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Differences in Childhood Leukemia Incidence and Survival Between Southern Thailand and The United States: A Population-Based Analysis

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Background. Childhood leukemia incidence and survival varies globally, and this variation may be attributed to environmental risk factors, genetics, and/or disparities in diagnosis and treatment. ***Procedure.*** We analyzed childhood leukemia incidence and survival trends in children aged 0–19 years from 1990 to 2011 in Songkhla, Thailand (n = 316) and compared these results to US data from the Surveillance, Epidemiology, and End Results (SEER) registry (n = 6,738). We computed relative survival using Ederer II and estimated survival functions using the Kaplan–Meier method. Changes in incidence and 5-year survival by year of diagnosis were evaluated using joinpoint regression and are reported as annual percent changes (APC). ***Results.*** The age-standardized incidence of leukemia was 3.2 and 4.1 cases per 100,000 in Songkhla and SEER-9, respectively. In Songkhla, incidence from 1990 to 2011 significantly increased for leukemia (APC = 1.7%, $P = 0.031$) and acute lymphoblastic leukemia (ALL) (APC = 1.8%, $P = 0.033$). Acute myeloid leukemia (AML) incidence significantly increased (APC = 4.2%, $P = 0.044$) and was significantly different from the US ($P = 0.026$), where incidence was stable during the same period (APC = 0.3%, $P = 0.541$). The overall 5-year relative survival for leukemia was lower than that reported in the US (43 vs. 79%). Five-year survival significantly improved by at least 2% per year from 1990 to 2011 in Songkhla for leukemia, ALL, and AML ($P < 0.050$). ***Conclusions.*** While leukemia and ALL incidence increased in Songkhla, differences in leukemia trends, particularly AML incidence, may suggest etiologic or diagnostic differences between Songkhla and the US. This work highlights the importance of evaluating childhood cancer trends in low- and middle-income countries. Pediatr Blood Cancer 2015;62:1790–1798.

Key words: childhood leukemia; incidence; joinpoint regression; Southeast Asia; survival; Thailand

INTRODUCTION

Leukemia is the most common malignancy in those under the age of 15 years, accounting for one out of three cases of childhood cancer. The two major subtypes of leukemia seen in children are acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), which account for 80 and 17% of leukemias diagnosed, respectively.[1] Childhood leukemia continues to be a global public health problem as the incidence of this malignancy appears to be steadily increasing,[2,3] and disparities in survival and diagnosis persist in low- and middle-income countries (LMICs), like Thailand, when compared to high-income countries (HICs), like the United States (US). For instance, the age-standardized incidence of childhood leukemia in the US is 4.2 cases per 100,000 with a 5-year survival of 82% for the period 2003–2011,[2] while data from the Thai Pediatric Oncology Group indicate that the age-standardized incidence is 3.8 cases per 100,000 with a 5-year survival of 57% for the period 2003–2005.[4] Better characterization of incidence and survival are key to understanding why global disparities exist in order to improve childhood leukemia diagnosis and prognosis in LMICs.

As Thailand and many other LMICs undergo socio-economic development, childhood disease burden has shifted from infectious to chronic diseases, including childhood cancers. In 2008, 84%, or an estimated 148,000 cases, of childhood cancer were diagnosed in LMICs, where over 80% of children live. Furthermore, 94% of deaths from childhood cancer worldwide occurred in these regions.[5] Rapid industrialization and economic development may increase exposure to undetermined risk factors that may be associated with childhood leukemia,[6] but the increase in childhood leukemia incidence may also be attributable to improved reporting and reductions in competing causes of death.[7] Nevertheless, leukemia survival rates continue to remain low in many LMICs.[8] In fact, incidence and survival from childhood leukemia has been proposed to serve as an indicator of economic and healthcare development.[9] However, childhood cancer surveillance is a problem in many LMICs due to barriers in healthcare access and underdeveloped or nonexistent population-based cancer registries.

Within Asia, high-quality population-based cancer registries monitor less than 5% of the population.[5] Surveillance for childhood leukemia in LMICs may pose additional challenges, as childhood leukemia is rare, symptoms are nonspecific and resemble

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APC, annual percent change; API, Asian or Pacific Islander; ASR, age-standardized incidence rates; DCO, death certificate only; HICs, high-income countries; ICCC, international classification of childhood cancers; LMICs, low- and middle-income countries; NOS, not otherwise specified; SEER, surveillance, epidemiology, and end results registry; US, United States

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infections, and early death can occur before diagnosis.[10] Precise statistics from cancer registries can identify gaps and outline directions to address the burden of childhood leukemia in LMICs, and therefore, resources can be allocated to improve childhood leukemia diagnosis, treatment, and survival.[8,11] Songkhla is located in southern Thailand, is a unique and ethnically diverse region within Southeast Asia, and has a long-standing cancer registry with standardized reporting and monitoring.[12] Because there is limited information on childhood leukemia in Thailand and how its epidemiology differs when compared to HICs, we evaluated trends in childhood leukemia incidence and survival using data from the Songkhla Cancer Registry in Thailand and compared to data from the Surveillance, Epidemiology, and End Results (SEER-9) registry in the US.

