Childhood Cancer Incidence and Survival in Thailand: A Comprehensive Population-Based Registry Analysis, 1990-2011

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Abbreviation	**Full Term**
LMICs	Low- and middle-income countries
ThaiPOG	Thai Pediatric Oncology Group
DCO	Death Certificate Only
ICCC	International Classification of Childhood Cancer
%MV	Percent of morphologically verified cases
%DCO	Percent of cases verified by death certificate verification only
ASR	Age-standardized incidence rate
IRR	Incidence rate ratio
APC	Annual percent changes

ABSTRACT

Background: Southeast Asia is undergoing a transition from infectious to chronic diseases, including a dramatic increase in adult cancers. Childhood cancer research in Thailand has focused predominantly on leukemias and lymphomas or only examined a short period of time. This comprehensive multi-site study examined childhood cancer incidence and survival rates in Thailand across all international classification of childhood cancer (ICCC) groups over a 20-year period.

Methods: Cancer cases diagnosed in children ages 0-19 years (n=3,574) from 1990-2011 were extracted from five provincial population-based Thai registries, covering approximately 10% of the population. Descriptive statistics of the quality of the registries were evaluated. Age-standardized incidence rates were calculated using the Segi world standard population, and relative survival was computed using the Kaplan-Meier method. Changes in incidence and survival were analyzed using Joinpoint Regression and reported as annual percent changes (APC).

Results: The age-standardized incidence rate of all childhood cancers during the study period was 98.5 per million person-years with 91.0 per million person-years in 1990-2000 and 106.2 per million person-years in 2001-2011. Incidence of all childhood cancers increased significantly (APC=1.2%, $p<0.01$). The top three cancer groups were leukemias, brain tumors, and lymphomas. The 5-year survival for all childhood cancers significantly improved from 39.4% in 1990-2000 to 47.2% in 2001-2011 ($p<0.01$).

Conclusions: Both childhood cancer incidence and survival rates have increased, suggesting improvement in the healthcare system as more cases are identified and

treated. Analyzing childhood cancer trends in low- and middle-income countries can improve understanding of cancer etiology and pediatric healthcare disparities

INTRODUCTION

While childhood cancer remains relatively rare compared to adult cancers, a childhood cancer diagnosis is a major medical and psychological stressor with lifelong impacts, even in the context of increasing survival rates. Whereas comprehensive registries in many high-income countries capture incidence and survival rates, global incidence and survival rates of childhood cancers remain less well understood. A global study of childhood cancers across 62 different regions found that the age-standardized incidence rate (ASR) was 140.6 per million person-years in children 0-14 years, with the most common cancers being leukemias, central nervous system tumors, and lymphomas.[1] The ASR increased from 124.0 per million person-years in the 1980s to 140.6 per million person-years in years 2001-2010.[1] Over 90% of deaths due to childhood cancer occur in low- and middle-income countries (LMICs), illustrating how countries with limited resources are confronted with major healthcare challenges in treating pediatric cancer.[2,3] Additionally, deaths due to childhood cancer are increasing in developing regions.[4] While 80% of young patients with cancer in Africa are likely to die, 80% in high-income countries survive.[5] A combination of factors, including later diagnosis, limited access to imaging facilities and treatment options, and population-specific genetic and environmental risk factors likely contribute to this disparity between developed and developing countries.[5]

In recent decades, many LMICs—including Thailand—have undergone an epidemiologic transition, during which disease burden has largely shifted from infectious to chronic.[6] Many research efforts focus on adult cancer rates, but less is known about

pediatric cancers in Thailand. In 2001, pediatric oncologists formed the Thai Pediatric Oncology Group (ThaiPOG) to standardize treatment protocols for diagnosis and treatment of childhood cancers in Thailand.[7] ThaiPOG published a report of 999 new cancer cases from 20 cancer registry centers in 2003 with leukemias being the most commonly diagnosed cancer group (42.6% of the cases).[8] While this report provided a snapshot of the incidence of pediatric cancers during one year, the report could not elucidate trends of diagnoses or survival over time to better understand childhood cancer burden in Thailand.

Previous research has shown that overall incidence of childhood cancer in Thailand was lower than in high-income countries, but incidence rates increased 32.5% from 1988-1994 to 1995-1997.[9] Similar to other regions in the world, leukemias, brain tumors, and lymphomas made up the majority of the cases, and there was a peak for incidence between ages 1 and 5 years.[1,9,10] Leukemia incidence and survival rates in southern Thailand increased between 1990 and 2011 but remained lower than in the United States.[11] As Thailand continues to develop and disease burden shifts to non-communicable illnesses, cancer trends may become increasingly similar to high-income regions. Understanding these changing trends and disparities in childhood cancer between developed countries and LMICs may provide insights to biological and environmental causes of pediatric cancers, resulting in greater potential to influence clinical guidelines and health policy.

The present study reports the overall burden of all childhood cancer (cases occurring in children ages 0-19) in Thailand from 1990 to 2011. By analyzing both incidence and survival trends from registry data for all cancer cases by sex, age group, and cancer type, we can better understand the burden of childhood cancer in Thailand and predict future diagnostic and survival rates.

METHODS

Study population

Childhood cancer cases diagnosed between 1990 and 2011 were extracted from five population-based cancer registries in Thailand located in Chiang Mai, Lampang, Khon Kaen, Songkhla, and Surat Thani (Fig. 1). In each hospital or medical center that contributed to these registries, cases were determined from medical records, pathology reports, imaging reports, and hospital tumor registries using a nationally standardized form.[12] These data forms were checked for duplication and entered into a database using the International Association of Cancer Registry's CanReg software program.[12]

Thailand cancer registries utilize both active and passive follow-up methods and track the vital status of cases from the hospital at which they were treated. [12] Children may move outside the original catchment area, so unique national personal identification numbers are used to track patients. In addition to registry-based diagnosis data, mortality records and the national death registry from Provincial Chief Medical Offices at the Ministry of Public Health were used to supplement case information.[12] Death certificates were reviewed and matched with case records at each registry, and cases that were unable to be traced were registered as diagnosed by death certificate only (DCO).[13]

Data extraction and variables

Childhood cancer cases were identified using ICD-O-3 histology and site codes and categorized into international classification of childhood cancer (ICCC) groups.[14] Twelve ICCC groups were included: leukemias, lymphomas, brain and spinal neoplasms, neuroblastomas, retinoblastomas, renal tumors, hepatic tumors, malignant bone tumors, soft

tissue sarcomas, gonadal and germ cell tumors, malignant epithelial tumors and melanomas, and other and unspecified malignant neoplasms.[15] For each case, the data contained a registry identification number, date of birth, age, sex, date of diagnosis, date of last contact (alive or dead), site of cancer, histology, method of diagnosis, extension of cancer, and number of primary tumors.[12]

Population denominator data for incidence rate calculations came from the Thailand population censuses in 1990, 2000, and 2010 conducted by the National Statistical Office. These censuses provided annual estimates by age group (0-4, 5-9, 10-14, and 15-19 years) and sex in Thailand.[13] In between census years, populations were estimated using a log-linear function between the two adjacent census values, and populations beyond 2010 were estimated and reported by the Office of the National Economic and Social Development Board.[16]

Statistical analysis

Data quality was measured as the percentage of cases morphologically verified (%MV), meaning cases diagnosed based on histology results, and as the percentage of death certificate only (%DCO) cases.[12] Since data from Surat Thani were only available in years 2001-2009, sensitivity analyses were conducted both with and without these cases to determine the effect on incidence and survival trends.

