

RESEARCH ARTICLE

Relationship between Exposure to Pesticides and Occurrence of Acute Leukemia in Iran

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Abstract

Background: One of the causes of acute leukemia can be exposure to certain chemicals such as pesticides. This study determined the relationship between exposure to pesticides and the occurrence of acute leukemia in Fars province, south of Iran. **Materials and Methods:** Between April 2011 and April 2013 in a case-control study conducted in Nemazee Hospital in Shiraz, Southern Iran; 314 subjects diagnosed with acute leukemia (94 pediatric cases and 220 adults) were enrolled to determine any correlation between exposure to pesticides and the occurrence. Controls (n=314) were matched by sex and age. **Results:** There was a history of exposure to pesticides among 85% of pediatric cases and 69% of their controls and 83% of adult cases and 75% of their controls while 87.5% of pediatric cases and 90% of adult cases reported exposure to intermediate and high doses of pesticides and among the controls, the exposure to low doses of pesticides was 70.5% and 65%, respectively. Exposure to indoor pesticides was seen among most of cases and controls. Being a farmer was at a significantly more increased risk of developing acute leukemia in comparison to other jobs, especially for their children. **Conclusions:** Exposure to pesticides was shown to be one of the most important causes of acute leukemia. It seems that there is a need to educate the people on public health importance of exposure to pesticides especially during school time to reduce the risk of malignancies during childhood.

Keywords: Pesticides - leukemia - relationship - Iran

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Introduction

Cancer is still a significant health problem in developing countries, and one that is likely to increase in future. In Iran, cancer is a public health problem among several non-communicable diseases and is the third common cause of mortality in Iran, after cardiovascular diseases and accidents. In Fars Province, southern Iran, acute lymphoblastic leukemia (ALL) has the first age-specific cancer among the 5 major cancers in males with an average annual crude incidence rate of 2.54 and ASR of 2.10 while these figures for acute myeloblastic leukemia (AML) is 1.96 and 0.64. The average annual crude incidence rate of ALL in females was shown to be 1.81 and ASR of 1.5. These figures for AML were 1.44 and 1.36 (Mehrabani et al., 2008).

Karimi et al. (2008) found that fever (74%) as the common symptom in ALL and AML patients reported that knowledge of the signs and symptoms and types of presentations of childhood leukemia may help a physician to improve the patient's outcome (Karimi et al., 2008).

Pesticides as chemical substances may minimize harmful effects of living organisms such as fungi, insects, weeds, and rodents which live on or around plants, animals, and man and decrease the nutritive value of nutritional sources during storing and consumption. They compromise subgroups such as herbicides, fungicides, insecticides, nematocides, acaricides, and rodenticides; among them insecticides are commonly used as one of pesticide subgroups. They can have chemical origins such as organo-chlorine carbamate, or organic phosphor or biological origins like pyrethroides and pyrethrins (Yildirim et al., 2013).

In several case control studies, a significant relationship was noticed between acute leukemia (lymphoblastic and myeloblastic subtypes) and exposure to pesticides (Richardson et al., 1992; Beard et al., 2003; Graillot et al., 2013), especially in children (Buckley et al., 1989; Lowengart et al., 1987; Meinert et al., 2000), and even with prenatal exposure; occupational or household, during pregnancy of mothers (Kyle, 2001; Ma et al., 2002; NRDC, 2003; Ferreira et al., 2013). Molecular

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epidemiologic research provided compelling evidence that environmental factors were major contributors to human carcinogenesis and that the risk of developing cancer was strongly influenced by genetically determined differences (Nebert et al., 1996; Perera et al., 2000).

Polymorphism in genes coding for xenobiotic transport and metabolizing enzymes like glutathione S-transferases (GSTs), cytochromes P-450 (CYP), and membrane transporters such as those encoded by the multiple drug resistance (ABCB1/MDRI) genes were shown to be largely responsible for inter-individual differences in the ability to activate and detoxify mutagenic/carcinogenic agents and individual susceptibility to cancer and specifically to acute leukemia (Infante-Rivard et al., 1999; Perera et al., 2000; Canalle et al., 2004; Urayama et al., 2007; Chokkalingam et al., 2012).