METHODS

Study Population

Data on childhood leukemia cases were obtained from the Songkhla Cancer Registry. This registry actively collects information on cancer cases from all 16 districts located in the Songkhla Province. Details of the Songkhla Cancer Registry have been described previously.[12–15] Briefly, the registry was established in 1989 and captures cancer cases from 23 sources that include Songklanagarind Hospital, Hat Yai Hospital, Songkhla Hospital, and the population registration office of the Songkhla Province. Patients with a suspected diagnosis of any cancer were referred from community hospitals and other healthcare centers to the Songklanagarind, Hat Yai, or Songkhla hospitals. The Songkhla registry monitored a population of approximately 1.5 million in 2010,[16] and the Thai National Statistical Office estimates that Muslims and Buddhists comprise 25 and 75% of the population, respectively.[17] From the Thai National Census, the proportion of the population in Songkhla under 19 years of age has decreased from 42% (n = 457,200) in 1990 [18] to 29% (n = 428,700) in 2010.[16]

In order to compare childhood leukemia trends between Thailand and the US, we obtained SEER research data from SEER*Stat. [19] SEER is a cancer registry program of the National Cancer Institute that tracks cancer incidence and survival in the US. SEER-9 captures approximately 10% of population in the United States and has collected incidence and survival data since 1973. SEER-9 includes registries in Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah, and oversamples minority populations in the US that include Blacks, Asians, Pacific Islanders, Native Americans, and Hispanics. The proportion of children under age 19 in the US population covered by SEER-9 has declined slightly from 29% in 1990 to 27% in 2010. [20] We collected case listing and survival information from reported childhood leukemia cases diagnosed age 0–19 from SEER-9 registries from 1990 to 2011.

Data Extraction and Variables

Childhood leukemia cases were identified using their ICD-O-3 histology and site codes [21] and categorized into International Classification of Childhood Cancer (ICCC) groups. The ICCC groups included in this analysis were as follows: I, leukemia; I(a), ALL; I(b), AML; I(c), chronic myeloproliferative diseases (CML); and I(e), not otherwise specified (NOS) leukemia. No cases of ICCC group 1(d), myelodysplastic syndrome and other myeloproliferative diseases, were diagnosed in Songkhla.[22] Denominator data for incidence rate calculations were obtained from the Thailand population censuses conducted in 1990, 2000, and 2010.[16,18,23] Annual inter-census populations in Songkhla were estimated by assuming an exponential change between each census by each 5-year age groups (i.e., 0–4, 5–9, 10–14, and 15–19 years) and sex. Mortality life tables for Thailand by sex and 5-year age groups in 1990, 2000, and 2012 were obtained from the Global Health Observatory,[24] and we interpolated the probability of dying for the inter-census years. Variables included in the registry were age at diagnosis, year of diagnosis, vital status, date of diagnosis, date of last contact, histology, site, religion, sex, and location of diagnosis. The denominator data for incidence rate calculations for SEER-9 were obtained from population data provided by the US Census for SEER.[20] All cause mortality data and life tables for SEER-9 were provided by the National Center of Health Statistics (NCHS) for SEER.[25]

Statistical Analysis

Descriptive analyses. Age, sex, and vital status were compared among the SEER-9 and Songkhla registries. As age was not normally distributed, median age was compared using the Mann–Whitney test. Pearson χ^2 tests were used to compare the distribution of leukemias diagnosed by 5-year age group at diagnosis, sex, and vital status among these registries. To analyze the incidence trends from 1990 to 2011, age-standardized incidence rates (ASR) were calculated using Songkhla or US populations by year of diagnosis, standardized using the WHO world standard 2000 population [26] and presented as cases per 100,000.

Analysis of incidence trends. Joinpoint regression was used to analyze trends under a log-linear model and to compute the annual percent change (APC) in age-standardized incidences using the Joinpoint Regression Program version 4.0.4.[27] Permutation tests determined number of joinpoints, slope of the trends, and their significance.[28] When no cases were present, a half-case was added to enable computation on the log-linear scale.[27] The trends between Songkhla and SEER-9 were compared for parallelism, which tests differences in slopes, and coincidence, which tests the similarity in incidence rates.[29]

Analysis of survival. Relative survival was computed using mortality and life tables obtained from the National Statistics Office from 1990 to 2011 and from NCHS from 1990 to 2011 in US.[25] Cases were excluded from the survival analysis if their basis for diagnosis was death certificate only (DCO) or unknown, did not have any follow-up, or unknown vital status. These rates were computed using the Ederer II method [30] and survival functions were generated using the Kaplan–Meier method (product limit). [31] We used the R package, survival, to analyze relative survival for Songkhla,[32] and computed relative survival within the SEER*Stat software for SEER-9.[33] In Songkhla, we compared the relative survival by sex, religion, and year cohort (1990–1994, 1995–1998, 1999–2002, 2003–2006) using the log-rank test from 1990 to 2011. The 5-year relative survival rates from each year of diagnosis from 1990 to 2006 in Songkhla and SEER-9 were computed, and these trends were analyzed using joinpoint regression under a linear model,[27] and the trends were tested for parallelism and coincidence between each registry.

