Childhood leukaemia in Costa Rica, 1981–96

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Summary

Childhood leukaemia incidence in Costa Rica during 1981–96, among the highest in the world, was analysed by histology, gender, birth year, time period of diagnosis, age at diagnosis and region. Numbers of cases were extracted from the database of the National Cancer Registry (RNT) of Costa Rica. Person–years at risk were calculated from census data and post-census population estimates. During the follow-up, 918 cases of leukaemia in children under 15 years (510 boys, 408 girls) were reported to the RNT (41% of all childhood malignancies), with an overall age-standardised incidence rate of 56 per million person–years. Acute lymphocytic leukaemia (ALL) represented 79% and acute non-lymphocytic leukaemia (ANLL) 16% of the cases, with rates of 43 and 9 per million person–years respectively. There were downward trends in incidence of total leukaemias, ALL and ANLL and 'not otherwise specified' (NOS) combined. Incidence of ALL was highest at 1–4 years of age in boys and girls, whereas ANLL peaked in girls during the first year of life. During 1991–96, the decrease in ALL was significant (P = 0.042). A multivariable Poisson regression model identified significant excesses of ALL for boys, for age groups 1–4 and 5–9 years and for three out of seven regions. Possible reasons for the high rates in Costa Rica are discussed.

Introduction

Leukaemias are the most common cancers of childhood, accounting for 25–35% of the incidence of all childhood cancer in most populations.[1,2] Comprehensive reviews are available on histopathology, demographic characteristics, time trends and international variations in childhood leukaemia.[2–4] Peak incidence occurs between 1 and 4 years of age. Rates among boys usually exceed those among girls by 10–40%. In white populations, up to 75–80% of childhood leukaemias are acute lymphocytic leukaemias (ALL), also known as acute lymphoblastic leukaemia, whereas 15–17% represent acute non-lymphocytic leukaemias (ANLL). In Asia and in black US populations, incidence rates of total leukaemia are lower and proportions of ANLL higher than among whites. The incidence of ALL increased in the US during 1977–95.[5] Information from developing countries on childhood cancer rates is limited.

Known or suspected risk factors of childhood leukaemia include gender, age, genetic factors, ethnicity, socio-economic status, small families, birthweight, parental, child and prenatal exposure to ionising radiation, electromagnetic fields, chemical agents, dusts, fumes, spores, drugs and infections, and medical histories of parents and child.[1,5] Subtypes of childhood leukaemias may have different aetiologies. Known risk factors for ALL include male gender, age 2–5 years, high socio-economic status, *in utero* and post-natal ionising radiation and a number of genetic conditions, particularly Down's syndrome.[5]

In Costa Rica, X-ray examinations of pregnant women were not common during the observation period of the current study. Occupational exposures to

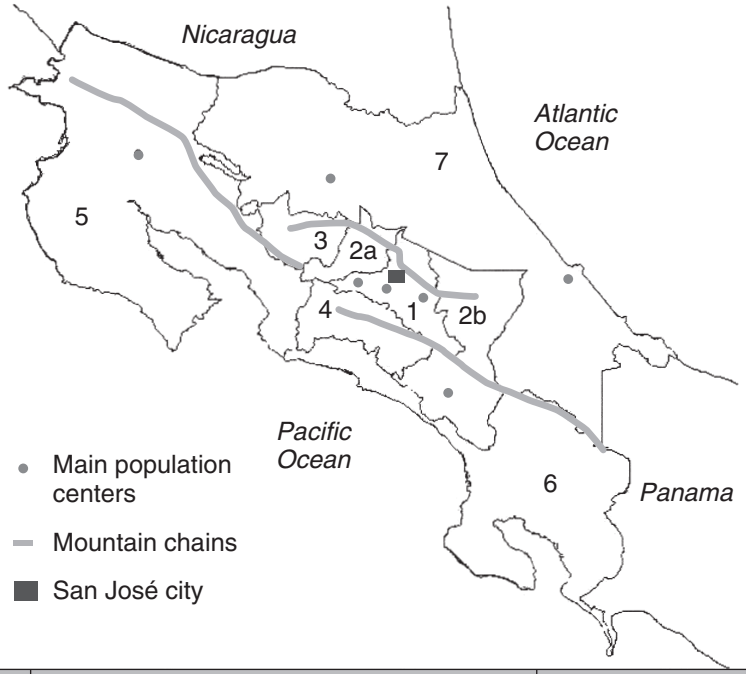
ionising radiation among pregnant women are rare in Costa Rica (no nuclear installations, no women in underground mining, few exposed in roentgenological applications). The prevalence of Down's syndrome (8.5 per 10 000 live births in 2000)[6] is not particularly high (e.g. 12.8 in Australia in 1996, 10.1 in Finland in 1997, 11.1 in Canada in 1997).[7] On the other hand, high radon concentrations have been measured in residential houses in the metropolitan area of San José, the capital city of Costa Rica.[8,9]

