

Urbanization and childhood leukaemia in Taiwan

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- Background** In the 1980s socioeconomic development was dramatically rapid in the urbanized municipalities of Taiwan due to a prospering economy. This study addressed the question: Could differences in the incidence of childhood leukaemia (age <15) be demonstrated between urban and rural communities in Taiwan between 1981 and 1990?
- Methods** The log-linear regression model was used to assess the effects of age, level of urbanization, and calendar year on the variation of childhood leukaemia incidence rates between 1981 and 1990.
- Results** Between 1981 and 1990, the overall incidence rate of childhood leukaemia increased by 20% (rate ratio (RR) = 1.2, 95% CI: 1.0-1.5). As compared to rural areas, metropolitan regions showed a significantly higher incidence rate during the study period (RR = 1.3, 95% CI: 1.1-1.6). This urban-rural difference was particularly notable among children <5 years old (RR = 1.5, 95% CI: 1.2-1.9). Dose-response analysis further indicated that risk of childhood leukaemia was monotonically associated with levels of urbanization. The significant gradient in the risk of childhood leukaemia with urbanization was contributed solely by children in the 0-4 years age group.
- Conclusions** We noticed a relationship between urbanization and risk of leukaemia in children. Because of a dramatic influx of people into metropolitan areas during the 1980s, our findings may have provided support for the putative association between 'population mixing' or 'population density' and risk of childhood leukaemia. Whether such association can be attributable to virus infection or other aetiologically related leukemogens warrants further investigations.
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Taiwan has experienced rapid socioeconomic development resulting in changes in many aspects of lifestyle and disease patterns in the past 30 years. In the 1950s infectious diseases were the predominant cause of deaths in children. Today, accidents and malignancies are the leading causes of death for children below the age of 15. Among childhood cancers, leukaemia is the most common one.

Childhood leukaemia incidence rate has shown a global variation in which African countries generally experience a lower risk.¹ Competing causes of death and underdiagnosis of cancer

have been suggested to account for such variation. Nonetheless, factors associated with modernization could have contributed to a higher childhood leukaemia incidence rate in the developed world as well. Epidemiological studies have shown that risk of childhood leukaemia is associated with socioeconomic status as measured by residential area and paternal occupation.^{2,3} Because modernization, urbanization, and socioeconomic status are known to be highly interrelated, these epidemiological findings may suggest that factors associated with urbanization have played a role in the causation of childhood leukaemia. Between 1980 and 1990 Taiwan has experienced a remarkably dramatic advancement in economic development resulting in rapid urbanization and enormous lifestyle changes. The purpose of the present study is to investigate whether such a rapid economic development in Taiwan, along with urbanization and lifestyle changes, has affected the occurrence of childhood leukaemia. We used the data of incident childhood leukaemia cases reported

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Table 1 Age-specific distribution of types of childhood leukaemia in Taiwan, 1981–1990

Age	Acute lymphoblastic leukaemia		Non-lymphoblastic leukaemia		Chronic leukaemia & unclassified		All types	
	No. (%)	rate (10 ⁻⁵)	No. (%)	rate (10 ⁻⁵)	No. (%)	rate (10 ⁻⁵)	No. (%)	rate (10 ⁻⁵)
0–4	417 (61.1)	2.3	142 (20.7)	0.8	124 (18.2)	0.7	683 (100.0)	3.8
5–9	246 (64.6)	1.3	108 (28.3)	0.6	27 (7.1)	0.1	381 (100.0)	2.0
10–14	199 (45.8)	1.1	134 (30.9)	0.7	101 (23.3)	0.5	434 (100.0)	2.3
0–14	862 (57.6)	1.6	384 (25.6)	0.7	252 (16.8)	0.5	1498 (100.0)	2.8

to Taiwan's Cancer Registry Center between 1981 and 1990 to explore time trends and geographical variations of childhood leukaemia incidence rates.

Materials and Methods

Study subjects and base population

All childhood leukaemia cases (*International Classification of Diseases for Oncology* (ICD-O) codes 980–994) diagnosed between 1979 and 1990 in Taiwan were retrieved from the national cancer registry. For each case, sex, age at diagnosis, type of leukaemia, and district of residence were collected for analysis. The accuracy and completeness of cancer registry were evaluated elsewhere.⁴ It suggested that the registration for the first 2 years is less complete. To avoid a false sense of rising secular trend in childhood leukaemia, the 1979 and 1980 data were excluded from the analyses. The annual district-age-specific (0–4, 5–9, 10–14 years) population sizes between 1981 and 1990 were derived from the national annual census statistics published by Ministry of the Interior of Taiwan. With the above information, we were able to calculate annual district-age specific incidence rates of childhood leukaemia.

