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Childhood leukemia mortality and farming exposure in South Korea: A national population-based birth cohort study

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ABSTRACT

Objectives: The aim of this study was to evaluate the relationship between leukemia mortality and exposure to farming among children in South Korea.
Methods: A retrospective cohort study of South Korean children was conducted using data collected by the national birth register between 1995 and 2006; these data were then individually linked to death data. A cohort of 6,479,406 children was followed from birth until either their death or until December 31, 2006. For surrogate measures of pesticide exposure, we used residence at birth, paternal occupation, and month of conception from the birth certificate. Farming and pesticide exposure indexes by county were calculated using information derived from the 2000 agricultural census. Poisson regression analyses were used to calculate rate ratios (RRs) of childhood leukemia deaths according to indices of exposure to agricultural pesticides after adjustment for potential confounders.
Results: In total 585 leukemia deaths were observed during the study period. Childhood leukemia mortality was significantly elevated in children born in rural areas (RR = 1.43, 95%CI 1.09–1.86) compared to those in metropolises, and in counties with both the highest farming index (RR = 1.33, 95%CI 1.04–1.69) and pesticide exposure index (RR = 1.30, 95%CI 1.02–1.66) compared to those in the reference group. However, exposure–response associations were significant only in relation to the farming index. When the analyses were limited to rural areas, the risk of death from leukemia among boys conceived between spring and fall increased over those conceived in winter.
Conclusions: Our results show an increase in mortality from childhood leukemia in rural areas; however, further studies are warranted to investigate the environmental factors contributing to the excess mortality from childhood leukemia in rural areas.

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1. Introduction

Leukemia is the most common form of childhood cancer in the world, accounting for around 30% of all cancers diagnosed in children younger than 15 years of age [1]. However, risk factors for the disease remain largely unknown, and the established causal factors – such as ionizing radiation and congenital genetic syndromes – together explain less than 10% of the cases. Several other environmental agents have been put forward to explain its etiology; these include parental smoking, electromagnetic fields, socioeconomic status, infection, and pesticides [2].

Several reviews of epidemiological studies examining the potential association between childhood leukemia and residential pesticide exposure have been conducted [3,4]. Despite this existing epidemiological literature (suggesting elevated childhood leukemia risks related to household environmental pesticide exposure), the evidence for a causal relationship between exposure to agricultural pesticides and childhood leukemia is still limited. Studies on this topic among Asian populations are also lacking, and the results vary between countries due to differences in exposure and demographic characteristics. Moreover, most findings on childhood leukemia and pesticides were from case–control studies.

In South Korea, the incidence of childhood leukemia was 5.0 per 100,000 population in 2010, accounting for 33.2% of all cancer incidence among children aged 0–14 years [5]. South Korea has traditionally been an agricultural nation, and it still retains as of 2011 a farming population of about three million (approximately 6% of the total population). The quantity of pesticides used was

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recorded as 19,131 tons [6], and average pesticide consumption was 10.6 kg per hectare in 2011 – higher than that in other developed countries with intensive agriculture [7]. Despite widespread agricultural pesticide exposure in the Korean population, no study has examined the relationship between childhood leukemia and this exposure in South Korea.

Therefore, the aim of this study is to examine the relationship between extent of farming and pesticide use in the county of residence, paternal occupation, and season of conception and mortality from childhood leukemia in South Korea by using national population-based retrospective birth cohort data from 1995 to 2006.

2. Materials and methods

2.1. Data sources

Details of the study design and of the population have been described previously [8,9]. In brief, data from the national birth and death registration databases of Statistics Korea were used to establish a retrospective cohort of all children born in South Korea between 1995 and 2006. Records from the national birth registration database contain information on each child born (e.g., birth date, gender, address of residence at birth, personal identification number, and birth characteristics such as birth weight and gestational duration), as well as on its parents at the time of the birth of the child (e.g., age, education, and occupation). Of the 6,813,945 total births between 1995 and 2006, we excluded 5.3% of the records that lacked a complete personal identification number – an omission due mainly to administrative disagreements between the district offices of residence and those of birth registration. A total of 6,479,406 records of live births which occurred between 1995 and 2006 in South Korea were obtained and linked to the national death registration database for the same period via their unique personal identification numbers. These individuals were followed from birth until their death or until the end of the follow-up period on December 31, 2006. The maximum age at death was 11 years old. The causes of death in the registered death data are coded according to the *International Classification of Diseases, 10th Revision* (ICD-10) [10]. A leukemia death was defined as a case marked with ICD codes between C91 and C95.