RESULTS

Data Quality

Three hundred and sixteen cases of childhood leukemia were reported in the Songkhla Registry from 1990 to 2011. Of these leukemia cases, 304 (96%) and 273 (86%) were included in the incidence and survival analyses of childhood leukemia, respectively. Cases diagnosed based on unspecified methods (n = 10) or whose follow-up was an extreme outlier were removed from the incidence analysis. Two cases of AML were removed from the incidence and survival analysis after examining initial descriptive statistics because their follow-up time was determined to be an extreme outlier (greater than 8,000 days). In addition to this criterion, leukemia cases were excluded from the survival analysis if their basis for diagnosis was DCO (n = 10), did not have any follow-up (n = 16), or unknown vital status (n = 5). In the Songkhla registry, 85% of the leukemia cases were included in the survival analysis. Ninety-four percent of the total leukemia cases included in the registry were histologically confirmed by either positive histology or positive cytology of hematology. For both AML and ALL, over 95% of cases were diagnosed by positive histology or positive cytology based on hematology, and no cases were diagnosed based on DCO in these groups. The proportion of diagnoses based on positive cytology, DCO, and unknown decreased from 23, 4, 5 in 1990–1999, respectively, to 11, 2, 1% in 2000–2011, respectively ($P < 0.001$). No differences were observed based on age group at diagnosis.

Demographic and Histologic Characteristics

In both Songkhla and SEER-9, males were more likely to be diagnosed with leukemia than females (Table I). In Songkhla, the mean age at diagnosis for leukemia, ALL, and AML was 7.9, 6.4, and 10.3 years, respectively. Childhood leukemia was diagnosed at significantly older age in Songkhla compared to SEER-9 (mean age = 7.1 years, $P = 0.018$). Significantly higher proportion of deaths from leukemia, ALL, and AML occurred among the cases of the Songkhla registry compared to the SEER-9 ($P < 0.001$).

The distribution of childhood leukemia subtypes was significantly different between SEER-9 and Songkhla ($P < 0.001$) (Table II). There was a greater proportion of NOS leukemia and lower proportion of ALL in Songkhla than observed in SEER-9. The proportion of CML diagnosed in Songkhla was double compared to SEER-9 (5.6 and 2.7%, respectively), and this proportion remained consistent by decade of diagnosis. In Songkhla, the distribution of leukemia subtypes was not significantly different between males and females ($P = 0.530$) while the distribution of leukemia subtypes significantly differed by gender in SEER-9 ($P = 0.032$). The distribution of leukemia subtypes by age group at diagnosis significantly differed within each registry ($P < 0.001$). In Songkhla, ALL accounted for 66 and 28% of cases diagnosed in ages 0–4 and 15–19, respectively, whereas the proportion of AML increased by age group at diagnosis from 16% in age 0–4 to 40% in age 15–19. This trend was also observed in SEER-9. In Songkhla, the childhood leukemia subtype distribution differed between those diagnosed prior to 2000 and after 2000 ($P = 0.031$). The proportion of NOS leukemia decreased from 23% in 1990–1999 to 11% in 2000–2011. While ALL accounted for 55% of leukemia cases diagnosed in both 1990–1999 and 2000–2011, AML increased from 17% in 1990–1999 to 27% in 2000–2011.

TABLE I. Descriptive Characteristics and Age-Standardized Incidences Across Groups

	Leukemia					ALL					AML				
	Songkhla		SEER9			Songkhla		SEER9			Songkhla		SEER9		
	n (%)	ASR	n (%)	ASR	*P*	n (%)	ASR	n (%)	ASR	*P*	n (%)	ASR	n (%)	ASR	*P*
n	304	3.2	6,738	4.1		169	1.8	5,080	3.1		69	0.7	1,267	0.8	
Sex					0.795					1					0.962
Male	167 (55%)	3.4	3,764 (56%)	4.5		96 (57%)	2.0	2,882 (57%)	3.5		37 (54%)	0.7	666 (53%)	0.8	
Female	137 (45%)	3.0	2,974 (44%)	3.7		73 (43%)	1.6	2,198 (43%)	2.8		32 (46%)	0.7	601 (47%)	0.8	
Age group					0.148					0.436					0.581
0–4 years	121 (40%)	5.5	3,110 (46%)	7.5		80 (47%)	3.6	2,524 (50%)	6.1		19 (28%)	0.9	452 (36%)	1.1	
5–9 years	72 (24%)	3.0	1,510 (22%)	3.7		51 (30%)	2.1	1,258 (25%)	3.1		11 (16%)	0.5	190 (15%)	0.5	
10–14 years	54 (18%)	2.2	1,075 (16%)	2.6		22 (13%)	0.9	738 (15%)	1.8		16 (23%)	0.6	261 (21%)	0.6	
15–19 years	57 (19%)	2.2	1,043 (15%)	2.6		16 (9%)	0.6	560 (11%)	1.4		23 (33%)	0.9	364 (29%)	0.9	
Mean Age (sd)	7.9 (5.9)		7.1 (5.6)		0.018	6.4 (5.0)		6.5 (5.1)		0.903	10.3 (6.5)		9.0 (6.6)		0.113
Status					<0.001					<0.001					<0.001
Alive	117 (38%)		5,216 (77%)			81(48%)		4,277 (84%)			15 (22%)		671 (53%)		
Dead	182 (60%)		1,522 (23%)			85 (50%)		803 (16%)			52 (75%)		596 (47%)		
Unknown	5 (2%)		0 (0%)			3 (2%)		0 (0%)			2 (3%)		0 (0%)		