Except for leukemia, exposure to pesticides causes elevated rates of non-Hodgkin's lymphoma (NHL) and multiple myeloma (Zakerinia et al., 2012), childhood brain tumor, NHL, sarcoma and Wilm's tumor (NRDC, 2003), soft-tissue sarcoma (NCAMP home, 2001), and NHL or soft-tissue sarcoma (Costa, 2010).

Pesticides such as M1-null as well as glutathione S-transferase T1-active genotypes were shown to increase individual susceptibility to bladder cancer (Matic et al., 2014). Beranger et al.'s findings denoted to the feasibility of a case-control study focusing on the correlation between TGCT and environmental pesticide exposures during early and later life (Beranger et al., 2014). Yildirim et al. (2014) did not notice any relationship between pesticide usage and esophageal or gastric cancer (Yildirim et al., 2014).

Based on controversies, this study was undertaken in a case-control study on acute adult and childhood leukemia in Fars province to investigate any correlation between insecticides exposure and the development of acute leukemia.

Materials and Methods

The patients who were diagnosed as new cases of acute leukemia and were admitted in the adult and pediatric Hematology-Oncology Ward of Nemazee Hospital, Shiraz University of Medical Sciences, during the years 2011-2012, and through 2013 (adults only) were interviewed for any exposure to pesticides and the dose of exposure. Interviews were conducted directly with the adult subjects and their next of kin, and parents of pediatric cases.

Controls were hospital patients who were randomly chosen among subjects admitted in Emergency Room of Nemazee Hospital. Controls were matched by age, sex, and state of residence at the time of interview. Among enrolled subjects, 94 were pediatric controls and 94 were pediatric cases and 220 were adult controls and 220 were adult cases.

A variety of diagnoses were included. Patients with cancer and previous history of organ transplantation were excluded. Cases and controls were interviewed and a questionnaire contained detailed information on sociodemographic characteristics (including age, sex, place of residence) and occupational history was completed by each subject. Questions regarding occupational history

of adult patients and parents of pediatric cases were asked for each job for at least during the last year.

The interviewer listed a series of exposures to pesticide at home or at work. The subjects were asked about any extra jobs in crop farming too. For each of these exposures, the subject specified the kind of exposure, the reason, the frequency, the duration of exposure, and the interval from the first and the last exposure and the disease presentation. In this study, the term pesticide referred primarily to insecticides, herbicides, and fungicides.

With regards to the kinds of pesticides, only few patients remembered the name of the product, but almost all of them knew the specific usage of the pesticide (to control ants, flies, cockroaches, aphids, weeds, fungi, molds, etc.). Subjects were specifically asked about its form (spray, liquid, powder), the place (farm, garden, kitchen garden, kitchen, kitchen cabinet, rooms, etc.) of usage, the relative amount, and the frequency of usage (per day, week, month, year) of pesticides.

According to the amount of usage, the toxicity was graded as low, moderate, and high exposures. For example, if one had used insecticide in spray form daily or weekly for months to years, or using powder type of insecticides along the corners of the living rooms or kitchen or even in the kitchen cabinets repeatedly, or had heavily sprayed the farm or garden without protective equipment, even if only once, were scored as high dose exposure. Low dose exposures and occasional ones were scored as low exposures; like home insecticide spraying every few months, or using powder every year, or handling and application of pesticides with some protection, although dermal and inhalational exposure had occurred the next few days by working in the farm without protective clothing. The moderate toxicity was scored as the amount of exposures between the low and high toxicities. Information was also collected from the next-of-kin of adult cases with acute leukemia too.

Multinomial logistic regression was used to estimate the odds ratios and the 95% confidence intervals to measure association between pesticide exposure and acute leukemia risk; at home, in the garden, or on farm. The pesticide exposed people were compared to non-exposed ones. T-test and Chi-Square test for differences between groups were used to compare cases and controls with respect to age, sex, and occupation. Two-sided P values were considered statistically significant at the 0.05 level.

Results

Among all enrolled subjects, no statistically significant difference was observed between cases and controls with respect to age and sex. Out of pediatric leukemia cases, 53 (56%) were male and 41 (44%) were female, 69 (73%) had ALL and 25 (27%) had AML. The median age for male ALL cases was 8 years (range: 1-14 years) and for female ALL cases was 5 years (range: 2-14 years). The median age for male AML cases was 13 (range: 1-14 years) and for female AML cases was 6 years (range: 1.5-13 years).

