improvements in diagnosis, therapy and supportive care.

The dramatic decrease in mortality observed for childhood leukemia, which accounts for ~50% of all childhood cancer

Table 3. The APC of childhood cancer mortality rates (boys)

Country	Trend 1		Trend 2		Trend 3		Trend 4		AAPC	
	Years	APC	Years	APC	Years	APC	Years	APC	Last 10 observations	Last 5 observations
Total malignant tumors										
Japan	1970–1979	−1.58*	1979–2006	−3.78*					−3.8*	−3.8*
Canada	1970–2004	−3.64*							−3.6*	−3.6*
United States	1970–1998	−3.22*	1998–2005	−0.26					−0.3	−0.9
Italy	1970–1985	−2.32*	1985–1989	−8.69	1989–1993	6.96	1993–2003	−5.89*	−5.9*	−5.9*
UK	1970–2005	−2.93*							−2.9*	−2.9*
New Zealand	1970–2004	−2.50*							−2.5*	−2.5*
Leukemia										
Japan	1970–1976	−1.10	1976–2006	−4.77*					−4.8*	−4.8*
Canada	1970–2004	−5.00*							−5.0*	−5.0*
United States	1970–1984	−4.95*	1984–2005	−3.39*					−3.4*	−3.4*
Italy	1970–2003	−3.69*							−3.7*	−3.7*
UK	1970–2005	−3.74*	2003–2005	−27.41					−9.6	−16.4
New Zealand	1970–1997	−2.12*	1997–2004	−18.03*					−14.7*	−18.0*
Lymphomas										
Japan	1970–1985	0.39	1985–2006	−8.56*					−8.6*	−8.6*
Canada	1970–2004	−6.10*							−6.1*	−6.1*
United States	1980–2005	−5.63*							−5.6*	−5.6*
Italy	1970–2003	−4.46*							−4.5*	−4.5*
UK	1970–2005	−4.56*							−4.6*	−4.6*
New Zealand	1970–2004	−2.57*							−2.6*	−2.6*
Central nervous system tumors										
Japan	1980–2006	0.48							0.5	0.5
Canada	1980–2004	−2.13*							−2.1*	−2.1*
United States	1980–2005	−1.07*							−1.1*	−1.1*
Italy	1980–2003	−2.19*							−2.2*	−2.2*
UK	1980–2005	−1.25*							−1.2*	−1.2*
New Zealand	1980–2004	−0.86							−0.9	−0.9
Malignant kidney tumors										
Japan	1970–2006	−4.12*							−4.1*	−4.1*
Canada	1970–1996	−7.91*	1996–2004	17.70*					14.5*	17.7*
United States	1970–1987	−5.46*	1987–2005	−1.73*					−1.7*	−1.7*
Italy	1970–2003	−4.91*							−4.9*	−4.9*
UK	1970–2005	−3.64*							−3.6*	−3.6*
New Zealand	1970–2004	−1.99							−2.0*	−2.0*
Malignant bone tumors										
Japan	1980–2006	−2.03*							−2.0*	−2.0*
Canada	1980–2004	−2.32*							−2.3*	−2.3*
United States	1980–1990	−4.41*	1990–2005	1.31					1.3	1.3
Italy	1980–2003	−4.43*							−4.4*	−4.4*
UK	1980–2005	−2.93*							−2.9*	−2.9*
New Zealand	1980–2004	−0.23							−0.2	−0.2

*P < 0.05.

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

deaths, is consistent with improvements in survival, particularly for patients with acute lymphoblastic leukemia. This increase in survival is due to more effective antileukemic therapy, such as multidrug chemotherapy protocols, with a reduction in the number of relapses and resistant disease, but also due to improvements in supportive care, such as antibiotics, antifungal treatment, blood banking, transplant procedures and pediatric intensive care. In fact, the 5-year survival rate of acute lymphoblastic leukemia increased from 20% to 30% in the 1960s to 60% to 75% in the 1980s in developed countries. Current survival rates are ~80% for acute lymphoblastic leukemia (ALL) [8] and 50%–70% for acute myelogenous leukemia. In Japan, a population-based study in Osaka prefecture indicated that the 5-year survival rate of childhood leukemia increased from 32.4% in 1975–1984 to 60.4 in 1985–1994 [1]. National incidence trends could not be

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

Country	Trend 1 Years	APC	Trend 2 Years	APC	Trend 3 Years	APC	Trend 4 Years	APC	AAPC Last 10 observations	Last 5 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
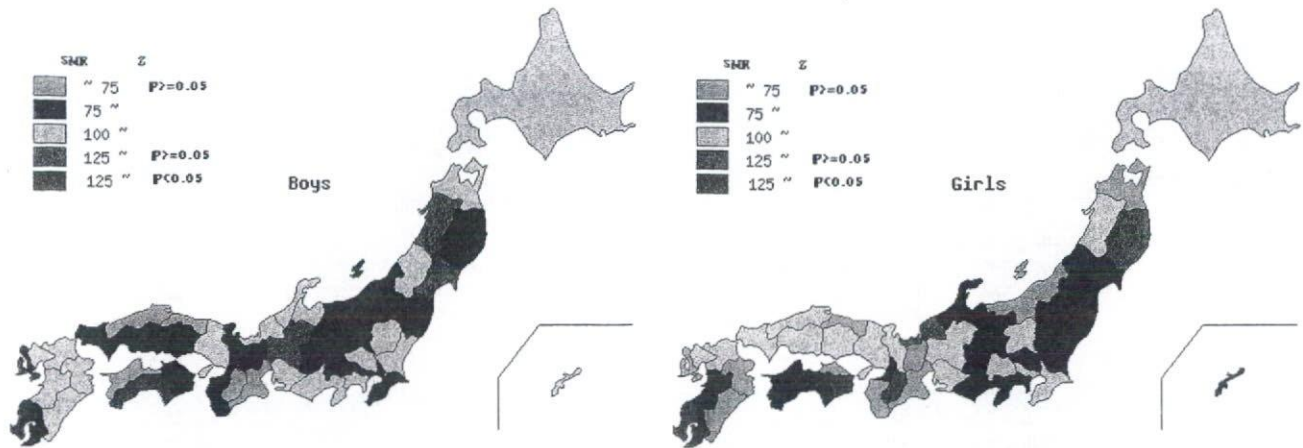
Figure 3. Standardized mortality ratios for childhood cancer in Japan, 2000–2006 by prefecture.

