Original Article

Cancer Incidence Patterns Among Children and Adolescents in Taiwan From 1995 to 2009: A Population-Based Study

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BACKGROUND: Currently, little information is available on childhood cancer incidence rates in Eastern Asia. The objective of this study was to report the first population-based cancer surveillance of children and adolescents in Taiwan. **METHODS:** Data from the Taiwan Cancer Registry were examined for cancer frequencies and incidence rates among individuals ages birth to 19 years from 1995 to 2009. Types of cancers were grouped according to the International Classification of Childhood Cancer. Rates were compared by sex and age. For further comparisons with other countries, rates were age standardized to the 2000 world standard population in 5-year age groups. Trends in incidence rates also were evaluated. **RESULTS:** In total, 12,315 individuals were diagnosed with childhood cancers, for an age-standardized incidence rate (ASR) of 132.1 per million person-years from 1995 to 2009. The male-to-female incidence rate ratio was 1.19. Overall, leukemias were the most common cancer (ASR, 39.1 per million person-years), followed by central nervous system neoplasms (15.8 per million person-years), and lymphomas (15.3 per million person-years). During the 15-year study period, the incidence rates increased by 1% annually. Compared with other countries, the rate of hepatic tumors was 2 times greater in Taiwan. The rate of germ cell neoplasms in Taiwan was similar to that in the United States and was 1.3 to 1.9 times greater compared with Canada, Brazil, Israel, and Japan. **CONCLUSIONS:** Based on the current data, the observed increase in overall incidence rates was attributable only marginally to improvements in case ascertainment and diagnostic procedures. The high rates of malignant hepatic tumors and germ cell neoplasms in Taiwan suggest variations in the background risk factors. ***Cancer* 2014;120:3545-53.**

KEYWORDS: adolescents, cancer, childhood, epidemiology, incidence, Taiwan.

INTRODUCTION

Childhood cancer is rare, comprising approximately 1% of all cancers in the United States and Europe.[1-3] Epidemiological surveillance is very difficult because of the diversity and rarity of childhood cancer. Currently, little information is available for approximately 80% of the world's population living the developing countries.[3-5]

In Taiwan, children and adolescents (ages birth to 19 years) make up 21.3% of the total population (4,975,411 of 23,344,213 individuals in June 2013).[6] In this age group, Taiwan Cancer Registry (TCR) data demonstrate that the average annual numbers of newly diagnosed cancer cases and cancer deaths were 842 and 252, respectively, from 1995 to 2009,[7] representing 0.9% of all newly diagnosed cancer cases and 0.49% of cancer deaths in 2009.

Childhood cancers are grouped more meaningfully according to histology and primary site based on the standard scheme of the International Childhood Cancer Classification (ICCC).[8] In a previous TCR report on childhood cancer incidence, childhood cancers were categorized only according to the 12 main ICCC groups and were not categorized further into the 47 subgroups.[9] Thus, by examining the reported data over the 15-year period from 1995 to 2009, the objectives of this study were to fill the data gap in the childhood cancer incidence in Taiwan according to the 47 ICCC subgroups, to contribute to etiologic research, and to highlight the importance of public health. We analyzed the data targeted at the age range from birth to 19 years because most childhood cancers affect children ages birth to 14 years, but

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We express our deep gratitude to the Taiwan Cancer Registry staff for their contributions in data collection, validation, and routine analyses. We also are grateful to Dr. Shu-Chiung Chiang (Institute of Hospital and Health Care Administration, National Yang-Ming University) for statistics consulting. We greatly appreciated the valuable comments suggested by anonymous reviewers from the journal *Cancer*.

DOI: 10.1002/cncr.28903, **Received:** December 28, 2013; **Revised:** April 13, 2014; **Accepted:** June 5, 2014, **Published online** July 16, 2014 in Wiley Online Library (wileyonlinelibrary.com)

some peak at ages 15 to19 years; thus, we wanted to follow the international standards recommended by the International Agency for Research on Cancer (IARC), in which the suggested age range is from birth to 19 years, whenever possible instead of ages birth to 14 years.[10] Furthermore, it is known that ethnic variations exist in the incidence of childhood cancer.[4] Because up to 98% of the population of Taiwan is Han Chinese,[6] in this study, we also wanted to provide more comprehensive information for comparing data on Han Chinese with data from other ethnic groups.

MATERIALS AND METHODS

Data Collection

Incidence data for this study were obtained from the TCR, which is organized and funded by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan. The TCR is population-based and began registration of all cancers in 1979. In addition, Taiwan's National Health Insurance program, a mandatory universal health insurance program with a coverage rate of up to 99%,[11] was first launched in 1995, enabling all individuals to easily access medical services and prompt treatment. After the enactment of the Cancer Control Act in 2003, hospitals with a capacity of >50 beds that provided outpatient and hospitalized cancer care were mandated to submit cancer data to the central cancer registry, which enhanced the completeness of registration and case ascertainment and improved the quality of cancer data collection.[7,9] In terms of data quality of the TCR according to the quality indicators defined by the IARC, the percentage of death certificate only cases (DCO%) fell from 19.63% in 1995 to 1.15% in 2009. The percentage of microscopically verified cases (MV%) is another indicator of data validity; and, although it varies according to the type of cancer, the MV% was 90.75% in 2009 for all cancers combined. The indicators described above reveal the high quality of the TCR and its remarkable improvement over time.