Descriptive analyses, including case counts and age-specific rates, were conducted to evaluate the distribution of childhood cancer types. Age-standardized incidence rates (ASRs) were calculated for each cancer group and were standardized using the Segi world standard population estimates. Incidence rates are presented in cases per million by decade

of diagnosis, sex, and age at diagnosis. Incidence rate ratios (IRRs) were used to compare the ASRs.

Analysis of incidence trends was completed using Joinpoint Regression Program version 4.0.4. This allowed for examination of trends using log-linear models and computed annual percent changes (APC) in age-standardized incidences. Permutation tests determined the appropriate number of joinpoints (years of trend change), the slope of trends between joinpoints, and significance. The Joinpoint Regression Program does not allow for years with zero case counts. Therefore, if no cases were present for a given year, a half-case was added to the age group with the largest population.[11] If more than three half-case corrections were needed for a given ICCC group or subgroup, the APC was not computed.

Relative survival was evaluated using mortality and life tables from the National Statistics Office in Thailand from 1990 to 2011. Survival analyses excluded cases if their basis of diagnosis was death certificate only or unknown, if they did not contain any follow-up information, or if they had an unknown vital status. To analyze relative survival rates, the survival package in R was used. Relative survival results were computed using the Ederer II method, and survival functions were produced by the Kaplan-Meier survival method. Log-rank tests compared relative survival by sex, decade of diagnosis, and age group. One- and five-year relative survival rates were computed for each ICCC group from 1990 to 2011. These relative survival trends were then analyzed using Joinpoint Regression under a piecewise linear model.

RESULTS

Data Quality

In total, 3,574 childhood cancer cases were reported between 1990 and 2011. The Chiang Mai registry contributed the largest proportion of cases (30.2%), while Surat Thani, the newest registry (with only nine years of data), contributed the fewest (6.8%) (Table 1). Including cases from Surat Thani did not significantly affect the trend analyses. Overall, 86.1% of the cases were verified histologically, and only 4.2% were diagnosed by death certificate only (DCO). Songkhla had the highest %MV at 89.9%, while Surat Thani had the lowest (%MV=75.4%). Between the first and second decade of diagnosis, case counts increased, morphologically verified cases increased by 1.2% and DCO cases decreased by about 1.1%. The youngest and oldest age groups (0-4 years and 15-19 years) contributed the most cases to the dataset (28.0% and 30.9%, respectively), while cases that were diagnosed at 5-9 years of age only contributed to 19.0% of the dataset. Case counts were highest for leukemias (34.8%), brain and spinal neoplasms (12.3%) and lymphomas (11.2%). After cases with ambiguous vital status or diagnosed by DCO or autopsy were removed, there were 3,379 cases (94.5% of the total cases) included in the survival analyses.

Incidence Analyses

The age-standardized incidence rate (ASR) from 1990 to 2011 for all cancer groups was 98.5 per million person-years (Table 2). Leukemias, brain and spinal neoplasms, and lymphomas were the three most prevalent cancer groups overall, with ASRs of 36.1, 12.0, and 10.3 cases per million person-years, respectively. Additionally, the age-specific incidence rates varied by age at diagnosis, with the greatest incidence rate in cases

diagnosed at 0-4 years (123.7 cases per million person-years) and the lowest age-specific incidence rate in patients diagnosed at 5-9 years (73.1 cases per million person-years). From the first decade (1990-2000) to the second decade (2001-2011), the ASR of all cancer groups combined increased from 91.0 to 106.2 per million person-years (Table 2). The IRR of childhood cancers diagnosed in the second decade compared to the first decade was 1.2 (95% CI: 1.1, 1.3).

In males, the overall ASR for all cancer groups was 104.8 per million person-years for the entire study period (Table 2). The three highest ICCC group ASRs among males were for leukemias, lymphomas, and brain and spinal neoplasms, with values of 40.8, 13.6, and 12.7 per million person-years, respectively. In females, the overall ASR for all cancer groups throughout the entire study period was 91.8 cases per million person-years. Leukemias, brain and spinal neoplasms, and gonadal/germ cell neoplasms had the highest ASRs for females, with values of 31.2, 11.4, and 8.6 per million person-years, respectively. Overall, the IRR of female cancer cases to male cancer cases was 0.8 (95% CI: 0.8, 0.9). The ASRs for neuroblastomas, soft tissue sarcomas, gonadal/germ cell tumors, and carcinomas and epithelial neoplasms were higher in females than males.

Based on Joinpoint Regression results, overall pediatric cancer incidence increased significantly by 1.2% (95% CI: 0.8, 1.7) each year (Table 3). Additionally, incidence of leukemias and gonadal and germ cell neoplasms increased annually, by 1.5% (95% CI: 0.5, 2.5) and 2.4% (95%CI: 0.1, 4.9). For all cancer groups combined, male and female incidence trends are parallel ($p>0.05$) , but they are not coincident ($p<0.01$). Joinpoint Regression analyses suggested multiple trends to best fit the male incidence data. While early years in the study period fluctuated between decreasing and increasing trends, the only significant trend was an annual increase of 8.0% in years 2007-2011 (95% CI: 0.6, 15.9). Overall, the average APC for males 1990-2011 was 1.8 (95% CI: -0.9, 4.5).

Leukemias and gonadal and germ cell neoplasms both increased significantly for males, with an annual increase of 1.6% (95% CI: 0.3, 3.0) and 5.3% (95% CI: 1.3, 9.6). In females, the APC was 1.0% (95% CI: 0.3, 1.7). Leukemias were the only ICCC group for females that showed a significant annual change, with an increase of 1.4% per year (95% CI: 0.1, 2.7). While both males and females had significant annual increases in incidence of leukemias, the trends were not coincident ($p<0.01$).