Age-standardized rates (ASR) per 100,000. Distributions compared using Pearson's χ^2 test (categorical variables) and Wilcoxon rank sum test for age.

TABLE II. Descriptive Characteristics by Childhood Leukemia Subtype by Registry

	Songkhla					SEER-9				
	ALL	AML	CML	NOS	*P*	ALL	AML	CML	NOS	*P*
n	169 (55.6%)	69 (22.7%)	17 (5.6%)	49 (16.1%)		5,080 (75.8%)	1,267 (18.9%)	179 (2.7%)	176 (2.6%)	
Sex					0.530					0.032
Male	96 (57.5%)	37 (22.2%)	11 (6.6%)	23 (13.8%)		2,882 (77.1%)	666 (17.8%)	94 (2.5%)	92 (2.5%)	
Female	73 (53.3%)	32 (23.4%)	6 (4.4%)	26 (19.0%)		2,198 (74.1%)	601 (20.2%)	85 (2.9%)	84 (2.8%)	
Age group at diagnosis					<0.001					<0.001
0–4 years	80 (66.1%)	19 (15.7%)	2 (1.7%)	20 (16.5%)		2,524 (81.9%)	452 (14.7%)	28 (0.9%)	77 (2.5%)	
5–9 years	51 (70.8%)	11 (15.3%)	3 (4.2%)	7 (9.7%)		1,258 (83.5%)	190 (12.6%)	23 (1.5%)	35 (2.3%)	
10–14 years	22 (40.7%)	16 (29.6%)	5 (9.3%)	11 (20.4%)		738 (68.8%)	261 (24.3%)	47 (4.4%)	27 (2.5%)	
15–19 years	16 (28.1%)	23 (40.4%)	7 (12.3%)	11 (19.3%)		560 (53.7%)	364 (34.9%)	81 (7.8%)	37 (3.6%)	
Decade of diagnosis					0.031					0.841
1990–1999	70 (54.7%)	22 (17.2%)	7 (5.5%)	29 (22.7%)		2,131 (75.5%)	539 (19.1%)	73 (2.6%)	79 (2.8%)	
2000–2011	99 (56.3%)	47 (26.7%)	10 (5.7%)	20 (11.4%)		2,949 (76.0%)	728 (18.8%)	106 (2.7%)	97 (2.5%)	

Distributions compared using Pearson's χ^2 test.

Leukemia Incidence

From 1990 to 2011, the age-standardized incidence rates (ASR) for leukemia and ALL were lower in Songkhla, 3.2 and 1.8 cases per 100,000, respectively, compared to SEER-9, 4.1 and 3.1 cases per 100,000, respectively (Table I). The ASR for AML was similar between Songkhla and SEER-9, 0.7 and 0.8 cases per 100,000, respectively. In joinpoint regression results, leukemia incidence significantly increased in Songkhla by 1.7% annually ($P = 0.031$) and in SEER-9 by 0.8% annually ($P < 0.001$) from 1990 to 2011. The leukemia incidence trends between Songkhla and US were determined to be parallel ($P = 0.199$) but not coincident ($P < 0.001$) as incidence in SEER-9 was higher than in Songkhla (Fig. 1A). ALL incidence significantly increased in Songkhla by 1.8% annually ($P = 0.033$) and in SEER-9 by 0.9% annually ($P < 0.001$) (Fig. 1B). The ALL incidence trends between SEER-9 and Songkhla were parallel ($P = 0.386$) but not coincident ($P < 0.001$). In 1992, no cases of AML were diagnosed in Songkhla, and we applied a half-case correction (see Methods). AML incidence has been significantly increasing in Songkhla by 4.2% annually ($P = 0.036$) while AML incidence has remained stable in SEER-9 (APC = 0.3%, $P = 0.540$) from 1990 to 2011 (Fig. 1C). The AML incidence trends were not parallel ($P = 0.026$) but coincident ($P = 0.102$). In a subgroup analysis within the SEER-9 Asian or Pacific Islander (API) population (data not shown), AML incidence has been significantly decreasing by 3.1% annually ($P = 0.015$), and the annual ASR declined from 1.1 cases per 100,000 in 1990 to 0.5 cases per 100,000 in 2011.