In early reports of cancer in Costa Rica, leukaemias were the most common childhood malignancies (39%), and the gender and age distributions appeared to be similar to those described internationally. The remarkable observation was that incidence rates were among the highest in the world: 59 per million for total leukaemia and 45 per million for ALL in 1987.[1,3,4,10]

This is the first detailed analysis of childhood leukaemia rates in Costa Rica, providing a framework for aetiological research on childhood leukaemia in the country.

Methods

The National Cancer Registry (Registro Nacional de Tumores, RNT) of Costa Rica was created in 1976, and



Number	Region	Characterisation
1	Mid and Eastern Central Valley region	Mostly urban, industrial, services, some farming
2	a) Northern Central Valley region b) South Western Central Valley and Mid-South region	Semi-urban and rural; farming
3	Western mountain chain of Central Valley region	Rural, farming, moderate population density
4	Southern mountain chain of Central Valley region	Rural, farming, low population density
5	North-West region	Rural, farming, low population density
6	Southern Central Pacific and South Pacific region	Rural, farming, low population density
7	Eastern and Northern (Atlantic Region)	Rural, farming, low population density

Figure 1. Geographical regions with mountain chains and main population centres, Costa Rica, 1981–96.

Table 1. Childhood leukaemias in Costa Rica 1981–96 by diagnosis

	ICD-0	Cases	%	IR
Acute		869	94	51.6
Acute lymphocytic (ALL)	9821	725	79	43.1
Acute non-lymphocytic (ANLL)		144	16	8.5
Acute myeloid leukaemia (AML)	9861	121	13	7.2
Acute promyeloid leukaemia	9866	19	2	1.1
Acute monocytic leukaemia	9891	3	–	0.2
Erythroleukaemia	9840	1	–	0.1
Other		15	2	0.9
Chronic lymphocytic	9823	1	–	0.1
Chronic myeloid leukaemia	9863	14	2	0.8
NOS		34	4	2.0
Acute leukaemia NOS	9801	17	2	1.0
Monocytic leukaemia NOS	9890	2	–	0.1
Myeloid leukaemia	9860	1	–	0.1
Leukaemia NOS	9800	9	1	0.5
Lymphoid leukaemia NOS	9820	5	1	0.3
All		918	100	54.5

IR, incidence rate per million person–years. NOS, not otherwise specified.

coverage became nationwide in 1980. Notification to the RNT of each diagnosed cancer case is mandatory for all hospitals and clinics (both inpatient and outpatient), as well as for clinical and pathology laboratories (both public and private). Since 1980, the RNT has also received results of all histological examinations of biopsies with a diagnosis of cancer. In addition, the registry reviews death certificates at the Central Bureau of Statistics and Census (INEC) once a year and includes data on each cancer death in the RNT database. During the period covered by this report, 82% of leukaemia cases in children under 15 years of age were reported to the RNT by the National Children's Hospital, and the haematological department of the hospital diagnosed and classified each leukaemia case based primarily on bone marrow smears. Diagnoses based on smears became increasingly common over the observation period, reaching 98.2% in 1996.