The incidence rates for all cancers in children and adolescents (age range, from birth to 19 years) diagnosed from 1995 to 2009 were analyzed. Diagnoses were categorized into 12 main groups and 47 subgroups according to the ICCC version 3 (ICCC-3).[8] Only patients who were diagnosed with malignant tumors were included in the data. Patients who had tumors that were not classified by the ICCC-3 or who had in situ cancers were excluded from the final analysis to enable a comparison of the incidence between different countries. We abbreviated 7 of the 12 major ICCC-3 groups as follows: leukemias included leukemias, myeloproliferative diseases, and myelodysplastic diseases; lymphomas included lymphomas and reticuloendothelial neoplasms; central nervous system (CNS) neoplasms included CNS and miscellaneous intracranial and intraspinal neoplasms; neuroblastomas included neuroblastoma and ganglioneuroblastoma; soft tissue sarcomas (STS) included soft tissue and other extraosseous sarcomas; germ cell neoplasms included germ cell tumors (GCTs), trophoblastic tumors, and neoplasms of the gonads; and other epithelial neoplasms included other malignant epithelial neoplasms and malignant melanomas.

Analyses

Crude rates and age-standardized incidence rates (ASRs) were expressed per million person-years according to sex and are presented in accordance with the ICCC-3 into the main groups and subgroups described above. Rates, cumulative risks, standard errors, and 95% confidence intervals (CIs) were calculated according to previously published methods.[12] An ASR is a weighted average of the age-specific (crude) rates, in which the weights are the proportions of individuals in the corresponding age groups of a standard population. The potential confounding effect of age is reduced when comparing ASRs that are computed using the same standard population. In this study, ASRs were calculated by the direct method, using the 2000 world standard population based on 5-year age groups (ages birth to 4 years, 5-9 years, 10-14 years, and 15-19 years),[12] and were used to compare the rates with those in other countries. Incidence rates by single-year age were compared for specified disease groups as follows: leukemias, lymphomas, CNS neoplasms, germ cell neoplasms, embryonal tumors (including neuroblastomas, retinoblastoma, nephroblastoma, and hepatoblastoma), and certain adolescent tumors (including hepatic carcinomas, osteosarcomas, other specified STS, thyroid carcinomas, and nasopharyngeal carcinomas). Trends were analyzed using the Joinpoint regression model and permutation tests (Joinpoint Regression Program, version 4.0.4; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute, Bethesda, Md) to identify significant changes[13,14] in which up to 3 joinpoints were produced to express the annual percentage change (APC). This software takes trend data and fits the simplest joinpoint model that the data allow. The program starts with the minimum number of joinpoints and tests whether more joinpoints are statistically significant and must be added to the model. The grid search described by Lerman in 1980 was used to

fit the segmented regression function, the *P* value of each permutation test was estimated using Monte-Carlo methods, and the overall asymptotic significance level was maintained through a Bonferroni adjustment.[14] The APC was considered significant if the 95% CI did not include zero. To compare our data with the cancer incidence data for children and adolescents ages birth to 19 years from other countries, we compiled world rates by searching the databases available from the internet (Medline, National Center for Biotechnology Information, PubMed) and the annual reports of national cancer registries.

RESULTS

In total, 12,315 patients ages birth to 19 years were diagnosed with childhood cancers from 1995 to 2009, for a crude rate of 130.97 and an ASR of 132.08 per million person-years (Table 1). The cumulative risk of developing cancer at an age <20 years was 0.26% (1 in 385). In the rank order of cancers, leukemias were the most frequently diagnosed cancer (ASR, 39.12 per million), followed by CNS neoplasms (15.76 per million), and lymphomas (15.27 per million). Together, these 3 cancers composed greater than half (53.5%) of all childhood cancers. Sex-based differences in ASR were observed. For males, the 3 most common main groups were leukemias (42.70 per million), lymphomas (19.29 per million), and CNS neoplasms (16.85 per million). For females, the main groups ranked within the first 3 were leukemias (35.24 per million), other epithelial neoplasms (15.98 per million), and CNS neoplasms (14.59 per million). In total, 325 patients (191 males, 134 females) who had cancers that were categorized as *not classified by ICCC or in situ* were excluded from the final analysis. In terms of data-quality indicators defined by the IARC, the DCO% for all cancers combined fell about 10%, from 10.3% in 1995 to 0.6% in 2009 (average, 6.4% during 1995-1999, 1.1% during 2000 to 2004, and 0.4% during 2005-2009). The MV% results for all cancers combined were 93.7% (Table 2) during the 15-year study period (from 92.4% in 1995 to 94.3% in 2009; range, 91.5%-95.9%). The MV% varied from 92% (CNS neoplasms) to 99.4% (other epithelial neoplasms) for most main ICCC groups, with the exceptions of hepatic tumors (67.7%) and the group of other and unspecified malignant neoplasms (ICCC group XII; 54%). Furthermore, the proportion of ICCC group XII, which is another important indicator of change in quality of diagnosis, was an average of 0.9% throughout the study period (average, 0.7% during 1995-1999, 1.1% during 2000 to 2004, and 1.0% during 2005-2009).

Incidence Rate by Sex

The male-to-female (M/F) incidence rate ratio (IRR) was 1.19 for all cancers combined (Table 1). The ASR was 142.81 and 120.43 per million for males and females, respectively. Except for other epithelial neoplasms, males had higher incidence rates than females for most of ICCC groups. The male predominance was most pronounced for lymphomas.