Classification of urban/rural districts

Each district in Taiwan (a total of 361 districts) is given an index of one to eight according to its degree of urbanization. The level of urbanization was determined using the urban-rural classification of Tzeng and Wu, in which population density, age composition, mobility, economic activity and family income, educational level, and health and sanitation facilities were integrated into a single index.⁵ The district with the highest degree of urbanization, such as the Taipei metropolitan area, was given an index of one, while the mountainous areas with the least degree of urbanization were indexed as eight. For the purpose of study, we reclassified the districts into four levels of urbanization with urbanization indices of one or two combined into the category 'metropolitan', three or four into the category 'city', five or six into the category 'town', and seven or eight into the category 'rural area'.

Statistical analysis

Childhood leukaemia incidence rates were calculated for five 2-year periods i.e. 1981–1982, 1983–1984, 1985–1986, 1987–1988 and 1989–1990, for the age groups 0–4, 5–9 and 10–14 years, respectively. The log-linear model, with the natural logarithm of incidence rates as the dependent variable, was used to fit grouped data from three age groups (0–4, 5–9, 10–14), five 2-year periods (1981–1982 to 1989–1990), and four levels

of urbanization (metropolitan, city, town, and rural areas). The log-linear model was fitted with standard Poisson distribution assumption and was used to assess the effects of age, period, and urbanization on the variation of childhood leukaemia incidence rates.⁶ The ratio of two incidence rates was calculated using the formula e^m , where m is the regression coefficient. The statistical significance for the effect of childhood leukaemia incidence rates by age, period, and level of urbanization individually or combined was tested using analyses of deviance for the log-linear model. The analysis of deviance was also used to test for secular trend of incidence rates and for dose-response relationship between risk of childhood leukaemia and levels of urbanization by fitting a model with a term for period coded 1 to 5 and a term for levels of urbanization coded 1 to 4, respectively. We used GLIM computer package to fit the log-linear regression model.⁷

Results

Descriptive epidemiology

A total of 1498 cases of childhood leukaemia (<15 years old) diagnosed between 1981 and 1990 were reported to the Cancer Registry Center of Taiwan. Among them, 57.6% were acute lymphoblastic leukaemia, 25.6% were non-lymphoblastic leukaemia, and the other 16.8% were chronic leukaemia and those unclassified. The distributions of types of childhood leukaemia were not similar across age groups. Acute lymphoblastic leukaemia was the commonest subtype in all age groups with a pronounced peak at age 0–4, whereas the incidence rate of non-lymphoblastic leukaemia was rather similar in all age groups (Table 1).

The annual variation in age-specific incidence rates showed a significant increase of 20% (rate ratio (RR) = 1.2, 95% CI: 1.0–1.4) from 2.3 per 10⁵ in 1981–1982 to 2.7 per 10⁵ in 1989–1990 (Table 2). The incidence rate in children aged 0–4 was consistently higher than those of older ages over the study period (data not shown). Although variable, the incidence rates among children of different ages all showed a moderate but non-significantly rising trend in the 1980s.

Prediction of incidence rates by age, period and urbanization

We fitted separate models to assess the crude and adjusted effects of age, year of diagnosis (calendar year or period), and level of urbanization on the variation of childhood leukaemia incidence rates (Table 3). The model fitted with age or level of urbanization was significantly better than that fitted with the constant term alone, indicating that the variation in childhood leukaemia incidence rates can be significantly explained by age

Table 2 Age-specific relative risk estimates and 95% confidence interval (CI) of childhood leukaemia, using '1981-1982' as reference, in Taiwan, 1981-1990

Age		Calendar year					Test for trend in the rate of childhood leukaemia incidence		
		1981-1982	1983-1984	1985-1986	1987-1988	1989-1990	Deviance difference	DF ^a difference	P ^b
0-4	N ^c	142	147	130	124	140			
	RR ^a	1.0	1.0	1.0	1.0	1.2	2.09	1	>0.05
	CI ^a		0.8-1.3	0.8-1.3	0.8-1.3	1.0-1.5			
5-9	N	59	86	72	80	84			
	RR	1.0	1.4	1.1	1.2	1.4	1.68	1	>0.05
	CI		1.0-1.9	0.8-1.6	0.9-1.7	1.0-1.9			
10-14	N	64	98	87	112	73			
	RR	1.0	1.6	1.4	1.7	1.1	0.46	1	>0.05
	CI		1.1-2.1	1.0-1.9	1.3-2.4	0.8-1.5			
0-14	N	265	331	289	316	297			
	RR	1.0	1.2	1.1	1.2	1.2	3.32	1	>0.05
	CI		1.0-1.4	0.9-1.4	1.0-1.4	1.0-1.4			