The case records at the RNT database include patient name, a unique personal identification number, diagnosing facility, age, gender, place of birth, place of residence, method of diagnosis, primary site of cancer, date of first diagnosis, histological type and date of death. Notifications are reviewed for completeness and consistency and, if necessary, checked against original hospital records by technicians trained in medical registration. A computer program updates the case data and removes duplications.[11] Data collected since 1980 have been included in successive IARC publications of *Cancer Incidence in Five Continents*.[12–14] Inclusion in these IARC documents and the IARC evaluation of the data indicate a reasonably high quality of registration and reporting.

Data on cancer cases, restricted to children under 15 years of age who were newly diagnosed with leukaemia (ICD-O-1) between 1981 and 1996, were provided by the RNT. We applied rubrics from the International Classification of Childhood Cancers (see Table 1).[15,16]

The last available census in Costa Rica dates from 1984. In the absence of more recent direct census data, we used annual population estimates provided by the Central American Population Program of the Universidad de Costa Rica[17] for all other years in the study period to calculate person–years. Population estimates are based on deaths, births and migration data, as well as partial censuses and surveys such as the agricultural census. Incidence rates were calculated per million person–years and analysed for histology, gender, time period at diagnosis, age at diagnosis and region.

The 22 geographical subregions, as defined for health planning by the Ministry of Health, were collapsed into seven regions according to similarities in the distribution of economic activities, climate, altitude and population density. (see Fig. 1). Regional incidence rates were age standardised using the age structure of the Costa Rica national population as a standard. Tabular statistical analysis was performed with STATIS-

Table 2 Incidence rates (IR) per million person–years and male/female (M/F) ratios for leukaemia subgroups by age at diagnosis, Costa Rica 1981–96

	Age at diagnosis (years)					
	<1	1–4	5–9	10–14	Total	*P*
Acute lymphocytic leukaemia (ALL)						
IR, boys	26.1	75.5	49.0	26.5	47.4	<0.001
IR, girls	18.8	61.3	39.5	22.5	38.5	<0.001
IR, both	22.5	68.5	44.3	24.5	43.1	<0.001
M/F ratio	1.4	1.2	1.2	1.2	1.2	
Acute non-lymphocytic leukaemia (ANLL)						
IR, boys	9.8	11.0	8.8	5.4	8.4	0.109
IR, girls	17.1	10.6	4.4	9.7	8.7	0.002
IR, both	13.3	10.8	6.6	7.6	8.5	0.043
M/F ratio	0.6	1.0	2.0	0.6	1.0	
Other leukaemias						
IR, boys	1.6	3.8	0.4	0.4	1.4	<0.001
IR, girls	0.0	0.4	0.4	0.4	0.4	0.989
IR, both	0.8	2.2	0.4	0.4	0.9	0.015
M/F ratio	∞	9.0	1.0	1.0	3.8	
Total leukaemia						
IR, boys	42.4	93.7	58.4	34.8	59.4	<0.001
IR, girls	44.3	74.1	45.0	34.1	49.4	<0.001
IR, both	43.3	84.1	51.8	34.5	54.5	<0.001
M/F ratio	1.0	1.3	1.3	1.0	1.2	

P, significance of heterogeneity.

TICA software.[18] A Poisson regression model was fitted for the incidence of ALL, with region (seven regions), calendar period (three periods), gender and age (four groups) as simultaneous predictors. Log of person–years was taken as offset in the Poisson model, and the STATA release 5 statistical package was used.[19]

Table 3. Incidence rates per million person–years for leukaemia subgroups and time period of diagnosis, Costa Rica 1981–96

Leukaemia subgroups	Period of diagnosis		
	1981–85	1986–90	1991–96
ALL	46.6	40.7	42.1
NOS	2.6	2.7	1.1
ALL + NOS	49.2	43.4	43.2
ANLL	11.4	6.9	7.7
Others	0.9	1.1	0.9
Total	61.5	51.4	51.8

ALL, acute lymphocytic leukaemia; ANLL, acute non-lymphocytic leukaemia; NOS, not otherwise specified.

