RESEARCH COMMUNICATION

# A Case-Control Study on the Association Between Environmental factors and the Occurrence of Acute Leukemia Among Children in Klang Valley, Malaysia

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## Abstract

**Background: In Malaysia, acute leukemia is the most common cancer among children below the age of 15. A case-control study was here conducted for cases from the Klang Valley, Malaysia, who received treatment at the National University of Malaysia Hospital (HUKM) and Kuala Lumpur General Hospital (GHKL). The main objective was to determine any association with environmental factors. Methods: Case subjects were children aged below 15 years and diagnosed with acute leukemia in HUKM and GHKL between January 1, 2001 and May 30, 2007. Control subjects were children aged below 15 years who were diagnosed with any non-cancerous acute illnesses in these hospitals. A total of 128 case subjects and 128 control subjects were enrolled in this study. The information was collected using a structured questionnaire and a global positioning system (GPS) device. All factors were analyzed using unmatched logistic regression. Results: The analysis showed that the occurrence of acute leukemia among children was strongly determined by the following factors: family income (odds ratio (OR) 0.19, 95% confidence interval (CI): 0.09–0.42), father with higher social contact (OR 7.61, 95% CI: 3.78–15.35), number of elder siblings (OR 0.36, 95% CI: 0.18–0.77), father who smokes (OR 2.78, 95% CI: 1.49–5.16), and the distance of the house from a power line (OR 2.30, 95% CI: 1.18–4.49). Conclusions: Some socioeconomic, demographic, and environmental factors are strong predictors of the occurrence of acute leukemia among children in Klang Valley, Malaysia. In terms of environmental factors, it is recommended that future housing areas should be developed at least 200 m away from power lines.**

**Key Words:** Acute leukemia - case-control study - environmental factors

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## Introduction

In early days, acute leukemia was called cancer of white blood cells and the word 'acute leukemia' was actually first introduced by Friedrich in 1857 (Pinkel, 1999). Generally, acute leukemia is not categorized in the 10 most common types of cancer worldwide. Acute leukemia is classified according to the French-American-British (FAB) classification into two types; acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). The incidence of AML is less than that of ALL whereby the rates in most Asian countries except Hong Kong, India, China, and Japan, were reported to be less than 5/1000000 (Li et al. 1999). Although the incidence of ALL is higher, ALL proved more responsive to chemotherapy in one series (Ness et al., 2005).

At the end of the 20th century, the incidence rate of leukemia among children below 15 years old was 5.77/100 000 in Hong Kong, 3.65/100 000 in the United States, and 4.11/100 000 in France (Li et al., 1999). In Malaysia, the incidence rate of leukemia among children below 15 years was 3.5/100,000 (Lim 2000). In Peninsular Malaysia, leukemia is the most common type of cancer among children, as reported in the National Cancer Registry of Malaysia (NCR, 2003).

Several factors have been associated with acute leukemia among children. Steffen et al(2004) showed that living within 1 km from benzene-producing sites (petrol stations and vehicle repair garages) posed a high risk (OR 4.0, 95% CI: 1.5-10.3). In addition, a study by Knox (2006) showed that children who lived within 100 m from a main road were more likely to suffer from acute leukemia (OR 2.1, 95% CI: 1.9-2.2). Furthermore, Draper et al (2005) found children living within 200m of power lines to be at elevated risk (OR 1.69, 95% CI: 1.13–2.53).

These studies have showed that environmental factors contribute to the increased risk of acute leukemia among children. However, in Malaysia, such studies have hitherto not been done. Therefore, this case-control study has been conducted to determine the association between environmental factors and acute leukemia among children in Klang Valley.

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## Materials and Methods

*Subjects*

The case subjects were children below 15 years old with histological confirmed diagnosis of acute leukemia in HUKM and Kuala GHKL from January 1, 2001 to May 30, 2007. Control subjects were children below the age of 15 with an acute disease other than cancer, and have received treatment in these two hospitals between April and June 2007. All participants were residents of Klang Valley, Malaysia. Those who refused to participate were excluded. A total of 128 cases and 128 controls were finally enrolled in this study. This study was approved by the Research Ethics Committee of National University of Malaysia in March 2007.

*Data Collection*

Data were collected by using a structured questionnaire conducted in these hospitals. The questionnaire included questions on sociodemographic and economic characteristics, lifestyle, reproductive history, family history, and environment. Parents or guardians of the children were interviewed by the researcher or trained research assistants. After completing data collection, a global positioning system (GPS) device was used to locate the coordinates of all the subjects' houses. In addition, the coordinates of all environmental factors (power lines and petrol stations) were also recorded to verify locations. Before the coordinates were recorded, the coordinate readings from GPS device were ensured to be stabilized and read in open areas.