Survival

The 5-year relative survival rates in Songkhla over the study period were 43, 55, 16%, for leukemia, ALL, and AML, respectively (Table III). While there was no significant difference in survival by sex for childhood leukemia, ALL, and AML, females diagnosed with leukemia or ALL had better 5-year survival compared to males. For leukemia and ALL, the age group at time of diagnosis was significantly and inversely associated with survival ($P < 0.001$), but this association was not observed for AML survival. Survival was significantly and positively associated with year of diagnosis in leukemia ($P = 0.007$), ALL ($P = 0.015$), and AML ($P = 0.015$). Five-year survival improved between cases diagnosed from 1990–1994 and 2003–2006 for leukemia, ALL, and AML.

In Songkhla, 5-year survival for leukemia, ALL, and AML significantly improved annually by 1.9% ($P = 0.030$), 2.3% ($P = 0.042$), and 2.3% ($P = 0.041$) from 1990 to 2006, respectively (Fig. 2). In SEER-9, 5-year survival from leukemia, ALL, and AML also significantly improved annually by 1.0% ($P < 0.001$), 0.7% ($P < 0.001$), and 1.8% ($P < 0.001$), respectively. While 5-year survival in Songkhla for leukemia, ALL, and AML were significantly lower when compared to SEER-9 ($P < 0.010$ for all comparisons), the gains in 5-year survival were greater in Songkhla. The trends in 5-year survival for leukemia and AML were parallel between SEER-9 and Songkhla. However, 5-year survival for ALL in Songkhla increased more dramatically compared to SEER-9 ($P = 0.055$) from 1990 to 2006.

DISCUSSION

In this comprehensive descriptive analysis of childhood leukemia epidemiology in southern Thailand, our assessment of