When we compared incidence rates according to the ICCC subgroups, the highest M/F IRRs (>2) were observed for Burkitt lymphoma, intracranial and intraspinal GCTs, and nasopharyngeal carcinomas. Gonadal carcinomas occurred almost exclusively in females, with an M/F IRR of only 0.02. Females also predominated in other and unspecified malignant gonadal tumors, thyroid carcinomas, other specified malignant bone tumors, other specified and unspecified CNS neoplasms and malignant melanomas, with M/F IRRs ranging from 0.20 to 0.83.

Incidence Rate by Age

The age patterns of certain cancer groups are depicted in Figure 1. For leukemias (Fig. 1a), the most common subgroup was lymphoid leukemias, with a distinct peak observed among children ages 2 to 3 years. No apparent difference was observed in the age patterns of CNS neoplasm subtypes (Fig. 1b), except that intracranial and intraspinal embryonal tumors were more common before age 10 years. For lymphomas (Fig. 1c), the incidence of non-Hodgkin lymphomas gradually increased with age and reached a peak in adolescence. Hodgkin lymphoma was rare before age 11 years; however, there was a gradual increase in the incidence with age. In contrast to non-Hodgkin lymphoma and Hodgkin lymphoma, which were reported mainly during the second decade of life, the incidence of miscellaneous lymphoreticular neoplasms peaked in infancy, then declined rapidly during ages 1 to 4 years to a rate that was almost zero thereafter.

The patterns of age-specific incidence of principle embryonal tumors and certain adolescent tumors are depicted in Figure 1d,e; note that the former peaked during infancy in contrast to the latter, which peaked during adolescence. In the subgroups of germ cell neoplasms (Fig. 1f), the incidence rates of malignant gonadal GCTs and extracranial and extragonadal GCTs both peaked during the first year of life, and another peak during puberty also was observed.

Temporal Trends

Cancer incidence trends varied according to the ICCC groups (Table 2). Overall, the APC for total cancers was

TABLE 1. Annual Cancer Incidence Rates (per Million) Among Children and Adolescents Aged Birth to 19 Years by Sex and International Classification of Childhood Cancer, Version 3 Group and Subgroup: Taiwan, 1995 to 2009[a]