*Data Analysis*

Data analysis was divided into two sections. First, descriptive analysis was used for factors such as age, gender, ethnic group, educational status, family income, and occupation. The t-test and chi-square test were used for quantitative and qualitative data, respectively, for socioeconomic, reproductive, and environmental factors. Adjusted odds ratios were calculated by logistic regression analysis using the SPSS v.12.0 statistical package.

**Table 1. Characteristics of Respondents according to Ethnic Group, Age at Diagnosis, and Gender**

| Characteristics | | Cases | Controls | #$\chi$2 | p value |
|---|---|---|---|---|---|
| Ethnicity | Malay | 96 (75.0) | 91 (71.1) | 1.916 | 0.384 |
| | Chinese | 19 (14.8) | 27 (21.1) | | |
| | Indian | 13 (10.2) | 10 (7.8) | | |
| Age | 0–4 | 58 (45.3) | 72 (56.3) | 3.018# | 0.082 |
| | 5–9 | 53 (41.4) | 44 (34.4) | | |
| | 10–14 | 17 (13.3) | 12 (9.4) | | |
| Gender | Male | 76 (59.4) | 65 (50.8) | 1.910 | 0.167 |
| | Female | 52 (40.6) | 63 (49.2) | | |

#$\chi$2 value for trend

**Table 2. Univariate Analysis for Selected Study Variables**

| Variables | | Cases | Controls | OR | 95% CI | $\chi$2 value | p value |
|---|---|---|---|---|---|---|---|
| Maternal Education | Tertiary | 20 (15.6) | 26 (20.3) | 0.73 | 0.38-1.38 | 0.954 | 0.329 |
| | Secondary | 108 (84.4) | 102 (79.7) | | | | |
| Paternal Education | Tertiary | 29 (22.7) | 35 (27.3) | 0.78 | 0.44-1.37 | 0.750 | 0.386 |
| | Secondary | 99 (77.3) | 93 (72.7) | | | | |
| Family Income | ≥ RM2000 | 82 (64.1) | 106 (82.8) | 0.37 | 0.21-0.66 | 11.534 | 0.001* |
| | < RM2000 | 46 (35.9) | 22 (17.2) | | | | |
| Maternal Social Contact | High | 39 (30.5) | 28 (21.9) | 1.57 | 0.89-2.75 | 2.446 | 0.118 |
| | Low | 89 (69.5) | 100 (78.1) | | | | |
| Paternal Social Contact | High | 94 (73.4) | 45 (35.2) | 5.10 | 2.99-8.70 | 37.795 | <0.001* |
| | Low | 34 (26.6) | 83 (64.8) | | | | |
| No. of elder siblings | <2 siblings | 69 (53.9) | 97 (75.8) | 0.37 | 0.22-0.64 | 13.434 | <0.001* |
| | ≥ 2 siblings | 59 (46.1) | 31 (24.2) | | | | |
| Birth weight | ≥ 2.5 kg | 121 (94.5) | 118 (92.2) | 1.47 | 0.54-3.98 | 0.567 | 0.451 |
| | < 2.5 kg | 7 (5.5) | 10 (7.8) | | | | |
| Maternal age | ≥ 35 years old | 26 (20.3) | 9 (7.0) | 3.37 | 1.51-7.52 | 9.565 | 0.002* |
| | < 35 years old | 102 (79.7) | 119 (93.0) | | | | |
| Paternal age | ≥ 35 years old | 53 (41.4) | 33 (25.8) | 2.03 | 1.20-3.46 | 7.004 | 0.008* |
| | < 35 years old | 75 (58.6) | 95 (74.2) | | | | |
| Family history of cancer | Yes | 27 (21.1) | 11 (8.6) | 2.84 | 1.34-6.02 | 7.911 | 0.005* |
| | No | 101 (78.9) | 117 (91.4) | | | | |
| Down's syndrome | Yes | 7 (5.5) | 5 (3.9) | 1.42 | 0.44-4.61 | 0.350 | 0.554 |
| | No | 121 (94.5) | 123 (96.1) | | | | |
| Paternal smoking | Yes | 88 (68.8) | 48 (37.5) | 3.67 | 2.19-6.15 | 25.098 | <0.001* |
| | No | 40 (31.3) | 80 (62.5) | | | | |
| Attendance in daycare | Yes | 39 (30.5) | 36 (28.1) | 1.12 | 0.65-1.92 | 0.170 | 0.680 |
| | No | 89 (69.5) | 92 (71.9) | | | | |
| Distance to petrol station | ≤ 1 km | 83 (64.8) | 88 (68.8) | 0.84 | 0.50-1.41 | 0.440 | 0.507 |
| | > 1 km | 45 (35.2) | 40 (31.2) | | | | |
| Distance to main road | ≤ 100 m | 25 (19.5) | 11 (8.6) | 2.58 | 1.21-5.50 | 6.335 | 0.012* |
| | > 100 m | 103 (80.5) | 117 (91.4) | | | | |
| Distance to power line | ≤ 200 m | 52 (40.6) | 31 (24.2) | 2.14 | 1.25-3.66 | 7.862 | 0.005* |
| | > 200 m | 76 (59.4) | 97 (75.8) | | | | |