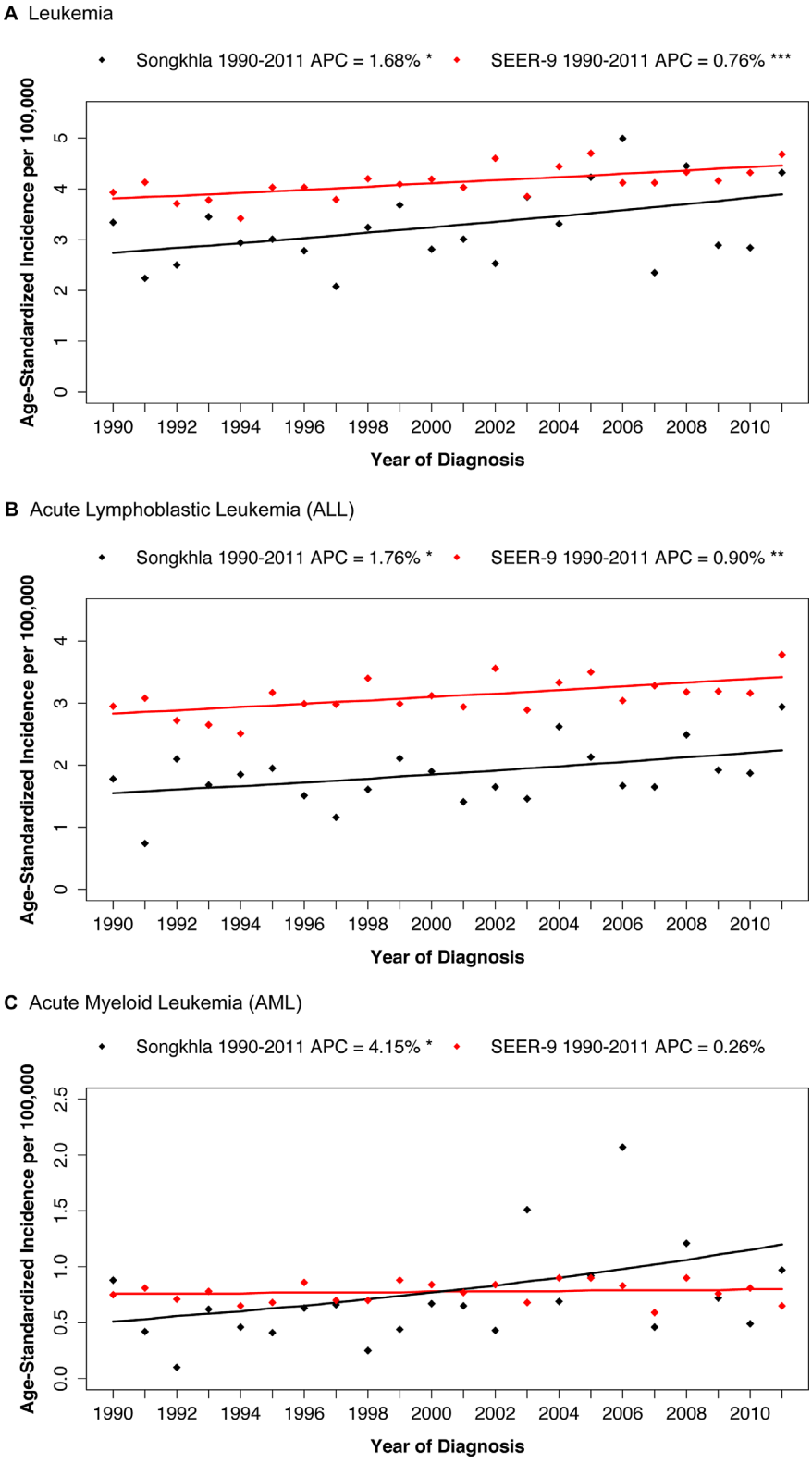

Fig. 1. Age-adjusted incidence by year of diagnosis, 1990–2011. (**A**) Black denotes Songkhla; red denotes SEER-9, (**B**) significance levels for joinpoint regression trends indicated by 0.05 (*), 0.01(**), and 0.001 (***).

TABLE III. Descriptive Statistics for Survival in Songkhla from 1990 to 2011

	Leukemia					ALL					AML				
	n	1-year	3-year	5-year	*P*	n	1-year	3-year	5-year	*P*	n	1-year	3-year	5-year	*P*
N	273	0.68 (0.03)	0.58 (0.03)	0.43 (0.03)		153	0.76 (0.03)	0.62 (0.04)	0.55 (0.04)		66	0.46 (0.06)	0.18 (0.05)	0.16 (0.05)	
Sex					0.274					0.154					0.799
Male	152	0.69 (0.04)	0.45 (0.04)	0.38 (0.04)		87	0.75 (0.05)	0.58 (0.06)	0.50 (0.06)		36	0.52 (0.08)	0.20 (0.07)	0.16 (0.06)	
Female	121	0.65 (0.04)	0.53 (0.05)	0.48 (0.05)		66	0.77 (0.05)	0.66 (0.06)	0.62 (0.06)		30	0.37 (0.09)	0.17 (0.07)	0.17 (0.07)	
Religion					0.303					0.342					0.570
Buddhist	220	0.69 (0.03)	0.50 (0.04)	0.44 (0.04)		122	0.78 (0.04)	0.64 (0.04)	0.58 (0.05)		55	0.48 (0.07)	0.18 (0.05)	0.18 (0.05)	
Islam	53	0.62 (0.07)	0.42 (0.07)	0.33 (0.07)		31	0.70 (0.08)	0.53 (0.10)	0.43 (0.10)		11	0.36 (0.13)	0.18 (0.10)	0.09 (0.07)	
Age group					<0.001					<0.001					0.350
0–4 years	109	0.67 (0.05)	0.55 (0.05)	0.50 (0.05)		74	0.75 (0.05)	0.66 (0.06)	0.59 (0.06)		19	0.28 (0.10)	0.11 (0.07)	0.11 (0.07)	
5–9 years	67	0.83 (0.05)	0.59 (0.06)	0.50 (0.06)		47	0.85 (0.05)	0.68 (0.07)	0.59 (0.07)		10	0.78 (0.13)	0.11 (0.08)	0.11 (0.08)	
10–14 years	47	0.62 (0.07)	0.47 (0.08)	0.39 (0.08)		20	0.70 (0.10)	0.55 (0.11)	0.55 (0.11)		15	0.48 (0.13)	0.32 (0.12)	0.32 (0.12)	
15–19 years	50	0.52 (0.07)	0.20 (0.06)	0.17 (0.06)		12	0.50 (0.15)	0.13 (0.09)	0.13 (0.09)		22	0.46 (0.10)	0.23 (0.08)	0.18 (0.08)	
Year Group					0.007					0.015					0.015
1990–1994	53	0.67 (0.07)	0.45 (0.07)	0.35 (0.07)		32	0.83 (0.07)	0.62 (0.09)	0.52 (0.09)		9	0.25 (0.13)	0 (0)	0 (0)	
1995–1998	48	0.64 (0.07)	0.41 (0.07)	0.34 (0.07)		26	0.65 (0.09)	0.46 (0.10)	0.42 (0.09)		9	0.33 (0.14)	0.11 (0.08)	0.11 (0.08)	
1999–2002	46	0.75 (0.07)	0.57 (0.07)	0.57 (0.07)		25	0.84 (0.07)	0.72 (0.09)	0.72 (0.09)		10	0.45 (0.15)	0.11 (0.08)	0.11 (0.08)	
2003–2006	63	0.69 (0.06)	0.53 (0.06)	0.48 (0.06)		30	0.80 (0.07)	0.73 (0.08)	0.67 (0.08)		22	0.63 (0.10)	0.32 (0.10)	0.27 (0.10)	

Reported as relative survival proportion (standard error). Differences in survival were compared using log-rank test.