Among adult leukemia cases, 166 (75%) had AML and 54 (25%) had ALL. Ninety nine cases (60%) of AML and 37 cases (69%) of ALL were male while the median age

Table 1. Pesticide Exposure in Pediatric Cases with Acute Leukemia in Fars Province, Iran, 2011-2012,

Exposure per year	Cases			Control No. (percent)	OR (95% CI)
	ALL	AML	Total No. (percent)		
<1	12	2	14 (15)	29 (31)	4.2 (2.2, 7.8), p≤0.001
1-5	20	6	26 (27)	42 (45)	
6-10	8	3	11 (12)	9 (9)	
>10	29	14	43 (46)	14 (15)	
Total	69	25	94 (100)	94 (100)	
The intensity of exposure					
Low	7 (12)	3 (13)	10 (12.5)	50 (70.5)	16.7 (7.2, 38.4), p≤0.001
Intermediate	8 (14)	4 (17)	12 (15)	13 (18.5)	
High	42 (74)	16 (70)	58 (72.5)	8 (11)	
Total	57 (100)	23 (100)	80 (100)	71 (100)	
The form of pesticide					
Spray			39 (49)	38 (54)	
Home (powder)			58 (73)	58 (82)	
Farm/Garden			30 (38)	15 (21)	
Spray and home			29 (36)	10 (14)	
Home and farm			9 (11)	2 (3)	
Spray and home and farm			7 (9)	1 (1)	

*ALL: Acute lymphocytic leukemia; AML: Acute myelogenous leukemia; No: Number; OR: Odds ratios; CI: Confidence intervals

Table 2. Pesticide Exposure in Pediatric Cases with Acute Leukemia in Fars Province, Iran, 2011-2012,

Exposure per year	Cases			Control No. (percent)	OR (95% CI)
	ALL	AML	Total No. (percent)		
<1	21	17	38 (17)	55 (25)	2.3 (1.5,3.4), p≤0.001
1-5	70	17	87 (40)	110 (50)	
6-10	29	6	35 (16)	22 (10)	
>10	46	14	60 (27)	33 (15)	
Total	166	54	220 (100)	220 (100)	
The intensity of exposure					
Low	14 (9)	4 (11)	18 (10)	108 (65)	17.3 (9.6,30.9), p≤0.001
Intermediate	56 (39)	18 (49)	74 (41)	36 (22)	
High	75 (52)	15 (40)	90 (49)	21 (13)	
Total	145 (100)	37 (100)	182 (100)	165 (100)	
The form of pesticide					
Spray			34 (19)	52 (31)	
Home (powder)			81 (45)	98 (59)	
Farm/Garden			62 (34)	12 (7)	
Spray and home			6 (3)	7 (4)	
Home and farm			12 (6.5)	4 (2)	
Spray and home and farm			2 (1)	3 (2)	

*ALL: Acute lymphocytic leukemia; AML: Acute myelogenous leukemia; No: Number; OR: Odds ratios; CI: Confidence intervals

for AML male cases was 34 (range: 14-87) and for AML female cases was 25 (range: 14-67) years. The median age for ALL male cases was 19 (range: 14-50), and for ALL female cases was 17 (range: 14-52) years.

Regarding the job of the father of pediatric acute leukemia cases; 24 out of 50 (48%) of the fathers of ALL cases were farmer. Two of pediatric patients (13 years old, each) were student while at the same time worked in farms too. Five fathers out of 13 (38%) cases of AML were farmers too [total=31 (48%)].

Regarding the job of adult leukemia cases; 43 (26%) AML patients were farmer, two were house keeper and seven were students. Twenty (37%) of ALL case were farmer, 3 were house keeper and 5 were student [total=63 (29%)]. In the control group, 6 were fathers

(6%) of pediatric cases and 15 (7%) were adult cases who were farmer. There was a significant increased risk for farmers (OR=14.7, 95% CI: 5.6, 38.4) and for fathers of the pediatric cases (OR=5.4, 95%CI: 3.0, 9.9.) and for adult cases too.