Survival Analyses

The five-year relative survival for all childhood cancers was 43.1% (95% CI: 41.1, 45.2) (Table 4). The highest and lowest five-year relative survival rates were for renal tumors at 71.1% (95% CI: 61.1, 82.7) and neuroblastomas at 20.6% (95% CI:12.7, 33.3), respectively. Relative survival significantly increased ($p<0.01$) from the first decade (39.4%, 95% CI: 36.7, 42.2) to the second decade (47.2%, 95% CI: 44.3, 50.3). Five-year relative survival was higher in 2001-2011 than 1990-2000 for all ICCC groups except brain and spinal neoplasms, gonadal and germ cell tumors, and bone tumors. However, in all groups and subgroups with lower survival in the second decade, the change was not significant. The one-year survival rate for all childhood cancers was 70.1% (95% CI: 68.5, 71.8) (Supplementary Table S1), with higher one-year survival rates in the second decade (73.5% (95% CI: 71.4, 75.7)) compared to the first decade (66.1% (95% CI: 63.6, 68.6)) and higher survival rates in females (72.4% (95%CI: 70.1, 74.8)) compared to males (68.2% (95% CI: 65.9, 70.5)).

Five-year relative survival of all ICCC groups combined was relatively the same for all age groups, ranging from 40.7% (95% CI: 36.2, 45. 7) for 5-9 years at diagnosis to 44.4% (95% CI: 40.7, 48.4) for 0-4 years at diagnosis. Age groups 0-4 years showed a significant

improvement in survival change per year (Supplementary Table S2). One-year relative survival increased 1.3% each year (95% CI: 0.8, 1.8) for cases diagnosed at 0-4 years; and five-year relative survival increased 1.0% each year (95% CI: 0.4, 1.7) for the same age group. Relative survival was coincident between age groups 0-4 and 15-19 years and between age groups 5-9 and 10-14 years.

The relative survival of females for all ICCC groups combined was significantly higher than for males ($p<0.01$). For all cancer groups combined, females had a relative five-year survival of 49.2% (95% CI: 46.3, 52.5) while males had a relative survival of 37.7% (95% CI: 35.0, 40.5) (Table 4). One-year and five-year relative survival rates in both males and females increased significantly per year (Fig. 2). One-year survival increased by 0.8% per year (95% CI: 0.4, 1.2) for males and increased by 0.7% per year (95% CI: 0.3, 1.2) for females when examining the full years of follow-up data (Supplementary Table S2). Five-year survival increased by 1.1% per year (95% CI: 0.3, 1.8) for males and 0.9% per year (95% CI: 0.1, 1.7) for females. We observed that survival trends between males and females were parallel ($p>0.05$), meaning both male and female trends have similar slopes. However, the trends between males and females for all survival intervals were not coincident or equal ($p<0.05$). Therefore, despite the difference in survival rates for males and females, the changes to survival trends were occurring similarly in males and females. When analysis of survival was restricted to the 1990-2006 cohort, which has full five-year follow-up, we observed similar and consistent results (Supplementary Table S2).

DISCUSSION

Using data from five high-quality population-based cancer registries in Thailand, we report incidence and survival rates of cancer in children ages 0-19 years from 1990 to 2011. Over 86.1% of the cases were verified histologically, indicating the robust data quality of the cancer registries. The overall ASR for all cancer groups was 98.5 cases per million person-years, and the top three cancer groups were leukemias, brain tumors, and lymphomas. Cancer incidence increased significantly each year during the study period. Five-year relative survival across all cancers was 43.1%, with females typically having higher rates of survival than males. One-year and five-year relative survival rates were generally increasing from the first to second decade, with significant gains in each leukemia subgroups (ALL, AML, unspecified), Burkitt's lymphoma, overall lymphomas ICCC gorup, and other and unspecified neoplasms. The few cancer groups that showed decreasing trends in survival were not statistically significant.

Leukemias contribute roughly one-third of the pediatric cancer cases in Thailand. ALL is most common, with an ASR of 22.2 per million person-years, and AML has an ASR of 7.8 per million person-years. Both AML and ALL incidence rates were increasing significantly per year, but AML was increasing at a faster rate (APC: 2.63%, 95% CI: 0.31, 5.01) compared to ALL (APC: 1.35%, 95% CI: 0.13, 2.58). Similar to incidence trends, the 5-year relative survival was higher in ALL at 44.2% (95%CI: 40.0, 48.7) than AML at 22.1% (95% CI: 17.0, 28.8). Both ALL and AML survival rates were increasing significantly by decade of diagnosis ($p<0.05$).

Germ cell tumor incidence showed a significant increase in the male population, with an APC of 5.3%. While our analysis is unable to draw conclusions about the cause of this increase in only the males, we cannot rule out that these cases were previously undetected and therefore underreported in earlier time periods.

A previous Thai study examining data between 1995-1997 found comparable rates of incidence.[9] This study used data from four of the same registries (Khon Kaen, Chiang Mai, Lampang, and Songkhla) but also included an additional registry in Bangkok. We elected not to utilize the Bangkok registry due to the fluidity of the population and difficulty in obtaining accurate underlying population estimates. Similar to the findings in this study, leukemias, central nervous system neoplasms, and lymphomas were the most common childhood cancers. Additionally, an examination of childhood leukemia in Songkhla and the United States showed similar incidence rates and trends as our report of Thai registries.[11] The population composition in Songkhla is unique compared to other regions; select religious groups in this region show significantly different rates of adult cancer.[17] Population and cultural factors such as these may impact incidence and survival.

Thai childhood cancer rates were similar to those in other Asian countries. In Taiwan, the ASR for all childhood cancers cases diagnosed 1996-2010 in children 0-14 years was 121.7 per million, and, in China, childhood cancer patients diagnosed 2000-2010 ages 0-14 years had an ASR of 87.1 per million.[18,19] The ASR in Taiwan has been increasing at the same rate as in Thailand, 1.2% per year, while China's childhood cancer incidence rate is increasing at 2.8% annually.[18,19] A global study evaluating 5-year survival rates of childhood leukemia patients found that patients in Thailand have lower survival rates than comparable populations in Taiwan, Japan, Malaysia, Korea, and India.[20]

Despite the increases in both incidence and survival in Thailand, high-income countries, including the United States, continue to show higher childhood cancer incidence and survival rates.[1,11] The lower incidence in Thailand may be driven by lack of access to diagnostic and imaging facilities and other shortages in healthcare resources. Not only does childhood cancer infrastructure differ between developed and developing countries, but there

are also clinical training and awareness differences which may prime physicians in high-income countries to look for signs of cancer earlier than physicians in developing countries.