Data for the international comparison of rates, as given in the Discussion, were extracted from *International Incidence of Childhood Cancer*, published by IARC.[3]

Results

Between 1981 and 1996, 918 cases of leukaemia in children under 15 years (510 boys, 408 girls) were reported to the RNT with an overall incidence rate of 55 per million person–years (Table 1). These cases represented 41% of all reported childhood malignancies. ALL accounted for 79% of all leukaemias, ANLL 16% (the acute myeloid subgroup of ANLL 13%) and 'others' and 'not otherwise specified' leukaemias 6%, with incidence rates of 43, 9 and 3 per million person–years respectively.

The incidence of ALL in both boys and girls had a significant peak at age 1–4 years (Table 2). ALL was about 20% more frequent in boys than in girls in all age

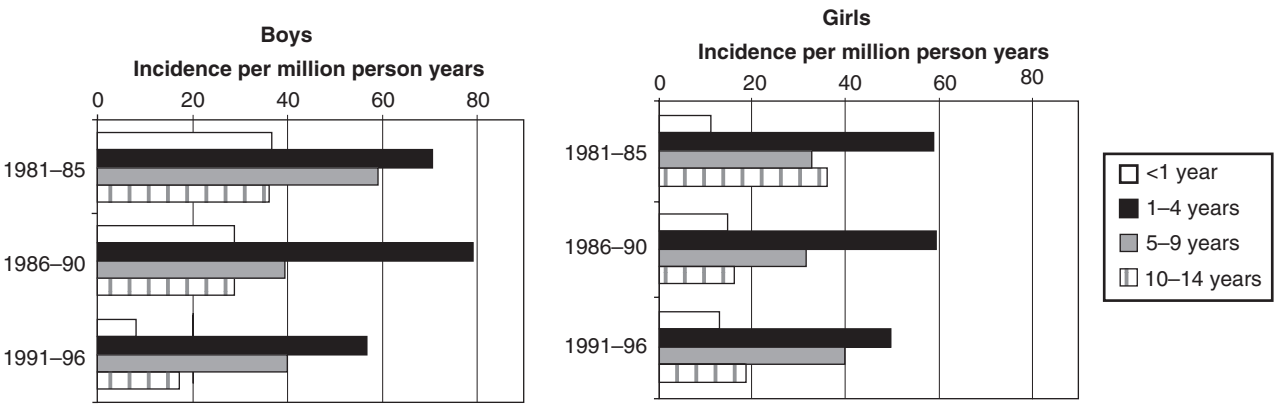


Figure 2. Acute lymphocytic leukaemia incidence rate in children under aged 15 years by gender, period of diagnosis and age categories, Costa Rica 1981–96.

Table 4. Numbers of cases and person–years, incidence rate ratios (IRR) and their 95% confidence intervals (CI) for children's acute lymphocytic leukaemias (ALL) in Costa Rica, 1981–96

Predictor	Cases	Person–years (millions)	IRR	95% CI
Southern mountain chain of Central Valley region	278	6.086	1.00	Reference
Mid and eastern Central Valley region	147	3.264	1.77	[1.05, 2.97]
Northern and south-western Central Valley and Mid-South region	43	0.859	1.75	[1.03, 2.97]
Western mountain chain of Central Valley region	15	0.578	1.94	[1.08, 3.49]
North-west region	91	2.446	1.44	[0.84, 2.49]
Southern central Pacific and south Pacific region	52	1.213	1.66	[0.94, 2.95]
Eastern and northern region (Atlantic Region)	89	2.467	1.38	[0.80, 2.39]
Period 1991–96	292	7.038	1.00	Reference
Period 1986–90	208	5.240	0.94	[0.78, 1.12]
Period 1981–85	215	4.636	1.10	[0.93, 1.32]
Girls	318	8.280	1.00	Reference
Boys	397	8.633	1.20	[1.03, 1.39]
Age 0 years	27	1.226	1.00	Reference
Age 1–4 years	314	4.905	2.91	[1.96, 4.31]
Age 5–9 years	242	5.676	1.93	[1.30, 2.88]
Age 10–14 years	132	5.107	1.17	[0.77, 1.77]

Poisson regression, with regions, time periods, genders and age groups as predictors. Number of cases = 715, excluding 10 with missing region.

groups. For ANLL, the male/female (M/F) ratio fluctuated over age categories from 0.6 in the youngest (<1 year) and in the oldest (10–14 years) age groups to 2.0 at age 5–9 years.