Only 6 (9%) out of ALL pediatric cases and 3 (12%) out of AML pediatric case [total=9 (10%)] were from Shiraz, southern Iran. Thirty seven out of 151 (25%) adult AML cases and 10 out of 49 (20%) adult ALL patients [total=47 (24%)] were from Shiraz, southern Iran. Fourteen (15%) of pediatric control group and 62 (28%) of adult control group were from Shiraz, southern Iran (p=0.128 and 0.415 for pediatric and adult cases respectively) while the difference was not statistically significant.

With regard to pesticide exposure in pediatric cases, 80 out of 94 (85%) reported exposure to pesticides while 46% had exposure more than 10 times per year, and 22% were exposed to indoor pesticides, and in 87.5%, the intensity of exposure was intermediate to high (Table 1).

Among adult cases, 182 out of 220 cases (83%) were had history of exposure to pesticides, 40% had 1-5 times exposure per year, 64% were exposed to indoor pesticides and among 90%, the intensity was intermediate to high (Table 2).

Twenty nine out of 94 (31%) of pediatric control groups and 55 out of 220 (25%) of adult control group had no pesticide exposure. In the pediatric control group, 42 (45%) had 1-5 exposure per year, 50 (70.5%) had low exposure, and 36% had indoor exposure. In the adult control group, 110 (50%) had 1-5 exposures per year, 108 (65%) had low exposure and 90% had indoor exposure (Table 1 and 2). Among most of pediatric and adult cases, the first and the last exposure until disease presentation were years and months respectively although there were cases with only one exposure.

Most people reported use of anti-ant and anti-cockroaches powder during the last month of year (March) for preparing for Iranian New Year (New Rooz), ant-flies in the summer time (indoor pesticides), and farmers reported use of pesticides at least twice per year, especially in the September (outdoor pesticides). Unfortunately no good protective clothing was used by most farmers.

In one case of 2.5 years old boy (HKh), there was a report of previous history of spraying insecticide all over the body. He was later treated with IV chemotherapy (daunorubicin and cytarabine) and was in remission in the past few years. The second case was a 25 years old male (AN) who was an agriculture engineer and worked in five greenhouse tunnels for 6 months. He reported the use of insecticides and fungicides every 2 weeks, in a humidity of 95% without any protective equipment. In June 2012, he was admitted with the diagnosis of AML and was under therapy by daunorubicin for 3 days and cytarabine for 7 days twice. In December 2012, he received allogeneic transplantation from peripheral stem cells (PSC) from his HLA identical sister. He was in remission with limited chronic graft vs. host disease. The 3rd case was a 23 years old female (ZA) who experienced dyspnea, sneezing and headache a few hours after sweeping the insecticide as an anti-ant white powder leaving in the room corners. In March 2013, she was admitted with the diagnosis of AML. After receiving standard induction chemotherapy, she achieved complete remission and received a successful allogeneic PSC from her HLA identical sister.

Discussion

Epidemiologic studies have consistently showed an increased risk of leukemia and exposure to certain petroleum-based chemicals and by-products, such as dioxins and polycyclic aromatic hydrocarbons, or benzene. A history of contamination from waste water from a nearby industrial facility to drinking water sources has been another cause of increased risk of leukemia (Yildirim et al., 2014).

Benzene was demonstrated as a well-documented leukemogen causing abnormalities in chromosomes 5 and 7 linkage (Gouveia-Vigeant and Tickner, 2003). In a case-control study for occupational risk factors of acute leukemia, there was a significant relationship between acute leukemia and high or medium exposure to benzene, as well as over 10 years of high or medium exposure to the exhausted gases. In addition, a significant relationship was observed with exposure to pesticides, especially with high or medium exposures and exposures lasting more than 10 years (Grailot et al., 2012).

In one study in an Australian population, the mortality of outdoor staffs who were working in an insecticide complex was compared with outdoor workers who were not occupationally exposed to insecticide. The mortality form pancreatic cancer was more frequent in exposed subjects and the standardized incidence ratio was 20.90 for myeloid leukemia in the highest exposure group in comparison to the controls (SMR=5.27) (Meinert et al., 2000).