While the ecological nature of a registry analysis does not provide opportunity for evaluation of potential risk factors, making us unable to discern if evolving trends are due to changes in risk factors, diagnostic factors, or external causes, the registry data did offer a large sample size covering several years. The registries may have been less precise in the first decade compared to the second decade, but including data over a longer period of time allows for more robust trend analysis. Additionally, establishment of population-based cancer registries and a network of cancer surveillance systems has been a priority of the Thai government. These registries have been working to identify cases from their regional hospitals, outpatient care centers, and diagnostic labs for multiple decades. The data has a low rate of death certificate only cases and a high rate of histologically confirmed cases, indicating high-quality data. It is also possible that registries missed cases. However, this was minimized by two factors: 1) Thailand offers universal healthcare, so most Thai citizens are likely to use some form of health services, and 2) registry data were collected from several different sources to optimize case ascertainment.

Increasing childhood cancer incidence and survival rates may suggest improvements in pediatric cancer detection, diagnosis, and treatment. Thailand also experienced several socioeconomic changes during the study period, including the introduction of universal healthcare, which may positively impact case reporting and treatment. Following the adoption of universal healthcare, utilization of health services in Thailand has increased, specifically for low-income, unemployed, or chronically-ill patients.[21] Patient populations who may have previously gone undetected are more likely to seek healthcare services. Other changes, such as increasingly Westernized diets and automobile pollution, could also be impacting incidence rates. With mortality and morbidity burden related to childhood cancer

increasing worldwide, it is important to better understand disease trends to effectively diagnose and treat those affected by the range of childhood cancers. This work provides the foundation for understanding the burden of childhood cancer in Thailand, and registry analyses will continue to offer insights to cancer diagnosis and treatment programs.

While our work contributes to understanding the incidence and survival of childhood cancer in Thailand, future investigations of specific risks and nuances of different cancer types may clarify causal links. Future research in LMICs should continue to examine risk factors for cancer occurrence and death, as well as examine predictors of late sequelae of treatment, to broaden the knowledge of global childhood cancer and improve medical protocols worldwide.

CONFLICT OF INTEREST STATEMENT

The authors certify that they have no affiliations with or involvement in any organization that has financial or non-financial interest in the subject matter discussed in this manuscript.

There are no conflicts of interest to report.

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LEGENDS

TABLE 1 Case counts, case frequencies, and quality of registry data by descriptive factors.

TABLE 2 Age-specific and age-standardized incidence rates (ASRs) for ICCC groups and subgroups. Incidence by age at diagnosis was calculated using age-specific rates, while overall incidence, incidence by decade of diagnosis, and incidence by sex were calculated using age-standardized rates. ASRs are represented as rates per million person-years.

TABLE 3 Annual percent change (APC) in incidence by ICCC group, subgroup, and sex. APC (% (95% CI)) was evaluated using log-linear models from Joinpoint Regression analyses. An asterisk (*) denotes a p-value <0.05 and 0.5 cases were added to age groups with the largest population when there were no cases of that ICCC group or subgroup for a given year. If more than three 0.5-case corrections were needed, the APC was not computed.

TABLE 4 Five-year relative survival (% (95% CI)) for ICCC groups and subgroups. Relative survival was calculated using the Kaplan-Meier method. Overall five-year relative survival is shown for ICCC groups and subgroup along with five-year relative survival by age at diagnosis, decade of diagnosis, and sex.

FIGURE 1 Map of Thailand showing the five provinicial population-based registries from which childhood cancer cases diagnosed 1990-2011 were extracted.