		Both Sexes		Males		Females		
ICCC-3 Group	No.	Crude Rate	ASR[a]	No.	ASR[a]	No.	ASR[a]	M/F IRR
I. Leukemias	3520	37.43	39.12	2004	42.70	1516	35.24	1.21
Lymphoid leukemias	2258	24.01	25.64	1309	28.44	949	22.61	1.26
Acute myeloid leukemias	888	9.44	9.55	485	10.06	403	8.99	1.12
Chronic myeloproliferative diseases	211	2.24	2.11	123	2.35	88	1.86	1.26
Myelodysplastic syndrome and other myeloproliferative diseases	46	0.49	0.52	26	0.56	20	0.47	1.18
Unspecified and other specified leukemias	117	1.24	1.30	61	1.29	56	1.32	0.98
II. Lymphomas	1470	15.63	15.27	963	19.29	507	10.93	1.76
Hodgkin lymphomas	324	3.45	3.15	207	3.94	117	2.30	1.71
Non-Hodgkin lymphomas except Burkitt lymphoma	721	7.67	7.38	481	9.50	240	5.08	1.87
Burkitt lymphoma	168	1.79	1.88	123	2.63	45	1.05	2.49
Miscellaneous lymphoreticular neoplasms	149	1.58	1.78	85	1.91	64	1.63	1.17
Unspecified lymphomas	108	1.15	1.09	67	1.31	41	0.85	1.53
III. CNS neoplasms	1449	15.41	15.76	805	16.85	644	14.59	1.15
Ependymomas and choroid plexus tumor	148	1.57	1.67	85	1.85	63	1.47	1.25
Astrocytomas	606	6.44	6.45	309	6.34	297	6.58	0.96
Intracranial and intraspinal embryonal tumors	415	4.41	4.61	243	5.19	172	3.97	1.31
Other gliomas	206	2.19	2.21	133	2.72	73	1.65	1.65
Other specified intracranial and intraspinal neoplasms	45	0.48	0.50	22	0.46	23	0.55	0.83
Unspecified intracranial and intraspinal neoplasms	29	0.31	0.32	13	0.28	16	0.36	0.78
IV. Neuroblastomas	587	6.24	7.17	346	8.07	241	6.20	1.30
Neuroblastoma and ganglioneuroblastoma	561	5.97	6.90	327	7.69	234	6.05	1.27
Other peripheral nervous cell tumors	26	0.28	0.27	19	0.38	7	—[b]	—[b]
V. Retinoblastoma	228	2.42	2.87	129	3.10	99	2.62	1.18
VI. Renal tumors	243	2.58	2.88	133	3.03	110	2.71	1.12
Nephroblastoma and other nonepithelial renal tumors	205	2.18	2.50	111	2.61	94	2.38	1.10
Renal carcinomas	37	0.39	0.37	22	0.42	15	0.31	1.35
Unspecified malignant renal tumors	1	—[b]	—[b]	0	—[b]	1	—[b]	—[b]
VII. Hepatic tumors	424	4.51	4.61	267	5.54	157	3.62	1.53
Hepatoblastoma	145	1.54	1.81	87	2.08	58	1.52	1.37
Hepatic carcinomas	183	1.95	1.84	118	2.28	65	1.35	1.68
Unspecified malignant hepatic tumors	96	1.02	0.97	62	1.18	34	0.74	1.59
VIII. Malignant bone tumors	705	7.50	6.98	414	7.88	291	6.02	1.31
Osteosarcomas	525	5.58	5.16	311	5.88	214	4.39	1.34
Chondrosarcomas	46	0.49	0.44	30	0.56	16	0.32	1.79
Ewing tumor and related sarcomas of bone	79	0.84	0.83	48	0.95	31	0.69	1.37
Other specified malignant bone tumors	43	0.46	0.43	18	0.34	25	0.52	0.65
Unspecified malignant bone tumors	12	0.13	0.12	7	—[b]	5	—[b]	—[b]
IX. Soft tissue sarcomas	933	9.92	9.66	511	10.18	422	9.09	1.12
Rhabdomyosarcomas	288	3.06	3.17	167	3.52	121	2.80	1.26
Fibrosarcomas, peripheral nerve sheath tumors, and other fibrous neoplasms	116	1.23	1.18	70	1.36	46	0.99	1.38
Kaposi sarcoma	5	—[b]	—[b]	1	—[b]	4	—[b]	—[b]
Other specified soft tissue sarcomas	429	4.56	4.29	217	4.20	212	4.39	0.96
Unspecified soft tissue sarcomas	95	1.01	0.96	56	1.07	39	0.83	1.29
X. Germ cell neoplasms	1267	13.47	13.29	683	14.08	584	12.42	1.13
Intracranial and intraspinal germ cell tumors	214	2.28	2.17	148	2.87	66	1.41	2.03
Malignant extracranial and extragonadal germ cell tumors	341	3.63	3.68	228	4.51	113	2.79	1.62
Malignant gonadal germ cell tumors	605	6.43	6.43	302	6.61	303	6.22	1.06
Gonadal carcinomas	91	0.97	0.85	2	—[b]	89	1.72	0.02
Other and unspecified malignant gonadal tumors	16	0.17	0.16	3	—[b]	13	0.27	0.20
XI. Other epithelial neoplasms	1376	14.63	13.29	576	10.78	800	15.98	0.67
Adrenocortical carcinomas	12	0.13	0.14	3	—[b]	9	—[b]	—[b]
Thyroid carcinomas	544	5.79	5.17	106	1.97	438	8.59	0.23
Nasopharyngeal carcinomas	181	1.92	1.71	134	2.45	47	0.91	2.68
Malignant melanomas	63	0.67	0.65	29	0.58	34	0.72	0.80
Skin carcinomas	77	0.82	0.76	41	0.77	36	0.75	1.02
Other and unspecified carcinomas	499	5.31	4.86	263	4.94	236	4.77	1.03
XII. Other and unspecified malignant neoplasms	113	1.20	1.17	65	1.32	48	1.01	1.30
Other specified malignant tumors	23	0.24	0.23	11	0.22	12	0.24	0.94
Other unspecified malignant tumors	90	0.96	0.94	54	1.09	36	0.78	1.41
Total	12315	130.97	132.08	6896	142.81	5419	120.43	1.19

Abbreviations: ASR, age-standardized rate; CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer, version 3; M/F IRR, male-to-female incidence rate (age-standardized rate) ratio.

Data include malignant tumors only.

[a] ASRs are per 1 million person-years and were age adjusted to the 2000 world standard population.

[b] There were <10 patients with these tumors and, to avoid presenting unstable data, the statistics are not displayed.

TABLE 2. Annual Percentage Changes in Childhood Cancer Incidence Rates by Groups According to International Classification of Childhood Cancer, Version 3 and by Sex Among Individuals Ages Birth to 19 years: Taiwan 1995 to 2009