childhood leukemia trends in Songkhla, Thailand suggests that while 5-year survival has improved, the annual incidence has also increased from 1990 to 2011. ALL was less common in Songkhla compared to US and other HICs. NOS leukemia was more frequently reported in Songkhla, especially, during the first half of the study period from 1990 to 1999. However, in Songkhla from 2000 to 2011, NOS leukemia was less frequently reported while AML was more frequently reported after 2000, suggesting that the classification of leukemia cases improved in the Songkhla registry over time. The later age of diagnosis in childhood leukemia in Songkhla compared to the US may suggest a delay in diagnosis,[34] which could have downstream consequences on leukemia progression, treatment efficacy, and survival. The ASR for childhood leukemia was lower in Songkhla compared to the US. This could be related to under reporting of childhood leukemia in Songkhla and/or population-specific differences related to childhood leukemia susceptibility and environmental exposures. When comparing childhood leukemia and ALL trends in Songkhla to the US, incidence was lower in Songkhla, but in both of these regions, childhood leukemia incidence has been increasing. In contrast, AML incidence greatly increased in Songkhla while remaining stable in the US. This dramatic increase in AML incidence in Songkhla may be associated with the presence of population-specific risk factors, change in detection, and diagnosis, or both.

Overall, survival from childhood leukemia improved in Songkhla, but was still lower than the US for the same period. In Songkhla, children diagnosed at a younger age had better survival than those diagnosed older for all leukemia and ALL; however, this effect was not observed for AML. Survival also improved by year of diagnosis for leukemia, ALL, and AML. Improvements in survival may be due to earlier diagnosis and better access to treatment possibly related to Thailand's shift to a universal healthcare system during the latter half of the study period. The 5-year survival for leukemia, ALL, and AML has improved over time in Songkhla. Childhood leukemia survival by year of diagnosis was variable due to the small number of cases diagnosed per year. In spite of this, disparities in survival persisted between the US and Songkhla for leukemia, ALL, and AML during the study period.

Our results for childhood leukemia survival and incidence in Songkhla, Thailand were similar, yet distinct, from what has been reported in Khon Kaen, which is in the northern part of Thailand, and other Asian countries, including Indonesia, China, and India. Similar to Songkhla, in Khon Kaen from 1985 to 2002, the ASR for leukemia was 3.2 cases per 100,000, and childhood leukemia incidence was increasing.[35] This may be due to common risk factors and other underlying population similarities. ALL and AML incidence in the Yogyakarta Special Province of Indonesia was 2.1 and 0.8 cases per 100,000, respectively, and childhood