The incidence of total leukaemias during the observation period varied between 37 per million in 1986 and 73 per million in 1987. ALL was responsible for most of the variation, from 27 per million in 1986 to over 55 per million in 1983 and 1987.

Rates of ALL by gender, period of diagnosis and age categories are shown in Fig. 2. The incidence peak occurred consistently in the age category 1–4 years during all time periods and among both boys and girls. The rate difference between boys and girls diminished towards the end of the study period in all age categories.

The incidence of total childhood leukaemias has decreased from 1981 to 1996 (Table 3). This is also true for ALL alone and ALL and 'not otherwise specified' combined.

Multivariable Poisson modelling of ALL incidence, with simultaneous adjustment for several contributing variables, showed a 20% excess for boys compared with girls; a three- and twofold occurrence of ALL among children aged 1–4 years and 5–9 years, respectively, compared with infants <12 months of age; and significant regional differences in the occurrence of ALL, in particular excesses in the most urban areas in the Central Valley and the western mountain chain bordering the Central Valley (Table 4).

Discussion

In summary, leukaemia represented 41% of all reported cancers in children under 15 years of age in Costa Rica during 1981–96, with an overall incidence rate of 55 per million person–years. The rate of ALL was 43 per million in all children and 76 per million in boys aged 1–4 years. The factors most strongly identified with elevated ALL were male gender, age 1–9 years and urban residence.

The observed rates are among the highest in the world, especially for ALL among boys aged 1–4 years. Costa Rican rates for lymphoid leukaemias in all boys (52 per million person–years during 1984–92; Table 5) exceeded those reported in Europe (22–47 per million), North America (18–58 per million), Oceania (30–48 per million), Africa (13 per million) and Asia (3–51 per million) and are comparable to rates in Hong Kong (51 per million) and Hispanics in Los Angeles, USA. (50 per million).[1–5] Also, among all childhood leukaemias in Costa Rica, the proportion of lymphoid leukaemia was high in comparison with South America and the Caribbean, but comparable to other popu-

Table 5. Leukaemia incidence rates during 1980s and 1990s at ages 0–14 years, per million person–years, age standardised to world standard population