	Both Sexes			Males		Females	
ICCC-3 Group	Years	APC (95% CI)[a]	MV%	Years	APC (95% CI)[a]	Years	APC (95% CI)[a]
I. Leukemias	1995-2009	2.3 (1.7, 3.0)[b]	98.9	1995-1997	−5.1 (−18.0, 9.8)	1995-2009	1.6 (0.4, 2.8)[b]
				1997-2003	6.4 (3.1, 9.8)[b]		
				2003-2007	−1.7 (−8.4, 5.5)		
				2007-2009	7.8 (−6.4, 24.1)		
II. Lymphomas	1995-2009	2.2 (0.7, 3.7)[b]	98.7	1995-2009	1.3 (−0.4, 3.1)	1995-2009	4.0 (1.1, 7.0)[b]
III. CNS neoplasms	1995-2009	2.1 (0.6, 3.7)[b]	92	1995-2009	1.9 (−0.7, 4.6)	1995-2009	2.7 (0.4, 5.1)[b]
IV. Neuroblastomas	1995-2009	1.7 (−0.5, 4.1)	96.8	1995-2009	3.0 (−0.1, 6.2)	1995-2009	0.1 (−3.5, 3.8)
V. Retinoblastoma	1995-2009	−0.1 (−2.8, 2.8)	92.1	1995-2009	2.1 (−2.6, 7.1)	1995-2009	−1.6 (−5.6, 2.6)
VI. Renal tumors	1995-2009	−1.1 (−4.0, 1.9)	98.8	1995-2009	−0.7 (−3.8, 2.5)	1995-2009	−1.6 (−5.3, 2.1)
VII. Hepatic tumors	1995-2009	−2.2 (−4.6, 0.3)	67.7	1995-2009	−3.2 (−5.7, −0.6)[b]	1995-2009	−0.5 (−4.3, 3.5)
VIII. Malignant bone tumors	1995-2009	0.1 (−1.8, 2.0)	98.7	1995-2009	−0.6 (−2.8, 1.6)	1995-2009	0.9 (−2.1, 4.0)
IX. Soft tissue sarcomas	1995-2009	2.5 (1.1, 3.9)[b]	98.6	1995-2009	2.2 (0.2, 4.2)[b]	1995-2009	2.8 (0.7, 5.0)[b]
X. Germ cell neoplasms	1995-2009	2.3 (0.8, 3.9)[b]	95.5	1995-2009	3.2 (1.2, 5.3)[b]	1995-2009	1.2 (−1.3, 3.8)
XI. Other epithelial neoplasms	1995-2009	−0.8 (−1.9, 0.3)	99.4	1995-2009	−2.4 (−4.3, −0.4)[b]	1995-2009	0.4 (−1.0, 1.9)
XII. Other and unspecified malignant neoplasms	1995-2009	5.8 (−3.8, 16.4)	54	1995-2009	5.8 (−6.3, 19.6)	1995-2009	4.3 (−3.9, 13.2)
Total	1995-2009	1.0 (0.5, 1.6)[b]	93.7	1995-2009	1.0 (0.3, 1.8)[b]	1995-2009	1.1 (0.2, 2.0)[b]

Abbreviations: APC, annual percentage change; CI, confidence interval; CNS, central nervous system, ICCC-3, International Classification of Childhood Cancer, version 3; MV%, percentage of microscopically verified cases.
[a] The APC was calculated using weighted least-squares regression.
[b] This value reflects a statistically significant difference at the $P<.05$ level.

1% during 1995 to 2009. The incidence rates rose significantly in the total population for leukemias, lymphomas, CNS neoplasms, STS, and germ cell neoplasms, with APCs ranging from 2.1% to 2.5%.

For males, the incidence rate rose significantly for leukemias during 1997 to 2003 (APC, 6.4%), and the incidence rates for STS and germ cell neoplasms (APC, 2.2% and 3.2%, respectively) rose during 1995 to 2009. In addition, significantly declined rates were observed for hepatic tumors (APC, −3.2%) and other epithelial neoplasms (APC, −2.4%); whereas, among females, significant increases in the incidence rates were observed for leukemias (APC, 1.6%), lymphomas (APC, 4%), CNS neoplasms (APC, 2.7%), and STS (APC, 2.8%).

Childhood Cancer Incidence by Country

Results from countries of the Western world (the United States and Canada), Latin America (Brazil), Western Asia (Israel), and Eastern Asia (Japan) are compiled in Table 3 for comparison.[5,15-18] Overall, childhood cancer incidence in Taiwan was lower than that in all other countries except Japan. Compared with countries other than Japan, the incidence rates for most main ICCC groups were similar or lower in Taiwan, except for hepatic tumors and germ cell neoplasms. The rate for hepatic tumors was >2 times greater compared with all the other countries, including the United States, Canada, Brazil, Israel, and Japan. The rate for germ cell neoplasms was among the highest, as in the United States, and was 1.3 to 1.9 times greater compared with the rate in countries other than the United States.

By contrast, the incidence rates of lymphomas, CNS neoplasms, and renal tumors were significantly lower than those of other countries except Japan. However, it is important to bear in mind the possibility that the lower rates of CNS neoplasms in Taiwan was the result of including only data on malignant tumors as that in the United States,[16] in contrast to the countries that included data on both benign and malignant tumors.[5,15,17,18] In addition, because Japan is the only country that conducted mass screening for neuroblastoma from 1984 to March 2004, a substantially higher incidence of neuroblastoma was likely to occur during this period.[19] Accordingly, comparisons between countries should be interpreted with caution.

DISCUSSION

In this study, we investigated childhood cancer incidence patterns and trends in Taiwan from 1995 to 2009 using data from the TCR. This relative large data set enabled us to evaluate incidence overall by sex and age based on the ICCC. The overall cancer incidence patterns generally were consistent with previous reports from Western countries, indicating that leukemias were the most common childhood cancer, males were more likely to be diagnosed