*significant

**Table 3. Logistic Regression Model for Acute Leukemia in Children**

| Risk factors | | | _ | Standard error | Wald | p value | Adjusted OR | 95% CI |
|---|---|---|---|---|---|---|---|---|
| Family Income | ≥ RM2000 | (1) | -1.649 | 0.399 | 17.119 | <0.001* | 0.19 | 0.09–0.42 |
| | < RM2000 | (0) | | | | | | |
| Paternal social contact | High | (1) | 2.030 | 0.358 | 32.211 | <0.001* | 7.61 | 3.78–15.35 |
| | Low | (0) | | | | | | |
| No. of elder siblings | < 2 | (1) | -1.015 | 0.385 | 6.958 | 0.008* | 0.36 | 0.18–0.77 |
| | ≥ 2 | (0) | | | | | | |
| Maternal age | ≥ 35 years | (1) | 0.381 | 0.560 | 0.463 | 0.496 | 1.46 | 0.49–4.38 |
| | < 35 years | (0) | | | | | | |
| Paternal age | ≥ 35 years | (1) | 0.286 | 0.394 | 0.526 | 0.468 | 1.33 | 0.62–2.88 |
| | < 35 years | (0) | | | | | | |
| Family history of cancer | Yes | (1) | 0.947 | 0.487 | 3.784 | 0.052 | 2.58 | 0.99–6.69 |
| | No | (0) | | | | | | |
| Paternal smoking | Yes | (1) | 1.021 | 0.316 | 10.411 | 0.001* | 2.78 | 1.49–5.16 |
| | No | (0) | | | | | | |
| Distance to main road | ≤100m | (1) | 0.236 | 0.469 | 0.254 | 0.614 | 1.27 | 0.51–3.18 |
| | >100m | (0) | | | | | | |
| Distance to power line | ≤ 200m | (1) | 0.831 | 0.342 | 5.911 | 0.015* | 2.30 | 1.18–4.49 |
| | > 200m | (0) | | | | | | |
| Constant | | | -0.358 | 0.504 | 0.506 | 0.477 | 0.70 | |

* significant OR

## Results

There were 256 subjects enrolled. In terms of ethnic groups, 187 (73%) were Malays, 46 (18%) were Chinese, and 23 (9%) were Indians. The median age at diagnosis for cases was 5 years (interquartile range (IQR): 3-7 years), whereas that for controls was 4 years (IQR: 1.6–6.9 years). Results from the Mann-Whitney test showed a significant difference between the two groups (p=0.007).

Table 1 shows subjectcharacteristics. In terms of age at diagnosis, no significant difference was found (p=0.082). There were 115 (44.9%) girls and 141 (55.1%) boys. According to gender, no significant difference was found through chi-square test or unadjusted OR (OR 1.42, 95% CI: 0.86-2.32). In addition, no significant difference was also found in ethnic group (p=0.384).

Table 2 illustrates the crude odds ratio for acute leukemia with socioeconomic, demographic, reproductive, genetic, lifestyle, and environmental factors. It was found that children with a family income of ≥ RM2000 have a lower risk of acute leukemia than those with a lower family income (OR 0.37, 95% CI: 0.21–0.66). In terms of social contact, children with high paternal social contact have higher risk of acute leukemia than those with low paternal social contact (OR 5.10, 95% CI: 2.99–8.70). The result supported the Kinlen hypothesis, which states that the rate of infection that causes acute leukemia increases in a situation where contact and communication are high (population mixing). However, in terms of maternal social contact, no significant risk was found. With regard to the number of elder siblings, children who have < 2 siblings have lower risk than those with ≥ 2 siblings (OR 0.37, 95% CI: 0.22–0.64). In terms of parental age, children with parents ≥ 35 years old have higher risk of acute leukemia than those with parental age of < 35 years old [(OR 3.37, 95% CI: 1.51–7.52) and (OR 2.03, 95% CI: 1.20–3.46), respectively]. It was also found that children with positive family history of cancer have a higher risk than those with negative family history of cancer (OR 2.84, 95% CI: 1.34–6.02). Moreover, children whose father smoked were also found to have higher risk of acute leukemia than those with fathers who do not smoke. (OR 3.67, 95% CI: 2.19–6.15). Lastly, in relation to environmental factors, children who live within 100 m to main road or 200 m to power line/substation have higher risk of acute leukemia than those who live outside those ranges [(OR 2.58, 95% CI: 1.21–5.50) and (OR 2.14, 95% CI: 1.25–3.66) respectively].