	Total leukaemias		Lymphoid leukaemias[a]	
	Boys	Girls	Boys	Girls
Costa Rica	63.3	52.3	51.7	40.7
Colombia, Cali	40.9	44.7	27.4	35.8
Ecuador, Quito	62.1	50.3	47.0	32.1
Peru, Lima	41.0	30.6	27.6	23.2
World (58), median (range)	44.9 (25.3–63.6)	37.7 (18.2–54.3)	35.9 (9.7–51.7)	31.1 (8.7–45.6)
Africa (1: Zimbabwe)	25.3	21.1	13.3	9.9
America, central and south (6)	47.2 (35.4–63.3)	43.6 (31.9–52.3)	35.3 (21.8–51.7)	33.4 (22.1–40.7)
America, north (11),	44.3 (25.5–63.6)	42.7 (22.0–54.3)	39.4 (18.2–50.2)	33.3 (11.6–45.6)
Asia (14)	41.1 (26.2–46.7)	28.8 (18.2–46.7)	25.7 (2.7–50.6)	16.6 (8.7–37.2)
Europe (23)	46.8 (36.8–56.2)	41.3 (29.3–51.3)	34.5 (22.3–47.0)	31.2 (17.4–40.8)
Oceania (3)	56.2 (51.9–58.7)	43.2 (30.6–44.0)	45.3 (30.3–47.7)	34.1 (13.1–34.6)
Top 10 rates	1. Hong Kong 64.5	1. US, LA Hispanics 54.3	**1. Costa Rica 51.7**	1. US, LA Hispanics 45.6
	2. US, LA Hispanics 63.6	**2. Costa Rica 52.3**	2. Hong Kong 50.6	2. Finland 42.0
	3. Costa Rica 63.3	3. Finland 51.3	3. US, LA Hispanics 50.2	3. Italy, Piedmont 40.8
	4. New Zealand, non-Maori 58.7	4. US, SEER, Hawaii, Hawaiians 51.3	4. New Zealand, non-Maori 47.7	**4. Costa Rica 40.7**
	5. US, LA non-Hispanic whites 57.6	5. Ecuador, Quito 50.3	5. Denmark 47.0	5. Sweden 39.3
	6. Australia 56.2	6. Italy, Piedmont 50.3	6. Ecuador, Quito 47.0	6. Denmark 38.4
	7. Czech Republic 56.2	7. Denmark 49.7	7. Australia 45.3	7. France, Paca and Corsica 38.3
	8. Denmark 56.2	8. Italy 48.4	8. Canada 44.8	8. Norway 37.3
	9. Canada 55.2	9. Sweden 48.4	9. US, LA non-Hispanic whites 44.8	9. Singapore, Chinese 37.2
	10. Singapore, Chinese 55.0	10. Spain, Valencia 46.8	10. Finland and US, NY white 41.8	10. Canada 36.9

From IARC Scientific Publication no. 144 (1998).[3] Figures in parentheses after continental region indicate numbers of populations with cancer registry reports in IARC (1998) (data from registries with a high proportion of death certificate-only registrations, underenumeration or inaccuracies in denominator populations were excluded). Medians are unweighted 50th centiles of rates.
[a]About 99% or more of lymphoid leukaemias are acute lymphocytic leukaemias.

lations with high rates, such as Canada, US Los Angeles Hispanics, US SEER whites, Finland and Australia.[3]

ANLL rates in Costa Rican children were high compared with other central and South American (and also Asian and African) countries, but comparable to rates in North America, Europe, Australia and the non-Maori population in New Zealand (Table 5).

The M/F ratio in Costa Rica was 1.2 for all leukaemias and also for ALL in our data. This is comparable to international data (Table 5; IARC 1998). It may be noteworthy that one of the lowest M/F ratios (0.9) was reported in Cali, Colombia. Within Costa Rica, the M/F ratio of ALL fluctuated in different regions during different time periods, the most dramatic change being a decrease from 1.7 to 0.8 in the mid- and eastern Central Valley from 1981–85 to 1991–96. In this case, there was a 42% decrease in incidence among boys and a 28% increase among girls. The 42% decrease in boys in this region was the only significant time trend, not observed among girls or boys in any other region. Consistent with findings in

other populations, the rates of ANLL among boys and girls were close to each other in Costa Rica.

Total leukaemia and ALL rates are highest among children under 5 years of age, with a decline in incidence at older ages until 10 years in a number of countries such as Great Britain, the United States, Puerto Rico, Ecuador, England, Wales, Australia, New Zealand and also Costa Rica.[2,4,5] Costa Rican rates of total leukaemia and ALL are comparable to those reported in Hispanic males in California, which may point to genetic susceptibility associated with ethnicity, probably linked with socio-economic conditions and environmental exposures.