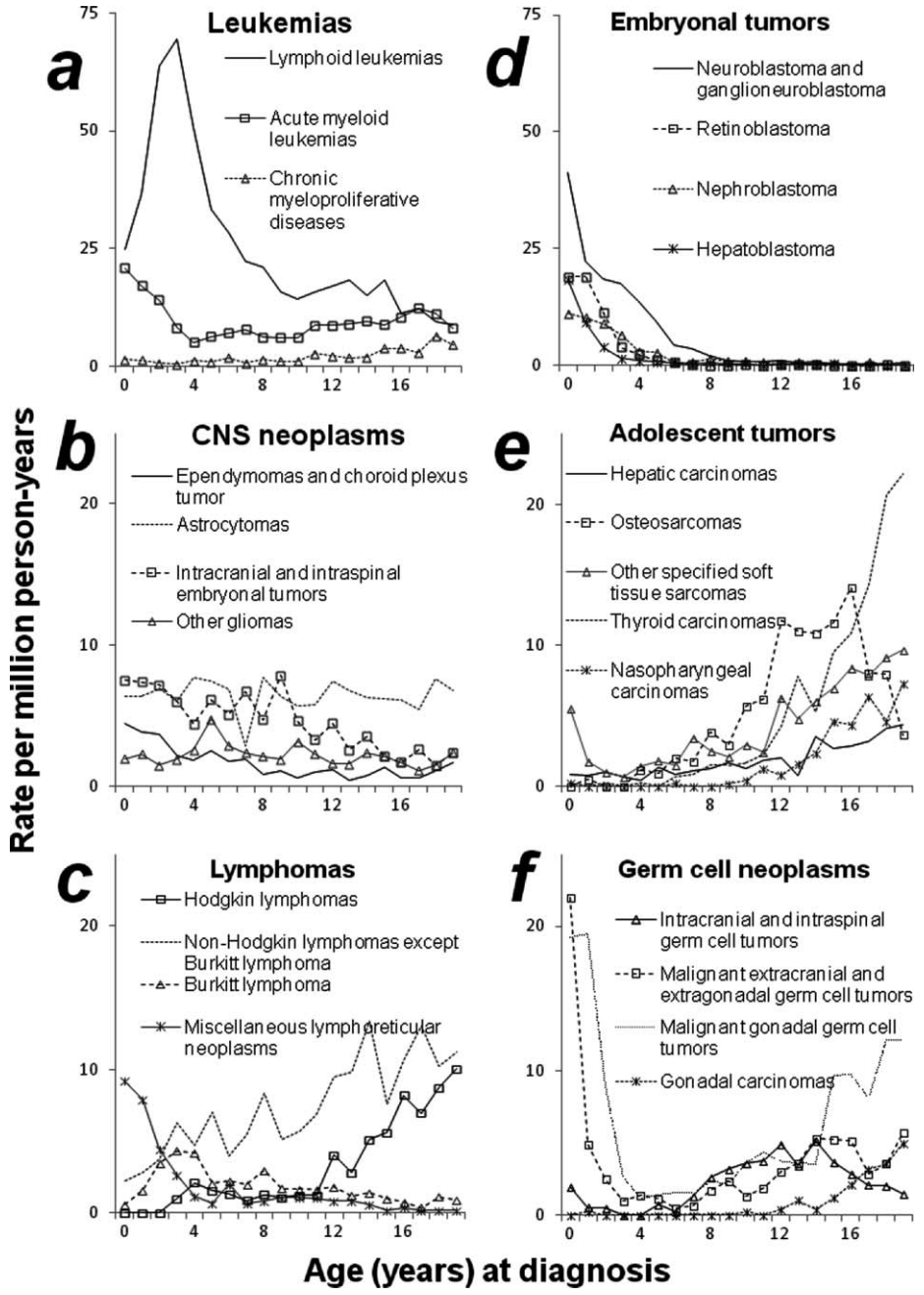

Figure 1. Cancer incidence rates are illustrated by disease groups, including (a) leukemias, (b) central nervous system (CNS) neoplasms, (c) lymphomas, (d) embryonal tumors, (e) adolescent tumors, and (f) germ cell neoplasms according to single-year age groups in Taiwan from 1995 to 2009.

with cancer than females, and cancer types varied by age and sex.[1,2,4,16] There were several novel findings in this study, including significant upward trends for all cancers combined and for certain cancer types and the high rates of hepatic tumors and germ cell neoplasms in Taiwan compared with other countries (Table 3). For the interpretation of variations in rates by country, more details considering the subgroups in the main ICCC categories along with sex-specific incidence rates are need and are clarified below.

Because the sex-specific incidence rates for ICCC subgroups were available only from the United States and Israel,[1,15,16] for the current study, we only further compared the results obtained in Taiwan with those from these 2 countries. For the subgroups of hepatic tumors, we

TABLE 3. Comparison of Cancer Incidence Rates Among Children and Adolescents Ages Birth to 19 Years in Different Countries According to International Classification of Childhood Cancer Group