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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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.
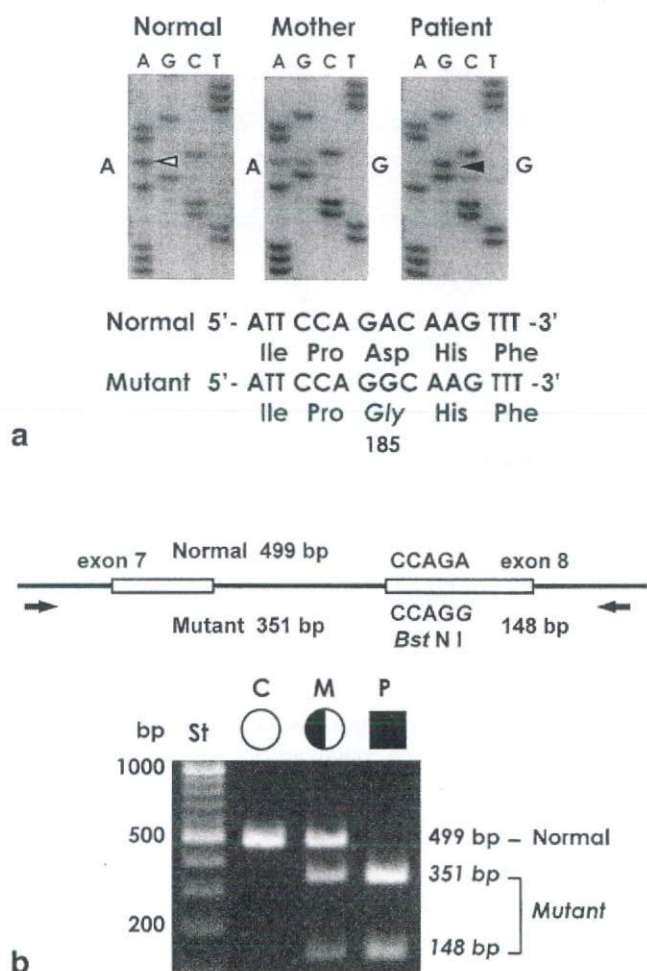

Fig. 1 Molecular genetic analysis of the HPRT gene. **a** Direct sequencing analysis of the DNA fragment including exons 7 and 8. DNA segments containing exons 7 and 8 were amplified from genomic DNA of the patient, his mother, and normal control by PCR described previously. The fragment was sequenced 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．

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 尿細管障害 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%，TBI1% 女：TBI例の無月経44% 卵巣機能回復Cy54% TBI10%，Bu+Cy1% 妊娠：Cy24%，TBI1%，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
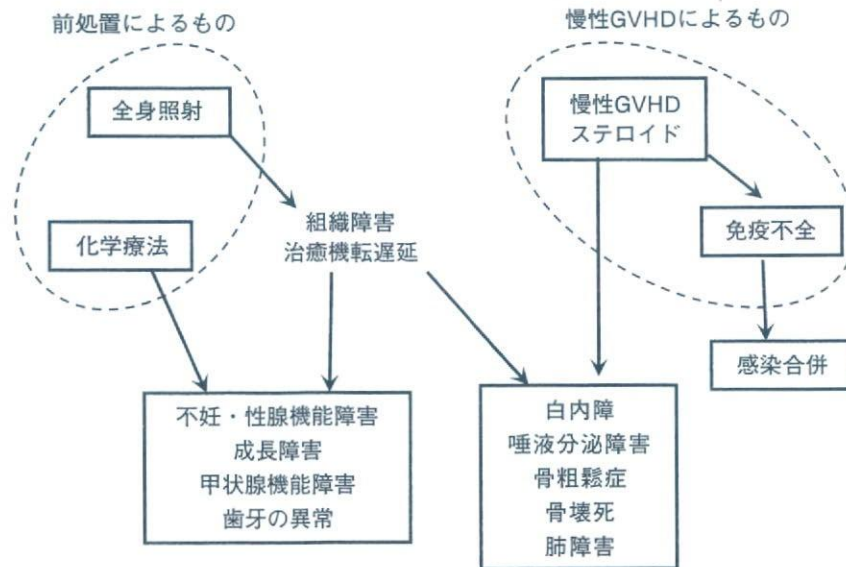

図1 移植に伴う晩期合併症の機序[3]

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．