Downward trends over time in the incidence of ALL seem not to result from diagnostic misclassification, as the decreasing trend is seen also when ALL and NOS leukaemias are combined. The quality of cancer registration has improved since 1990 and meets international quality standards, which is reflected in the Costa Rican data having been included in the IARC international cancer incidence statistics.[12–14] Several data-cleaning procedures were applied to the raw data for 1980–90 by one of us (ACR), and the entire RNT database has been the object of extensive checks for inconsistencies. Population estimates were based on procedures that combine annual records on births and deaths, previous censuses, electoral registries and household surveys. However, inaccuracies in population figures may have influenced the incidence rates differentially for the most recent time period, which is furthest away from the last census available. The fluctuations are not likely to be random, as the annual rates were based on a substantial number of cases. In addition, total population figures, as interpolated between census population counts in 1983 and 2000, are somewhat lower than estimated populations. This implies that the real incidences could be estimated by multiplying our estimated incidence rates by a factor of 1.033 (boys) and 1.023 (girls) on average. Direct population counts for all subgroups and subperiods were not available. The downward trends in the incidence of total leukaemias, ALL, ANLL and combined NOS leukaemias (Table 3) are not likely to be the results of errors in population estimates, as a similar trend was not seen in other childhood cancers, such as brain cancer.

High regional rates of ALL were found in the western mountain chain of the Central Valley, in the northern and south-western Central Valley and the mid-south, and in the mid and east Central Valley (especially among boys in 1981–85). The southern mountain chain of the Central Valley had consistently low rates. Regional trends in rates may be related to migration. Immigration from Nicaragua has become common in Costa Rica, and an increasing number of children in Costa Rica are born of Nicaraguan parents. Potential risk factors such as dietary habits and parental occupational exposures among Nicaraguans may be different from those among native Costa Ricans.

The classification of ALLs and non-Hodgkin lymphomas (NHL), in particular lymphoblastic lymphomas, may follow different practices in different localities.[1] However, this cannot explain the high incidence of ALLs in Costa Rica. First, even if there had been a considerable drift in diagnosis from lymphoblastic lymphomas to ALLs, it would have increased the incidence of the latter very little. Secondly, a drift from NHLs would be expected to diminish the reported NHL incidence (unless both malignancies are exceptionally frequent). However, childhood NHL incidence in Costa Rica is not low. In fact, it exceeds (9.6 per million) the average world figure for boys (median 7.5 per million). The Costa Rican NHL rate for girls (3.3) is comparable to the world average (3.3). Thirdly, alleged improvements in diagnosis would have either increased (by a higher detection rate) or decreased (via a declining false-positive rate) the rate of ALL, or the two tendencies would have mixed. No consistent trends were observed in the data. The high standard of medical specialists at the National Children's Hospital is long established and possibly improved over time. Diagnosis was based on bone marrow smears for 98% of the cases in 1996, and the rate of leukaemias 'not otherwise specified' has declined over the 16 years studied. Fluctuations in access to health care have not been documented, and their effects on the rates, if any, therefore remain unknown.

The high rates of childhood leukaemia in Costa Rica, particularly of ALL, thus seem to reflect a true situation. The underlying causes remain unknown. Costa Rica combines features of a developing and a developed country and has an interesting distribution of potential risk and preventive factors among the population. Indicators such as a life expectancy of 76 years, widespread childhood vaccination, a low infant mortality rate (13 per 1000 live births in 1998[20]) and a high level of electrification are comparable to developed and newly industrialised

countries, many of which have high rates of childhood leukaemia.

Pesticide use and exposure to other occupational and environmental agents such as diesel engine exhaust, hydrocarbon solvents, inorganic dusts and electromagnetic fields are frequently encountered in Costa Rica. Other potential risk factors include delayed exposure to infectious agents, small families, later interaction with other children, population mixing and genetic influences. We were not able to evaluate these factors in our data.

Costa Rica offers favourable conditions for the study of childhood leukaemia. It is one of the few developing countries with a satisfactory health care system, reliable population and disease registries, including a civil registry with a unique personal identification number and legally mandated cancer registration. The population is ethnically homogeneous, most Costa Ricans being mestizos (Caucasian–Indian) as a result of four centuries of racial mixing.[21] Indians, Blacks and Chinese account for approximately 1%, 2% and 1% of the population respectively.[22] To evaluate risk factors that might contribute to elevated rates of childhood leukaemia in Costa Rica, we are conducting a case–control study that includes the collection of detailed information on individual exposure to a number of potential risk factors.

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