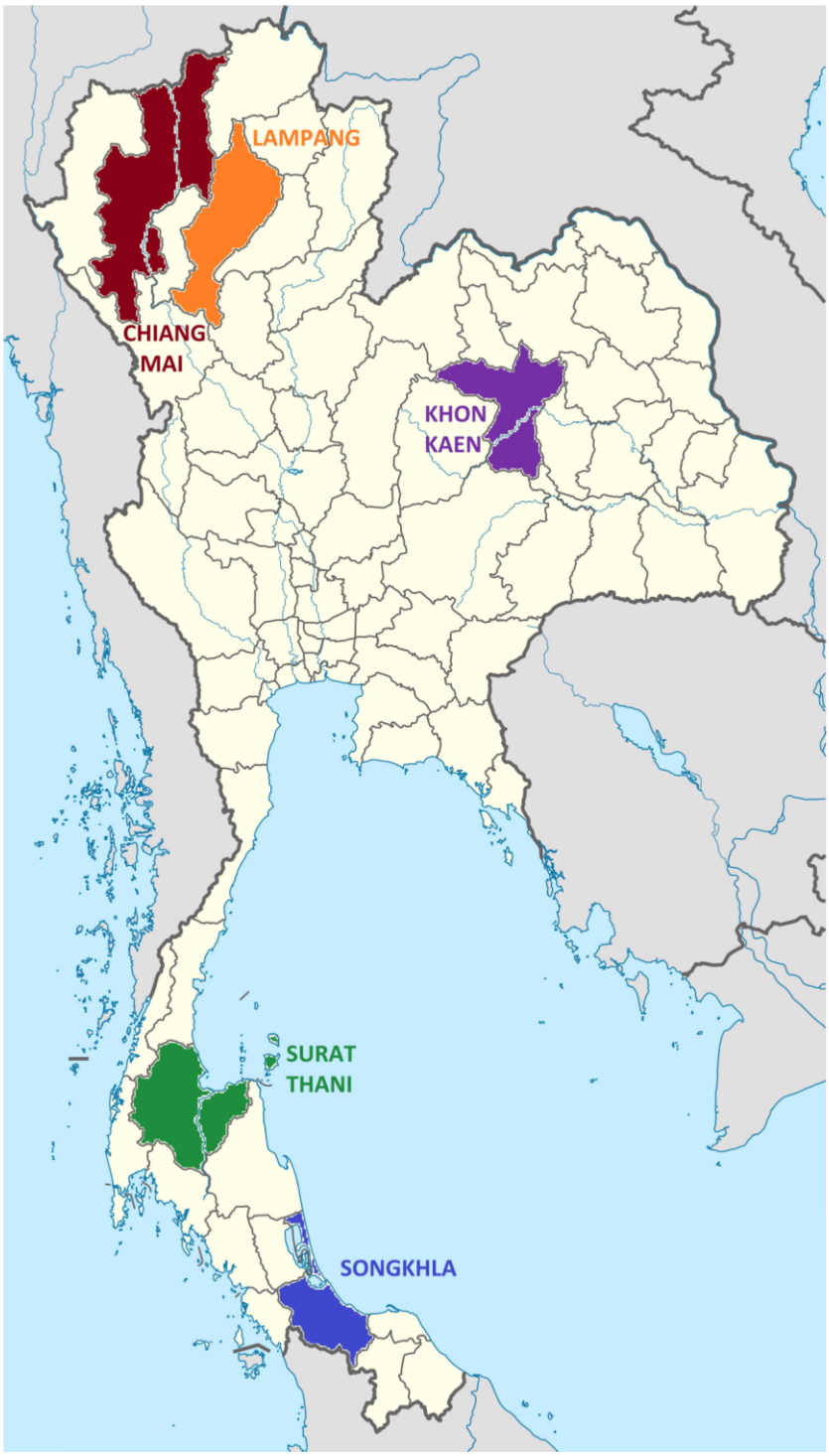
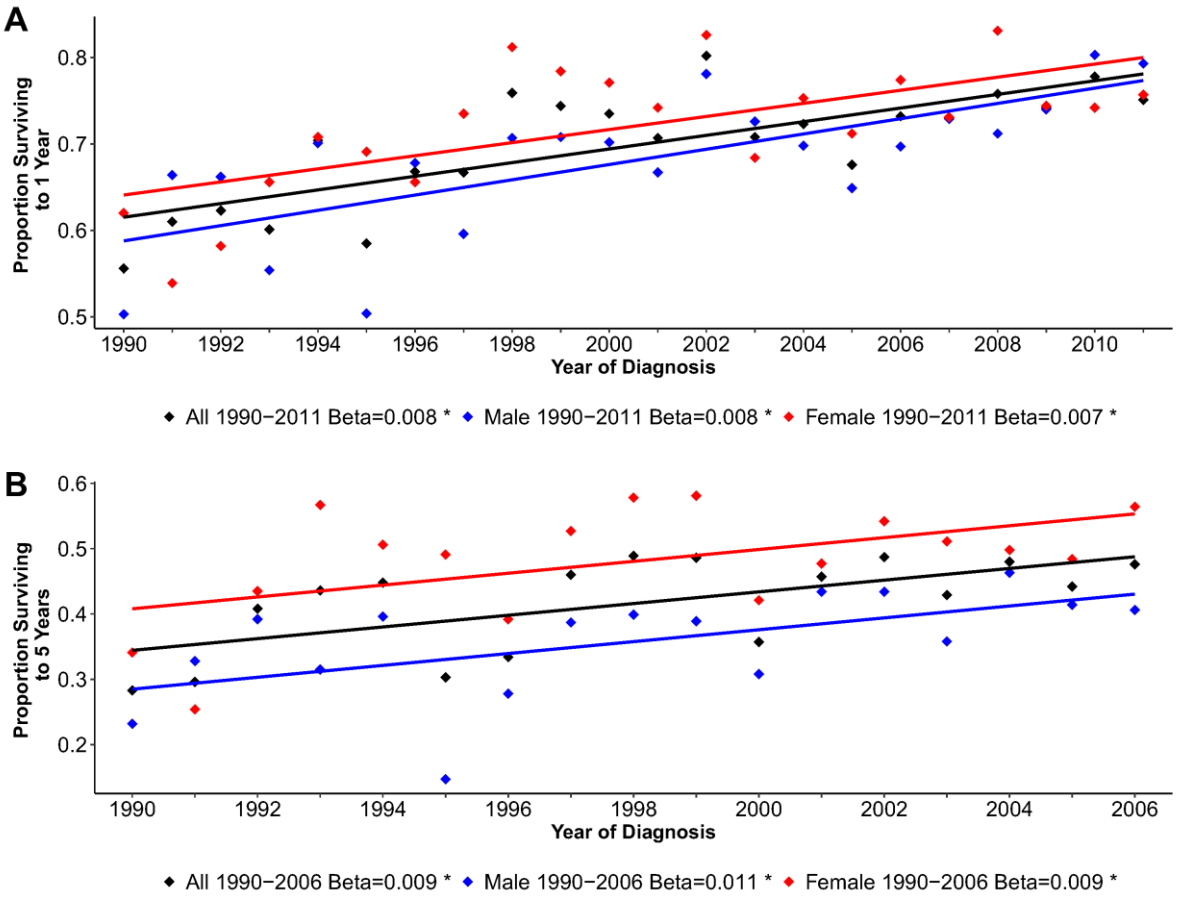


FIGURE 2 Relative survival rates of all ICCC groups combined are shown for males, females, and both sexes together. Blue denotes males, red denotes females, and black denotes both sexes combined. Beta values represent the amount of change in survival per year. One-year relative survival (A) and five-year relative survival (B) are both significantly increasing per year for males, females, and both sexes together. An asterisk (*) denotes a p-value <0.05.



SUPPLEMENTARY TABLE S1 One-year relative survival (% (95% CI)) for ICCC groups and subgroups. Relative survival was calculated using the Kaplan-Meier method. Overall one-year relative survival is shown for ICCC groups and subgroup along with one-

year relative survival by age at diagnosis, decade of diagnosis, and sex.

SUPPLEMENTARY TABLE S2. One- and five-year relative survival (% (95% CI)) by sex and age at diagnosis with full (1990-2011) and restricted (1990-2006) cohorts. The percent change in one- and five-year relative survival per year is shown for the restricted cohort (A), in which one-and five-year survival have the same follow-up years. Relative survival by sex is also shown using the full cohort, in which all available follow-up data are used for one-year survival (B). Percent change in relative survival per year by age group at diagnosis is also shown with the restricted cohort (C) and with the full cohort (D).

TABLE 1 Case counts, case frequencies, and quality of registry data by descriptive factors

	Cases	(%)	%MV[1]	%DCO[2]
Registry				
Chiang Mai	1,080	30.2	87.1	2.7
Khon Kaen	970	27.1	84.4	3.8
Lampang	435	12.2	86.2	4.6
Songkhla	845	23.6	89.9	3.9
Surat Thani	244	6.8	75.4	12.7
Sex				
Male	1,939	54.3	86.2	4.6
Female	1,635	45.7	86.1	3.7
Decade of Diagnosis				
1990-2000	1,645	46.0	85.5	4.8
2001-2011	1,929	54.0	86.7	3.7
Age at Diagnosis (Years)				
0-4	1,002	28.0	87.1	3.9
5-9	678	19.0	86.0	4.0
10-14	790	22.1	86.7	4.1
15-19	1,104	30.9	85.0	4.7
ICCC[3] Group				
Leukemias	1,245	34.8	98.6	1.4
Lymphomas	402	11.2	99.8	0.2
Brain and Spinal Neoplasms	440	12.3	58.0	6.8
Neuroblastomas	96	2.7	99.0	0.0