	Rate per Million (%)								
	USA/SEER, 2001-2003[a,b]		Canada, 2003-2007[c]	Brazil, 1995-2002[d,e]	Israel, 1995-2007[d]	Japan, 1993-2001[f]		Taiwan, 1995-2009[b,d]	
Variable	Males	Females	Both	Both	Both	Males	Females	Males	Females
Total no. of patients	19617	16829	6550	3667	4058	4006	3198	6896	5419
ICCC-3 group									
I. Leukemias	47.2 (27.1)	40.0 (25.4)	45.9 (27.4)	47.5 (23.3)	37.9 (22)	32.3 (31.9)	24.4 (30.7)	42.7 (29.9)	35.2 (29.3)
II. Lymphomas	27.8 (16)	20.3 (12.9)	26.4 (15.8)	30.6 (15)	34.9 (20.2)	12.2 (12)	6.3 (7.9)	19.3 (13.5)	10.9 (9.1)
III. CNS neoplasms	31.0 (17.8)	27.4 (17.4)	27.0 (16.1)	29.4 (14.4)	29.9 (17.4)	14.2 (14)	11.7 (14.7)	16.8 (11.8)	14.6 (12.1)
IV. Neuroblastomas	8.4 (4.8)	8.2 (5.2)	8.9 (5.3)	7.7 (3.8)	12.5 (7.2)	9.5 (9.4)	6.7 (8.4)	8.1 (5.7)	6.2 (5.1)
V. Retinoblastomas	3.2 (1.8)	2.8 (1.8)	2.5 (1.5)	7.0 (3.5)	2.2 (1.3)	1.7 (1.7)	1.6 (2)	3.1 (2.2)	2.6 (2.2)
VI. Renal tumors	6.2 (3.5)	7.1 (4.5)	7.0 (4.2)	9.2 (4.5)	6.7 (3.9)	2.3 (2.3)	1.6 (2)	3.0 (2.1)	2.7 (2.3)
VII. Hepatic tumors	2.2 (1.2)	1.7 (1.1)	2.2 (1.3)	1.3 (0.6)	1.5 (0.9)	2.0 (2)	1.5 (1.9)	5.5 (3.9)	3.6 (3)
VIII. Malignant bone tumors	10.0 (5.7)	7.8 (5)	8.8 (5.3)	18.2 (8.9)	9.7 (5.6)	5.8 (5.7)	4.6 (5.8)	7.9 (5.5)	6.0 (5)
IX. Soft tissue sarcomas	12.9 (7.4)	10.8 (6.8)	10.2 (6.1)	12.9 (6.3)	12.6 (7.3)	5.4 (5.3)	4.5 (5.7)	10.2 (7.1)	9.1 (7.6)
X. Germ cell neoplasms	13.2 (7.6)	8.1 (5.2)	9.8 (5.9)	8.8 (4.3)	6.9 (4)	7.3 (7.2)	7.4 (9.3)	14.1 (9.9)	12.4 (10.3)
XI. Other epithelial neoplasms	11.8 (6.7)	22.1 (14.1)	15.4 (9.2)	17.8 (8.8)	16.3 (9.4)	4.1 (4)	5.3 (6.7)	10.8 (7.5)	16.0 (13.3)
XII. Other and unspecified malignant neoplasms	0.6 (0.3)	1.0 (0.6)	3.1 (1.9)	13.1 (6.4)	1.4 (0.8)	4.5 (4.4)	3.8 (4.8)	1.3 (0.9)	1.0 (0.8)
Total	174.3 (100)	157.1 (100)	167.3 (100)	203.6 (100)	172.4 (100)	101.4 (100)	79.4 (100)	142.8 (100)	120.4 (100)

Abbreviations: Both, both sexes; CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer version 3; SEER, Surveillance, Epidemiology, and End Results Program.

[a] Li et al, 2008[16]: rates were age adjusted to the 2000 US standard population.

[b] Data include malignant tumors only.

[c] Rates were age standardized to the 1991 Canadian population.

[d] Rates were age adjusted to the world standard population.

[e] de Camargo et al, 2010[5]: only individuals aged ≤19 years were included.

[f] Marugame et al, 2007[18]: only crude rates were reported. Mass screening for neuroblastoma was initiated in 1984 and halted by March 2004.

observed that the difference in incidence was more pronounced in hepatocellular carcinoma (HCC) than in hepatoblastoma. The rate of HCC in Taiwan (1.84 per million) was approximately 3-fold higher than that in the United States (0.57 per million,) and Israel (0.5 per million). In addition, Taiwan (1.81 per million) had an approximately 1.6-fold higher rate of hepatoblastoma than the United States (1.0 per million) and Israel (1.1 per million).

For HCC, higher rates in Taiwan previously were associated with the high prevalence rate of hepatitis B virus (HBV).[20,21] To reduce the prevalence of HBV infection and further reduce the incidence of HCC, the government of Taiwan started the world's first nationwide HBV universal vaccination program in 1984.[20,21] Since then, there has been a significant decline in the incidence of HCC in children ages 6 to 14 years (7.0 per million in 1981-1986, 5.7 per million in 1986-1990, and 3.6 per million in 1990-1994).[21] Our data indicate that the incidence rates in a similar group ages 5 to 14 years have been reduced further to 1.58 per million during 1995 to 2009. The results also were consistent with a trend analysis, indicating a significant decreasing trend among males for hepatic tumors (APC, −3.2%) (Table 2) and reflecting the importance and substantial success of the vaccination program in Taiwan. However, the latest incidence rate for HCC disclosed in the study was still higher than that in other countries, suggesting that additional risk factors apart from HBV, including chronic infection with hepatitis C virus, diet/environmental factors (eg, alfatoxin), and genetic factors, also should be considered and investigated in Taiwan.[1,20,21]

The reasons for the higher rate of hepatoblastoma in Taiwan remain to be explored. In addition to the known genetic risk factors, including Beckwith-Wiedemann syndrome and familial adenomatous polyposis,[1] studies from Japan and the United States have demonstrated that factors associated with prematurity and its treatments may play a role in the occurrence of hepatoblastoma.[1,22] Therefore, the increasing numbers and survival of prematurity as a result of advancements in obstetric and neonatal care also may contribute to the high rate of hepatoblastoma.[23] Furthermore, other possible risk factors, including parental exposures to toxins/hormones, have been reported for which the risk of hepatoblastoma is still unknown and are worth further investigation.[1]

The incidence rate of germ cell neoplasms in the current study (ASR, 13.29 per million) (Table 1) was similar to that in the United States (11.6 per million) and was