Table 3 shows the adjusted odds ratios from logistic regression model for acute leukemia in children. It was found that the risk of acute leukemia is reduced in cases where the family income is ≥ RM2000 (OR 0.19, 95% CI: 0.09–0.42). It was also found that high paternal social contact increased the risk of acute leukemia (OR 7.61, 95% CI: 3.78–15.35). In addition, having < 2 elder siblings was also found to reduce the risk (OR 0.36, 95% CI: 0.18–0.77). Furthermore, paternal smoking was found to increase the risk of acute leukemia (OR 2.78, 95% CI: 1.49–5.16). In terms of environmental factors, a distance of 200 m from the residence to the power line/substation was found to increase the risk of acute leukemia (OR 2.30, 95% CI: 1.18–4.49).

## Discussion

The ethnic group distribution among children in this study is similar to that of the second report of National Cancer Registry (NCR 2003). However, the association of acute leukemia between ethnic groups, age at diagnosis, and gender was not significant. This shows that children would have higher risks of acute leukemia regardless of their ethnic group, age, and gender if they were exposed to particular hazards.

Children with family income of ≥ RM2000 have lower risk of acute leukemia than those with family income of < RM2000. This result is inconsistent with other studies9,10. In this study, family income may not be the exact indicator to measure socioeconomic status because

respondents may not have given the correct family income information because of secrecy. Other studies used census data to overcome this problem (Dockerty et al., 2001; Borugian et al., 2005).

Parental age ≥ 35 years old was not associated with acute leukemia in this study. This finding is also inconsistent with other studies (Dockerty et al. 2001; Podvin et al. 2006). Podvin et al. (2006) showed maternal age ≥ 35 years old to be associated with ALL in children. In our study, the number of AML cases was too small for analysis of leukemic subtypes.

Children with <2 elder siblings demonstrated a lower risk but the result is inconsistent with a study of Dockerty et al. (2001) and the hypothesis by Greaves (1997). However, the report by International Agency for Research on Cancer (IARC) mentioned that the association between number of siblings and acute leukemia was inconsistent as reported in previous studies (Little 1999).

Birth weight was not found to be associated with acute leukemia in this study. The result is inconsistent with studies by Podvin et al. (2006) and McLaughin et al. (2006), which showed increased risk with increased birth weight. There could be reciprocal relationship between birth weight and maternal weight that was not studied because of the difficulty in obtaining maternal weight.

Paternal smoking was found to increase the risk of acute leukemia in children in this study. This result is consistent with other studies (Little 1999; Chang et al. 2006). In addition, smoking has been associated with DNA damage (Fraga et al. 1996). Thus, this study shows a possible link between paternal smoking and acute leukemia, which in turn, can be avoided.

There was no association found in this study between children's attendance in a daycare center and acute leukemia. Nevertheless, among those who were sent to daycare, the association between acute leukemia and age ≥ 3 years old was found, in line with the Greaves hypothesis where prolonged period between first genetic mutation (fetal life) and second genetic mutation (childhood life) increasing the number of premature leukemic cells, and thus the risk of acute leukemia. Multivariate analysis was not possible because of the small sample size.

In terms of environmental factors, a distance of 200 m from the residence to power line was found to be associated with acute leukemia. This result is consistent with a study by Draper et al. (2005). Thus, this study adds more value in terms of evidence on the association between acute leukemia and environmental factors.

Several limitations that usually occur in hospital-based case-control studies have been identified. First, study subjects did not represent all cases within the population. In addition, some subjects were also not available for interviews because of the brief study period. Second, some selection bias may be present as the control groups were limited to the hospital's patients. It would have been better if the controls were from the general population. Third, information bias usually happens in the case-control study. In this study, some information were derived from health records, whereas other information was based on memory or from close relatives. Lastly, confounding bias may occur among the variables in the study; for example, the distance between the children's houses to main roads and power lines. Some power lines are located parallel to the main roads. Therefore, the hazard could come from either power lines or main roads, although the effect was controlled through multivariate analysis.

The present study suggests that some socioeconomic, demographic, and environmental factors are strong predictors for the occurrence of acute leukemia among children. Thus, it is recommended that an anti-smoking campaign be carried out to include the risk of acute leukemia in children whose parents are smokers. It is also recommended that future residential areas should be developed at least 200 m away from power lines.

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