^a DF = degree of freedom; RR = rate ratio.^b Statistical significance based on χ^2 test.^c Number of cases.**Table 3** Analysis of deviance for log-linear model, assessing the effect of age, calendar year (period), and urbanization level on the childhood leukaemia incidence in Taiwan, 1981-1990

Fitting	Deviance	DF ^a	Effect	Deviance difference	DF difference	P ^b
constant term	253.6	59				
constant + age	128.6	57	age ^c	125.0	2	<0.01
constant + period	244.4	55	period ^c	9.2	4	>0.05
constant + urbanization	242.0	56	urbanization ^c	11.6	3	<0.01
constant + age + period	117.6	53				
constant + age + urbanization	114.3	54				
constant + period + urbanization	233.2	52				
constant + age + period + urbanization	103.9	50	age ^d	129.3	2	<0.01
			period ^d	10.4	4	>0.05
			urbanization ^d	13.7	3	<0.01

^a DF = degree of freedom.^b Significance based on χ^2 test.^c Crude effect.^d Adjusted effect.

and level of urbanization individually. On the other hand, the crude effect of period on the variation in childhood leukaemia incidence rates was compared to null. In the assessment of adjusted effects, the addition of age to the period-urbanization model gave the most significant improvement. The adjusted effect of level of urbanization was statistically significant as well. Although the addition of period to the age-urbanization model gave some further improvement, such improvement was not statistically significant. The analysis of deviance indicated that both age and level of urbanization were able to significantly predict the variation in childhood leukaemia incidence rates.

Time trend of incidence rates by ages

Table 2 shows the secular trend of age-specific relative risk estimates, using the incidence rate of 1981-1982 as reference, of childhood leukaemia between 1981 and 1990. Over the 10-year

period, the overall incidence rate of childhood leukaemia increased by 20% (RR = 1.2, 95% CI: 1.0-1.4). The increase was particularly evident in children between 5 and 9 (RR = 1.4, 95% CI: 1.0-1.9). Nonetheless, the rising trends for the overall and for the three age-specific incidence rates were all compared to null statistically, suggesting again that the secular change of risks of childhood leukaemia was not significant.

Age-specific incidence rates by level of urbanization

Table 4 shows the overall and the age-specific relative risk estimates, using the incidence rate of rural areas as reference, of childhood leukaemia with increasing levels of urbanization. The metropolitan children experienced a 1.3 fold (RR = 1.3, 95% CI: 1.1-1.6) higher incidence rate than that of children in rural areas (2.9 per 10⁵ versus 2.2 per 10⁵). Further age-specific metropolitan/rural comparison showed that the rate ratio was

Table 4 Trend of relative risk estimates of childhood leukaemia with increasing level of urbanization, using 'rural area' as reference, by age in Taiwan, 1981–1990

Levels of urbanization					Test for trend in the rate of childhood leukaemia incidence			
Age		Rural area	Town	City	Metropolitan	Deviance difference	DF ^a difference	p ^b
0-4	N ^c	78	152	158	295			
	RR ^a	1.0	1.2	1.3	1.5	13.65	1	<0.01
	CI ^a		0.9-1.5	1.0-1.7	1.2-1.9			
5-9	N	40	86	87	168			
	RR	1.0	1.2	1.1	1.3	2.70	1	>0.1
	CI		0.8-1.7	0.8-1.7	0.9-1.9			
10-14	N	54	98	110	172			
	RR	1.0	1.1	1.2	1.1	0.48	1	>0.1
	CI		0.8-1.5	0.9-1.7	0.8-1.5			
0-14	N	172	336	355	635			
	RR	1.0	1.1	1.2	1.3	12.43	1	<0.01
	CI		1.0-1.4	1.0-1.4	1.1-1.6			

^a DF = degree of freedom; RR = rate ratio; CI = 95% confidence interval.

^b Statistical significance based on χ^2 test.

^c Number of cases.

mostly noted in children of 0–4 years old (4.4 per 10⁵ versus 2.9 per 10⁵, RR = 1.5, 95% CI: 1.2–1.9), and that the rate ratios for the other ages were only moderately and non-significantly elevated (Table 4). The trend analysis also suggested that the overall incidence rates showed a statistically significant urbanization gradient (*P* for trend test < 0.01), and the urbanization gradient was solely evident (*P* for trend test < 0.01) in children below 5 years old.