1.9-fold higher than that in Israel (6.9 per million).[1,15,16] Moreover, we observed remarkable variations compared with these 2 countries in the incidence rates of ICCC subgroups (Xa-Xc). Taiwan had a higher rate of intracranial and intraspinal GCTs (subgroup Xa) compared with Western countries, but the rate was consistent with the rates in Japan and Korea. However, those results were only provided with data on relative frequency (%) from a study in a single-institution setting.[24] In the current study, we have further filled the data gap by providing nationwide, population-based incidence rates from Taiwan, which indicated that Taiwan (2.17 per million) had a 1.3-fold higher rate than that in the United States (1.6 per million) and 3.6-fold higher than that in Israel (0.6 per million).[1,15]

For extracranial and extragonadal GCTs (subgroup Xb), there was considerable apparent variation in the incidence by sex. The rate of all cases combined in Taiwan (3.68 per million) was 2-fold higher compared with that in the United States and Israel (1.6 and 1.5 per million, respectively).[1,15] This difference was more pronounced in males (3-fold to 4-fold higher than in the United States and Israel) than in females (about 1.4 times higher than in the United States and Israel).[1,15,16]

For gonadal GCTs (subgroup Xc), the incidence for all cases combined was similar to that in the United States (6.43 vs 6.7 per million) and was 1.5-fold higher than that in Israel (4.2 per million).[1,15] More significant differences in rates by sex also were observed.[1] The rate of testicular GCTs in Taiwan (6.61 per million) was 40% lower than that in the United States (9.5 per million) but higher than that in Israel (5.2 per million).[15,16] However, the rate of ovarian GCTs in Taiwan (6.22 per million) was 1.5-fold to 1.9-fold higher than that in both the United States and Israel (4.23 and 3.2 per million, respectively).[15,16]

We have demonstrated that there were striking geographic/racial differences in the incidence of germ cell neoplasms among Taiwanese (Han-Chinese) and the population of the United States (Caucasian) and Israel (Jewish), as indicated above. On the basis of a data set of 12,315 cases, we have demonstrated that cancer incidence among children and adolescents in Taiwan increased significantly by an average 1% per year from 1995 through 2009. This increase could be represented by changes in the ASR from 128.2 per million observed during 1995 to 1999 and 137.7 during 2000 to 2004 to 142.8 during 2005 to 2009. Overall incidence has increased in both sexes. One of the debatable points is whether these trends truly increased or are a result of general improvements in the completeness of cancer registration or advances in diagnostic technology. The dramatic decline in the DCO% (10%) and the slight increase in MV% (2%) in this analysis suggest that the possibility cannot be excluded that improvements in ascertainment of all data sources and advanced diagnostic procedures resulted in the overall increase. Although such improvements may play a role, our findings could not be fairly interpreted by this reasoning. First, not all cancer groups had increased incidence. Second, the average increase has been faster in females (APC, 1.1%) than in males (1.0%), although the baseline cancer incidence was higher in males. The finding that rates increased disproportionately to the baseline rates contradicted the hypothesis of the improvements mentioned above that were expected to proportionately affect all cancer type-specific and sex-specific patient groups.[25] Furthermore, the small numbers of cases in ICCC group XII over the study period (average, 0.9% annually), along with the absence of a time trend, also provided no evidence supporting a role for improvements in cancer registration in the overall increase.[25] On the basis of these findings, we concluded that the basic indicators of data quality only marginally influenced the incidence trends.

Several limitations need to be considered regarding this analysis. First, the World Health Organization introduced a new system for classifying hematopoietic neoplasms in 2001,[26] and cases that were coded in the *International Classification of Diseases for Oncology, Second Edition* (ICD-O-2) were converted to the ICD-O-3 for World Health Organization subtype assignment.[27] Because myelodysplastic syndromes and other myeloproliferative diseases are considered malignant in the ICD-O-3 but not in the ICD-O-2, increases in the incidence rates of these conditions after 2001 may be the consequence of these changes. Second, data from most countries also include benign brain/CNS tumors[5,15,17,18]; however, our analysis was similar to that conducted in the United States, which was based on data from malignant tumors only,[16] possibly resulting in lower incidence rates for some cancers (ICCC groups III and Xa), and comparison with other countries was difficult. In addition, the methods of standardization for incidence rates were different between countries (eg, as indicated in Table 3, the US and Canadian studies used their own standard populations, which varied by year, but the results from Japan were not standardized). Furthermore, because Japan was the only country that conducted mass screening for neuroblastoma from 1984 to March 2004, the incidence of neuroblastoma would be expected to be higher during that period. Accordingly, these factors should be taken into

consideration when judging the incidence variations between countries.

In conclusion, based on our data, we attribute the observed increases in incidence rates marginally to improvements in case ascertainment and diagnostic procedures. Numerous risk factors and genetic factors are not well understood but may contribute to the observed changes. This analysis highlights the differences in incidence patterns by country. The rates of hepatic tumors and germ cell neoplasms in Taiwan were higher and deserve further investigations to elucidate the interplay of genetics and environmental risk factors. These population-based data were extremely important in promoting our understanding of the differences in these cancers by age, sex, histologic type, and primary site and the variations in incidence over time. These results may help to enhance the level of public discourse and may lay the groundwork for further research into the causes of these cancer trends.

FUNDING SUPPORT

This study was supported by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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