Retinoblastomas	76	2.1	98.7	0.0
Renal Tumors	94	2.6	81.9	1.1
Hepatic Tumors	78	2.2	48.7	9.0
Malignant Bone Tumors	190	5.3	91.6	3.7
Soft Tissue Sarcomas	178	5.0	100.0	0.0
Gonadal and Germ Cell Neoplasms	248	6.9	93.1	0.0
Malignant Epithelial Neoplasms	307	8.6	99.7	0.0
Other and Unspecified Neoplasms	220	6.1	0.1	39.1
All Registries, 1990-2011	3,574	100.0	86.1	4.2

[1] %MV is the percent of cases morphologically verified

[2] %DCO is the percent of cases diagnosed by death certificate only

[3] International Classification of Childhood Cancer

TABLE 2 Age-specific and age-standardized incidence rates (ASRs) for ICCC groups and subgroups by age at diagnosis, decade of diagnosis, and sex

ICCC Group	Overall[1]	Age at Diagnosis[2]				Decade of Diagnosis[1]				Sex[1]			
		0-4 Years	*5-9 Years*	*10-14 Years*	*15-19 Years*	*1990-2000*	*2001-2011*	**IRR**	**95% CI**	*Male*	*Female*	**IRR**	**95% CI**
I. LEUKEMIA	36.1	55.9	31.4	27.7	23.3	33.4	38.9	1.2	1.0, 1.3	40.8	31.2	0.7	0.7, 0.8
Acute lymphoblastic leukemia	22.2	37.2	22.8	14.9	8.9	21.2	23.2	1.1	1.0, 1.3	25.8	18.5	0.7	0.6, 0.8
Acute myeloid leukemia	7.8	9.5	5.4	8.0	7.9	6.3	9.2	1.4	1.1, 1.8	8.2	7.4	0.9	0.7, 1.1
Unspecified	4.8	8.4	2.6	3.2	4.2	4.8	4.9	1.0	0.7, 1.3	5.2	4.4	0.8	0.6, 1.1

II. LYMPHOMA	10.3	6.4	9.8	10.7	15.5	9.5	11.1	1.2	1.0, 1.5	13.6	6.8	0.5	0.4, 0.6
Hodgkin lymphoma	2.0	0.6	2.5	2.4	3.1	1.5	2.5	1.7	1.1, 2.7	3.1	1.0	0.3	0.2, 0.5
Non-hodgkin lymphoma	5.2	1.9	5.1	6.0	9.0	4.2	6.2	1.5	1.1, 2.0	6.5	3.8	0.6	0.4, 0.8
Burkitts lymphoma	0.9	1.2	1.4	0.5	0.4	0.9	1.0	1.1	0.6, 2.2	1.5	0.3	0.2	0.1, 0.5
Unspecified	1.4	0.9	0.6	1.6	2.7	1.7	1.0	0.6	0.3, 1.0	1.8	0.9	0.5	0.3, 0.9
III. BRAIN AND SPINAL NEOPLASMS	12	12.3	14.6	12	8.9	11.1	13.0	1.2	1.0, 1.4	12.7	11.4	0.9	0.7, 1.0
Astrocytomas	3.1	2.7	3.2	3.0	3.7	2.8	3.5	1.3	0.9, 1.9	3.1	3.2	1.0	0.7, 1.4
PNETs and medulloblastoma	2.8	3.8	3.4	2.8	0.5	2.8	2.7	1.0	0.6, 1.5	3.1	2.4	0.7	0.5, 1.1
Unspecified	5.0	4.3	6.7	5.0	3.9	4.9	5.1	1.1	0.8, 1.4	5.3	4.6	0.8	0.6, 1.1
IV. NEUROBLASTOMA	3.2	8.2	2.0	0.5	0.6	3.5	2.9	0.8	0.6, 1.2	2.7	3.7	1.3	0.9, 1.9
V. RETINOBLASTOMA	2.7	8.5	0.6	0.1	0.0	2.5	3.0	1.2	0.8, 1.9	2.7	2.8	1.0	0.6, 1.6
VI. RENAL TUMORS	3.2	9.0	1.5	0.2	0.5	2.5	4.0	1.6	1.0, 2.4	3.2	3.3	1.0	0.7, 1.5
VII. HEPATIC TUMORS	2.2	3.3	1.4	0.9	2.9	2.2	2.2	1.0	0.6, 1.5	2.9	1.5	0.5	0.3, 0.8
VIII. MALIGNANT BONE TUMORS	4.5	1.1	2.0	7.7	8.7	4.4	4.7	1.1	0.8, 1.4	5.3	3.8	0.7	0.5, 0.9
IX. SOFT TISSUE SARCOMAS	4.8	5.3	2.7	4.3	6.8	4.3	5.2	1.3	0.9, 1.7	4.5	5.1	1.1	0.8, 1.5
Rhabdomyosarcoma	1.8	3.2	1.2	1.4	1.2	2.0	1.7	0.9	0.5, 1.5	1.9	1.7	0.9	0.5, 1.5

Other specified	1.7	1.2	1.0	1.4	3.6	1.3	2.1	1.5	0.9, 2.5	1.3	2.1	1.6	1.0, 2.6
X. GONADAL AND GERM CELL NEOPLASMS	6.2	3.8	2.4	6.7	13.0	5.5	6.8	1.2	0.9, 1.6	3.8	8.6	2.2	1.7, 2.9
XI. CARCINOMAS AND EPITHELIAL NEOPLASMS	7.2	1.7	2.4	7.2	20.0	6.5	8.0	1.2	1.0, 1.6	6.1	8.3	1.3	1.1, 1.7
XII. OTHER AND UNSPECIFIED NEOPLASMS	6.0	8.0	2.3	4.3	9.2	5.6	6.4	1.2	0.9, 1.5	6.7	5.3	0.8	0.6, 1.0
All Cancer Groups	98.5	123.7	73.1	82.2	109.4	91.0	106.2	1.2	1.1, 1.3	104.8	91.8	0.8	0.8, 0.9

[1] Age-standardized incidence rates calculated per 1,000,000 person-years

[2] Age-specific incidence rates

TABLE 3 Annual percent change (APC) in incidence by ICCC group, subgroup, and sex

ICCC Group	**Overall** APC (95% CI)	**By Sex** APC (95% CI)	
		Males	*Females*
I. LEUKEMIA	1.5* (0.5, 2.5)	1.6* (0.3, 3.0)	1.4* (0.1, 2.7)
Acute lymphoblastic leukemia	1.4* (0.1, 2.6)	1.3 (-0.2, 2.8)	1.7 (-0.3, 3.6)
Acute myeloid leukemia	2.6* (0.3, 5.0)	2.9* (0.2, 5.8)	2.1 (-0.7, 5.0)
Unspecified	-1.6 (-4.5, 1.4)	-0.0 (-3.6, 3.7)	-2.6 (-6.4, 1.4)