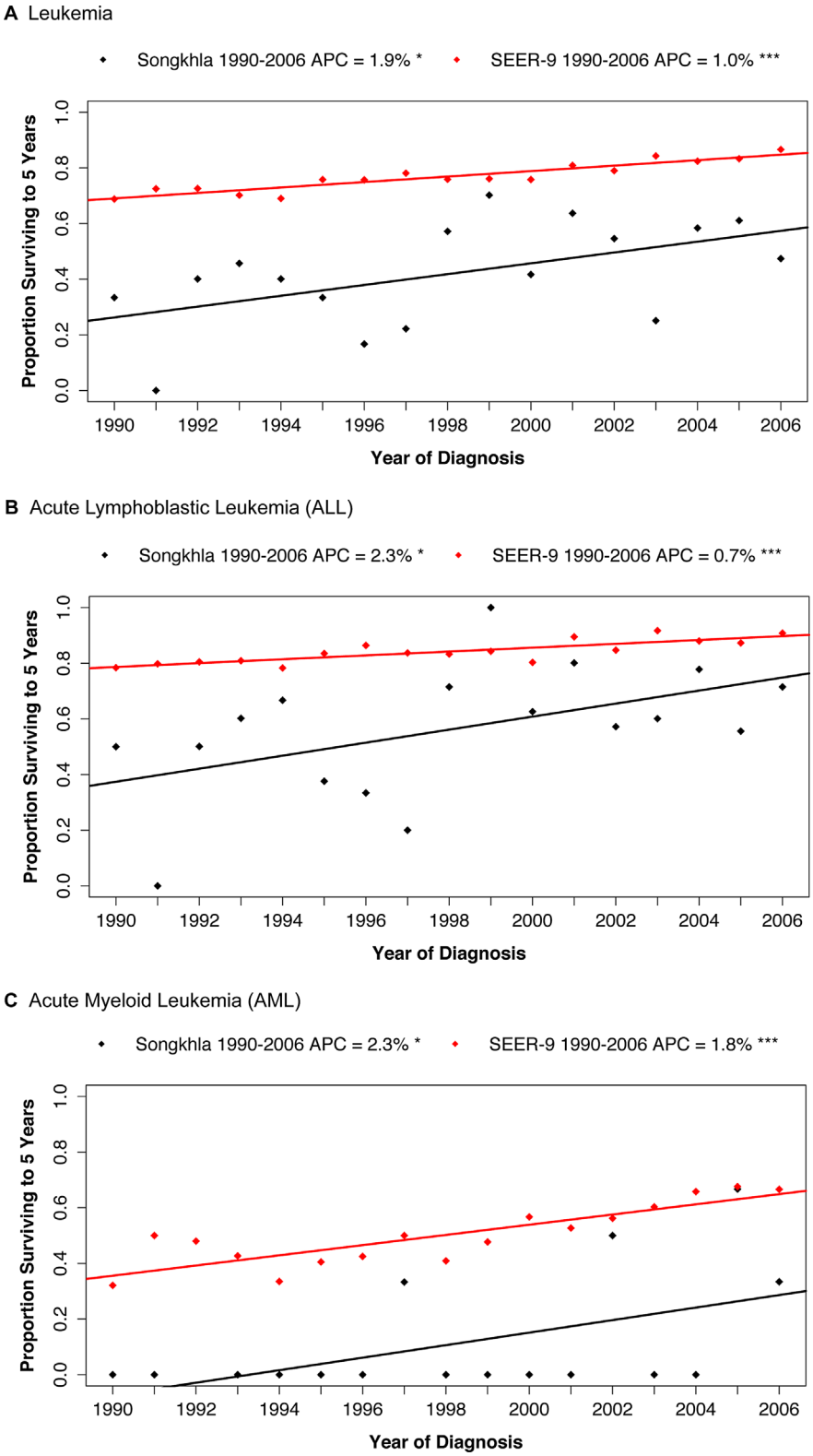

Fig. 2. 5-year survival by year of diagnosis, 1990–2006. (**A**) Black denotes Songkhla; red denotes SEER-9, (**B**) significance levels for joinpoint regression trends indicated by 0.05 (*), 0.01(**), and 0.001 (***).

AML accounted for 27.7% of leukemia cases diagnosed from 1998 to 2009.[36] These incidences were similar to Songkhla, and the elevated proportion of AML was also observed from 2000 to 2011 in the Songkhla registry. In Chennai, India, the absolute 5-year survival for childhood leukemia, ALL, and AML was reported to be 36, 39, and 31%, respectively, whereas 5-year survival for leukemia and ALL in Songkhla was higher.[37] In urban Shanghai, China from 1973 to 2005, trends in ALL incidence non-significantly increased and AML incidence significantly decreased, in contrast to ALL and AML incidence trends in Songkhla from 1990 to 2011.[38]

Out study must be considered in the light of certain limitations. First, the small number of cases diagnosed during this period may have resulted in spurious incidence and survival trends and associations. Within the API population in SEER-9, incidence and survival was also variable by year of diagnosis, and trends within both API (data not shown) and Songkhla were strong enough to obtain statistical significance. Second, the analyses were descriptive in scope, and it was impossible to elucidate whether these changes in incidence were due to changes in risk factors or diagnostic changes. Third, it is possible that some of the leukemia cases included in this analysis were misdiagnosed. To reduce this effect, we removed two cases of AML with over 22 years of follow-up and cases with unknown basis for diagnosis since their survival was significantly higher compared to histologically confirmed cases. Additionally, all DCO cases were diagnosed as NOS leukemia. Finally, survival trends were difficult to interpret, as the number of cases per year was small especially for AML.

Compared to other studies examining childhood leukemia in LMICs, our analysis has numerous strengths. The Songkhla Cancer Registry actively ascertains cases from across regional hospitals, tertiary care, and healthcare centers in the region and the population denominators were estimated from high quality census data from the Thai National Statistical Office. The rate of histologic confirmation is high in this registry, and the proportion of cases histologically verified has increased over time, which may contribute to the increased incidence of ALL and AML later in the study period. The Songkhla registry also actively follows each case, and takes advantage of universal health care in Thailand that allows for direct observation of long-term effects. The direct comparison between SEER-9 and Songkhla allowed us to observe differences in trends between HICs and LMICs. Population-based cancer registries that capture childhood cancers cases are crucial in LMICs, and by identifying trends in incidence and survival, we can determine if childhood cancer is being properly detected, diagnosed, and treated, and if necessary, develop interventions to improve diagnosis and prognosis in LMICs.[39] Population-based registries, which can be considered an unbiased source of cases, can also examine geographic variation and identify regional, ethnic, and other subgroup differences that may be associated with unique environmental or genetic risk factors.[40] The Songkhla registry is a rare and valuable data source for obtaining accurate estimates of childhood leukemia incidence and survival in a LMIC, and captures a unique and ethnically diverse population, where childhood leukemia has not been extensively studied.

In conclusion, childhood leukemia, ALL, and AML incidence and survival significantly increased in Songkhla, Thailand from 1990 to 2011, and both the incidence and survival were lower than in the US. While these increases in childhood leukemia incidence and survival suggest that detection, diagnosis, and treatment have improved in Songkhla, our results also expose the disparities in childhood leukemia detection, diagnosis, and treatment that persist between LMICs and HICs. Distinct differences in AML incidence between the US and Songkhla also suggested the presence of different etiologic and/or diagnostic factors. Additional studies are needed to characterize childhood leukemia trends in other regions of Thailand and other Southeast Asian countries such as Vietnam, Malaysia, and Indonesia, where population-based registries have been and are being implemented. These assessments are critical to improve diagnosis and treatment in these LMICs and to develop prevention strategies.

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