Discussion

Between 1981 and 1990 the incidence rate of leukaemia significantly increased by 20% in Taiwan's children under 15 years old. Although a slightly rising trend in the incidence rates was observed, this did not reach statistical significance. In addition, the overall incidence rate was significantly higher in metropolitan than in rural areas. Such metropolitan/rural difference was mostly notable in children aged <5 years. The dose-response analysis further showed a significant gradient in the incidence rates with levels of urbanization, in particular among children under ages of 5. The main results from the study may imply that factors related to modernization or urbanization could be associated with the occurrence of childhood leukaemia. These factors may include lifestyle changes, socioeconomic improvement, and growing diversity and the amount of environmental and industrial hazards.

One may reasonably postulate that improvements in cancer diagnosis, access to medical care, and registration completeness may account for a higher incidence rate of childhood leukaemia in Taiwan's urban regions. Because the significant urbanization-childhood leukaemia association was observed only in children less than 5 years old, the association found between level of urbanization and incidence rates would not be merely an artefact. Moreover, assessment of Taiwan's cancer registry also showed no urban/rural difference in registration completeness.⁴ Although improvements in cancer diagnosis, access to medical

care, and registration completeness made little contribution to the observed urbanization-childhood leukaemia association, they were likely to be responsible for the moderate secular increase in the incidence rates.

Similar findings have been reported in some previous studies. Two British studies concluded that there was evidence of a general tendency for lymphoid leukaemia to cluster in areas of higher socioeconomic status, in particular for those aged under 5.^{8,9} A review of other studies in the US, UK, and Australia also indicated higher risks of childhood leukaemia associated with higher socioeconomic status.¹ Because some indicators used in our study to determine levels of urbanization, such as family income, educational level, and health and sanitation facilities were highly related to socioeconomic status, our results may also suggest a possible relation of childhood leukaemia to higher socioeconomic status. Moreover, the similarity of age ranges (i.e. <5 years old) at which socioeconomic status most significantly associated with childhood leukaemia as reported in the British study and in this study was of particular interest. This may have an implication that a common aetiological factor manifested in different ways.

Childhood leukaemia has frequently been proposed as associated with exposure to infection as a result of population mixing.⁸ A recent study in the US showed a 40% higher risk in areas of high population density than in low population-density areas.¹⁰ One latest study of Chinese child population in Hong Kong also indicated significant evidence of clustering of acute lymphoblastic leukaemia in areas with extreme population mixing.¹¹ Taiwan's economy developed very rapidly in the 1980s. During this period there was a dramatic increase in population mixing arising from influxes of the rural population into metropolitan areas for better employment opportunities, and childhood leukaemia might have increased as a consequence of population mixing. As shown in Table 5, the population of all ages increased by 24.2% over the study period in metropolitan regions, and the metropolitan childhood population (<15 years)

Table 5 Changes in average population size between '1981–1982' and '1989–1990' by level of urbanization

Level of urbanization	Average annual population size & percentage of change					
	Total population			Child population		
	1981–1982	1989–1990	change (%)	1981–1982	1989–1990	change (%)
Metropolitan	6 383 593	7 930 500	↑24.2	2 131 911	2 216 919	↑4.0
City	3 815 107	4 765 222	↑24.9	1 280 081	1 332 460	↑4.1
Town	4 483 625	4 708 158	↑5.0	1 425 181	1 267 888	↓11.0
Rural areas	2 909 168	2 699 361	↓7.2	881 476	659 699	↓25.2

also increased by 4.0% within the same period. On the other hand, the total and childhood populations in rural areas decreased by 7.2% and 25.2%, respectively. Given the sustained decline in birth rates since the early 1960s in Taiwan, the increase in population in urban regions was largely due to the migration of people from rural parts of the island. From the above information, our study seems able to provide support for the putative association between population mixing and risk of childhood leukaemia. Whether the possible association between population mixing and risk of childhood leukaemia has been due to infection, however, cannot be substantiated in our study.

In summary, there was a general tendency for childhood leukaemia incidence to be higher in urban regions of Taiwan between 1981 and 1990. The association found between urbanization and risk of childhood leukaemia can be interpreted in two ways. Firstly, because population density was an integral element of urbanization and there was a notable population mixing in the 1980s, our result may provide empirical support for the hypothesis that population mixing may account for higher risks of childhood leukaemia possibly due to increased susceptibility to infection in children. Secondly, although our data are supportive of the 'infection' hypothesis for childhood leukaemia, our findings would not preclude the possibility that certain environmental hazards and/or urbanization-related lifestyle changes may have played important roles in causing the urbanization-leukaemia association in children. We therefore suggest that further research is desirable to examine whether the association between urbanization and childhood leukaemia can be attributable to an individual's exposure to virus infection or other urbanization-related hazards.

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