II. LYMPHOMA	1.4 (-0.1, 2.9)	1.5 (-0.3, 3.3)	1.1 (-1.4, 3.7)
Hodgkin lymphoma	3.9* (1.1, 6.8)	2.5 (-0.4, 5.6)	N/A [1]
Non-Hodgkin lymphoma	3.5* (1.1, 6.0)	3.4*(0.6, 6.3)	4.1* (0.1, 8.1)
Burkitt lymphoma	-0.2 (-3.6, 3.4)	-1.5 (-5.3, 2.4)	N/A [1]
Unspecified	-5.8* (-8.8, -2.7)	-4.2* (-7.5, -0.7)	N/A [1]
III. BRAIN & SPINAL NEOPLASMS	0.6 (-1.1, 2.3)	1.2 (-0.7, 3.4)	0.2 (-2.5, 3.0)
Astrocytomas	1.8 (-0.5, 4.1)	4.9* (1.3, 8.6)	0.7 (-4.2, 5.9)
PNETs and medulloblastoma	0.3 (-3.0, 3.7)	1.3 (-2.9, 5.7)	-1.2 (-5.3, 3.1)
Unspecified	-1.2 (-3.7, 1.5)	-1.9 (-5.0, 1.4)	-0.4 (-4.0, 3.4))
IV. NEUROBLASTOMA	0.1 (-2.8, 3.0)	-1.8 (-6.9, 3.5)	0.4 (-2.2, 3.1)
V. RETINOBLASTOMA	0.5 (-2.9, 4.0)	4.4 (-1.1, 10.2)	-2.2 (-6.5, 2.3)
VI. RENAL TUMORS	2.5 (-2.0, 7.2)	2.0 (-2.7, 6.9)	2.8 (-2.3, 8.1)
VII. HEPATIC TUMORS	-1.6 (-5.2, 2.0)	0.4 (-4.4, 5.5)	-2.4 (-7.6, 3.1)
VIII. MALIGNANT BONE TUMORS	0.7 (-1.7, 3.1)	-0.5 (-4.0, 3.2)	1.4 (-2.6, 5.7)
IX. SOFT TISSUE SARCOMAS	1.2 (-0.7, 3.1)	-0.2 (-3.4, 3.2)	1.6 (-2.3, 5.7)
Rhabdomyosarcoma	-0.3 (-3.9, 3.5)	N/A [1]	0.2 (-4.0, 4.5)
Other specified	4.0* (0.5, 7.6)	N/A [1]	4.0* (-0.1,

			8.2)
X. GONADAL & GERM CELL NEOPLASMS	2.4* (0.1, 4.9)	5.3* (1.3, 9.6)	1.1 (-1.3, 3.7)
XI. CARCINOMAS & EPITHELIAL NEOPLASMS	1.9 (-0.1, 3.9)	1.8 (-1.6, 5.3)	1.8 (-0.9, 4.5)
XII. OTHER & UNSPECIFIED NEOPLASMS	0.6 (-1.9, 3.2)	0.8 (-2.7, 4.4)	-0.8 (-3.8, 2.3)
All Cancer Groups	1.2 (0.8, 1.7)	1990-1999: -1.0 (-2.9, 0.9) 1999-2003: 6.0 (-3.8, 16.7) 2003-2007: -2.1 (-10.6, 7.3) 2007-2011: 8.0* (0.6, 15.9)	1.0 (0.3, 1.7)

* $p < 0.05$

[1]More than three half-case corrections would be needed for years without any cases, so APC was not computed

TABLE 4 Five-year relative survival (% (95% CI)) for ICCC groups and subgroups by age at diagnosis, decade of diagnosis, and sex

ICCC Group	Overall	Age at Diagnosis				Decade of Diagnosis		Sex	
		0-4	*5-9*	*10-14*	*15-19*	*1990-2000*	*2001-2011*	*Male*	*Female*
I. LEUKEMIAS	36.5 (33.4, 40.0)	44.0 (38.7, 50.0)	37.3 (31.0, 44.8)	35.0 (28.6, 42.7)	22.4 (16.7, 30.0)	30.6 (26.7, 35.1)	43.7 (38.9, 49.0)	34.3 (30.2, 38.8)	39.7 (34.8, 45.2)
ALL	44.2 (40.0, 48.7)	48.6 (42.2, 55.9)	42.5 (34.9, 51.7)	49.4 (40.7, 59.9)	21.8 (13.3, 35.5)	38.3 (33.1, 44.2)	52.3 (46.0, 59.4)	41.4 (36.1, 47.4)	48.2 (41.9, 55.6)
AML	22.1 (17.0, 28.8)	23.6 (15.1, 36.9)	29.0 (17.4, 48.3)	16.3 (8.6, 30.8)	21.6 (13.5, 34.7)	16.0 (9.9, 25.8)	26.5 (19.5, 36.1)	20.2 (14.0, 29.1)	24.5 (16.9, 35.4)
Unspecified	29.7 (21.8, 40.3)	51.8 (38.0, 70.8)	17.5 (7.4, 41.6)	22.4 (9.5, 52.8)	14.6 (6.3, 33.8)	23.1 (14.7, 36.3)	39.3 (26.4, 58.4)	26.3 (16.7, 41.4)	32.9 (21.7, 49.7)
II. LYMPHOMAS	49.3 (43.3, 56.0)	57.7 (44.5, 74.8)	57.9 (45.7, 73.4)	52.1 (41.3, 65.6)	40.5 (31.8, 51.6)	44.0 (36.6, 53.0)	53.1 (43.9, 64.3)	47.8 (40.5, 56.6)	51.3 (42.1, 62.6)
Hodgkin lymphoma	67.8 (54.6, 84.3)	100.2 (100.2, 100.2)	75.3 (54.0, 105.0)	81.8 (60.9, 109.9)	53.4 (35.0, 81.7)	74.0 (57.2, 95.6)	60.6 (41.7, 88.0)	64.7 (50.1, 83.6)	89.0 (75.9, 104.3)
Non-Hodgkin lymphoma	46.6 (39.0, 55.5)	46.8 (28.1, 77.8)	48.3 (33.3, 70.0)	49.0 (35.6, 67.4)	43.8 (33.4, 57.4)	43.3 (33.3, 56.4)	49.1 (38.6, 62.4)	44.5 (35.1, 56.6)	49.3 (38.0, 64.1)
Burkitt lymphoma	41.8 (25.4, 68.8)	53.6 (29.9, 95.9)	64.2 (42.4, 97.3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	15.4 (5.1, 47.0)	77.0 (58.0, 102.4)	41.7 (24.1, 72.2)	33.3 (10.3, 108.2)
Unspecified	33.4 (21.0, 53.1)	57.3 (28.2, 116.7)	33.3 (10.3, 108.3)	35.2 (17.3, 71.7)	25.7 (12.2, 54.1)	30.5 (17.6, 52.8)	45.3 (24.8, 83.1)	35.7 (20.1, 63.5)	31.0 (14.9, 64.6)
III. BRAIN AND SPINAL NEOPLASMS	34.1 (29.0, 40.0)	20.0 (12.0, 33.4)	34.7 (26.1, 46.1)	40.3 (31.0, 52.4)	39.4 (28.6, 54.3)	36.7 (29.8, 45.3)	31.6 (24.7, 40.5)	32.4 (25.7, 40.8)	35.9 (28.7, 44.9)
Astrocytomas	34.5 (25.6,	27.5 (13.1, 58.1)	34.9 (19.3, 63.1)	40.3 (24.6, 66.1)	33.2 (18.8,	42.3 (29.6,	26.6 (16.0,	35.5 (23.3,	33.1 (21.7,