2.2. Exposure indices

As indicators of potential exposure to risk factors associated with farming, including pesticides, we used five indices.

First, residence at birth – based on the 243 administrative districts in the cohort data – was categorized as metropolis, city, or rural area. Metropolises included Seoul and six other metropolitan cities in South Korea. Districts in the nine provinces outside these metropolises were classified into either cities or rural areas, depending on governmental administrative divisions by population size and rural characteristics.

Second, we calculated the farming index using following algorithm applied in our previous study [11]. County-specific farming index = (% of full-time farm household + % of part-time farm household × 0.3) × % of farm households weighted with farming years × % of farm households weighted with farm size. The calculation process of farming index by area is presented as an Appendix A. Full-time farm population refers to persons engaged exclusively in farming, while part-time farm population refers to farm workers who also were employed in non-farming jobs to earn money for more than 30 days during the course of a year. The score assigned to part-time farm population (i.e., 0.3) was weighted to reflect the intensity of farming compared with the full-time farm population based on our professional discretion. Farming years and farm size were categorized into quartiles, i.e., ≤20, 21–32, 33–45, ≥46 years for farming years and ≤0.43, 0.44–0.89, 0.90–1.65, ≥1.66 ha for farm size. Information on the number of farm households by county, as well as farm size and farming years of each farm household, was derived from the agricultural census conducted by Statistics Korea [12]. Agricultural censuses were taken every 10 years from when the first census was taken in 1960 until 1990, and since 1995 they have been conducted on a 5-year basis. We chose the 2000 census as it was the midpoint of our cohort data. Data on the number of total households and population by county in 2000 was drawn from the database maintained by Statistics Korea (http://kosis.kr). Each term of the numerator of farming index represents the agricultural labor by each county and provides an estimate of total farming level per county.

Third, we developed a pesticide exposure index for each county. The index was calculated by taking into account the area of cultivated land (A_i) and the frequency (F_i) and hours (H_i) of pesticide application for the major crops, and the algorithm was modified on the basis of a previous study [13]. The county-specific pesticide exposure index can be described as $\sum_{i=1}^{4} A_iF_iH_i/\text{population}$. The i represents the four major types of farming (i.e., rice, upland, fruit, and greenhouse) in South Korea. The crop-specific area by county was taken from the agricultural census, and F_i and H_i from a nationwide sampling survey of male farmers in South Korea in 2010 [14]. The numerator of the formula indicates an estimate of the total pesticide load. With total population of each county in the denominator, the pesticide exposure index provides an estimate of pesticides used per inhabitant.

Fourth, besides these three regional variables, we classified parental occupations obtained from national birth certificate data. Paternal occupation was grouped into non-manual (i.e., legislators, senior officials and managers, professionals, technicians and associate professionals, clerks, and service and sale workers), manual (i.e., craft and related trades workers, plant, machine operators and assemblers, and elementary occupations), others (i.e., students, the unemployed, homemakers, and armed forces), and skilled agricultural, forestry and fishery workers.

Finally, since parental exposure to pesticides may vary by month of conception, we defined month of conception for each child as subtracting the duration of gestation from the date of birth. The month of conception was categorized into four seasons; spring (March–May), summer (June–August), fall (September–November), and winter (December–February).

2.3. Statistical analysis

The number of person-years was calculated by summing the numbers of days from the date of birth to the date of death or to the end of the follow-up period (December 31, 2006). Poisson regression was used to calculate mortality rate ratios (RRs) and 95% confidence intervals (95%CIs) of leukemia death according to our surrogates of pesticide exposure. For farming index and pesticide exposure index, we assigned counties into one of four groups based on quartiles of each index based on the distribution of total subjects (i.e., <0.02, 0.02–27.9, 28.0–20,422.3, >20,422.3 for farming index and <0.006, 0.006–0.05, 0.06–0.54, >0.54 for pesticide exposure index). We adjusted for gender and birth year of children in the analyses in order to consider any gender difference in leukemia mortality and potential cohort effect due to rapid development of medical technologies or accessibility to high-quality medical facilities with birth year. To control for potential confounders, we also included the variable of maternal education and paternal job in the analyses, which have been reported as a significant risk

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