	46.4)				58.8)	60.3)	44.2)	54.0)	50.4)
PNETs and medulloblastoma	29.3 (20.6, 41.6)	19.4 (8.9, 41.9)	37.4 (22.9, 61.0)	35.0 (20.4, 60.1)	0.1 (0.0, 0.5)	31.2 (20.2, 48.1)	27.6 (15.8, 48.4)	28.8 (17.7, 46.7)	30.6 (18.8, 49.9)
Unspecified	32. (24.4, 42.4)	0.0 (0.0, 317.1)	32.4 (20.0, 52.6)	41.5 (27.6, 62.5)	36.5 (22.0, 60.7)	35.8 (25.5, 50.3)	28.7 (18.3, 45.0)	25.2 (16.3, 39.1)	40.8 (29.8, 55.9)
IV. NEUROBLASTOMAS	20.6 (12.7, 33.3)	21.5 (12.2, 38.0)	14.5 (4.8, 43.7)	100.2 (100.2, 100.2)	16.7 (4.2, 6.6)	15.9 (7.8, 32.4)	27.6 (151.2, 50.2)	9.0 (2.9, 27.5)	29.3 (17.9, 47.9)
V. RETINOBLASTOMAS	59.5 (47.9, 73.8)	58.7 (46.6, 74.0)	60.0 (32.1, 112.5)	100.1 (100.1, 100.1)	NA	57.2 (40.8, 80.2)	61.2 (46.7, 80.3)	53.1 (36.5, 77.2)	64.3 (49.9, 82.8)
VI. RENAL TUMORS	71.1 (61.1, 82.7)	78.9 (69.3, 90.0)	43.0 (20.8, 88.7)	50.0 (18.8, 133.3)	33.4 (10.3, 108.5)	62.9 (46.9, 84.5)	75.7 (63.9, 89.8)	79.8 (67.2, 94.9)	62.3 (48.3, 80.4)
VII. HEPATIC TUMORS	25.6 (15.7, 41.6)	35.9 (19.1, 67.2)	0.0 (0.0, 0.0)	37.6 (16.9, 83.7)	19.9 (8.8, 44.8)	25.8 (13.6, 48.9)	27.6 (15.2, 50.2)	30.1 (18.1, 50.3)	17.3 (6.5, 46.4)
VIII. MALIGNANT BONE TUMORS	27.4 (20.5, 36.7)	75.3 (52.0, 109.2)	12.9 (3.7, 44.9)	22.9 (13.7, 38.3)	28.9 (19.2, 43.5)	30.3 (21.0, 43.6)	23.3 (14.4, 37.9)	25.1 (17.1, 37.0)	30.7 (20.8, 48.5)
IX. SOFT TISSUE SARCOMAS	47.4 (38.1, 56.5)	41.5 (28.1, 61.3)	55.7 (34.1, 91.2)	49.1 (34.7, 69.5)	41.9 (28.5, 61.6)	43.4 (32.5, 58.0)	48.6 (37.2, 63.3)	39.3 (28.6, 54.2)	52.9 (41.5, 67.4)
Rhabdomyosarcoma	28.5 (18.7, 43.5)	35.5 (20.8, 60.7)	31.2 (12.3, 79.0)	20.9 (7.5, 58.4)	13.7 (3.7, 50.8)	29.6 (17.2, 51.2)	26.7 (13.9, 51.1)	23.4 (12.3, 44.4)	34.2 (20.0, 58.3)
Other specified	72.4 (59.7, 87.8)	55.8 (32.5, 95.8)	100.2 (100.2, 100.2)	75.9 (52.3, 110.1)	73.3 (57.9, 92.7)	63.7 (45.2, 89.8)	79.5 (65.5, 96.7)	67.4 (49.4, 91.9)	77.8 (62.9, 96.2)
X. GONADAL AND GERM CELL NEOPLASMS	64.5 (57.7, 72.0)	44.3 (27.4, 71.4)	78.7 (60.5, 102.5)	61.9 (49.7, 77.1)	67.7 (58.7, 78.1)	66.1 (57.1, 76.5)	63.4 (53.9, 74.6)	48.0 (35.9, 64.3)	70.8 (63.3, 79.4)
XI. MALIGNANT EPITHELIAL NEOPLASMS	61.1 (55.0, 67.9)	31.4 (14.2, 69.4)	57.7 (39.5, 84.2)	74.1 (62.9, 87.3)	58.5 (50.9, 67.3)	58.7 (50.3, 68.6)	63.4 (55.0, 73.2)	40.8 (32.0, 52.0)	75.6 (68.4, 83.6)
XII. OTHER AND UNSPECIFIED NEOPLASMS	51.9 (42.3, 63.7)	56.4 (42.0, 75.7)	62.6 (34.7, 112.8)	39.0 (18.2, 83.6)	50.9 (37.9, 68.4)	40.2 (27.1, 59.7)	59.2 (47.0, 74.7)	57.3 (44.5, 73.7)	45.4 (32.2, 63.9)
All Cancer Groups	43.1 (41.1,	44.4 (40.7,	40.7 (36.2,	44.3 (40.3,	42.5 (39.0,	39.4 (36.7,	47.2 (44.3,	37.7 (35.0,	49.2 (46.3,

45.2)	48.4)	45.7)	48.8)	46.4)	42.2)	50.3)	40.5)	52.2)