In a genotoxicity assay study to investigate the cytotoxic and genotoxic potential of several pesticides that persisted in the environment or their bioaccumulation in the food chain on human cell lines, a group of French researchers noted that DNA damage appeared early after exposure to pesticides (1 hour) (Lowengart et al., 1987). Elevated risks of leukemia, brain cancer, Wilms' tumor, Ewing's sarcoma, and germ cell tumors in childhood have been observed for children whose parents were occupationally exposed to pesticides, particularly for the offspring of farmers (Buckley et al., 1989). In West Germany, a population-based case-control interview study of parents of children with leukemia, NHL, solid tumors, and controls showed that parental occupational exposure to pesticides were correlated with childhood cancer regardless of the time period of exposure and the type of cancer (Buckley et al., 1989).

In Los Angeles, USA; from a population-based cancer registry, acute leukemia cases aging 10 years or less were included by interviewing the mothers. In this case-control study, an increased risk of leukemia was found for children whose parents used pesticides at home (OR=3.8) or in the garden (OR=6.5) and the risk was greater for frequent use (Ma et al., 2002).

In another study, occupational exposure of parents of children (under 18 years) with acute non-lymphocytic leukemia, the risk for parental pesticide exposure was substantially increased for children under age 6 years (OR for prolonged exposure to either parent=11.4) and for those with myelomonocytic and monocytic subtypes (OR=13.6). Moreover, there were significantly elevated risks for direct exposure of the child to pesticides in the household and for maternal exposure to household pesticides at the time of pregnancy. No significant association of specific recurring karyotype abnormalities and occupational exposures were found (Kyle, 2001).

Another study showed that exposure to household pesticides was associated with an elevated risk of childhood leukemia (Ferreira et al., 2013). Several studies revealed the linkage between exposure to pesticide and leukemia by both parents and children (Nebert et al., 1996;

Perera et al., 2000; NRDC, 2003).

The role of genetic susceptibility to environmental exposures in the etiology of leukemia was previously studied. The glutathione S-transferases (GSTs) are a family of enzymes involved in the detoxification of a wide range of chemicals, including important environmental carcinogens. Deletion polymorphisms of the GSTM1 and GSTT1 genes may result into an absence in enzyme activity in homozygous states. A heterozygous state and the allele variants seem to reduce the enzyme activity. The P-450 (CYP) cytochrome is an enzyme involved in the initial oxidation, reduction, or dealkylation of carcinogens, which can convert indirect carcinogens into active electrophiles capable of interacting with biological macromolecules. Various polymorphisms resulted into an increase in enzyme activity and/or inducibility, and were associated with a higher level of adduct formation and increased risk to certain type of carcinoma. A combined effect to GSTs and CYP mutation may increase the susceptibility to leukemia (Urayama et al., 2007). In another study, up to several folds increased risk of childhood leukemia was noticed with frequent prenatal use of indoor and garden insecticides and a gene polymorphism was seen to be involved in metabolism of carcinogenic substances (Chokkalingam et al., 2012).

The membrane transporters such as those encoded by the multiple drug resistance (ABCB1/MDR1) gene can act as efflux pumps to expel compounds from the cell. A haplotype of ABCB1, which encodes a membrane transporter of lipophilic compounds was shown to be significantly associated with childhood ALL risk and was shown to have a significant interaction with indoor insecticides (Zakerinia et al., 2012). In another study, the effect of xenobiotic (exogenous) chemicals, and ABCB1 mutation; and an elevated risk of (pre-birth) and childhood ALL was demonstrated with the use of indoor insecticides (NCAMP home, 2001).

Approximately 80-90% of households in the United States use residential pesticides. Children and adults can be exposed during the preparation and application of pesticides, or long after applications are completed. Delayed exposure can occur via inhalation of residual air concentrations or exposure to residues on surfaces, clothing, pets, bedding, food, dust, discarded pesticide containers, or pesticide application equipment (Paion et al., 1994; Chen et al., 2006).

The relative risk (RR) for developing hematologic malignancies and aplastic anemia in 3000 victims of chemical war injury to mustard gas during 1983-1988 was previously reported to be 8 for AML, 11 for ALL, 8 for chronic myelogenous leukemia, 11 for hairy cell leukemia, 5 for Hodgkin's lymphoma, 3 for NHL, 13 for Immuno-proliferative small intestinal diseases (IPSID) and 19 for aplastic anemia in comparison to the general population of Fars province, Southern Iran. For ALL patients, a very short latency period was noticed after exposure (median: 5 months) (Zakerinia et al., 1998). In a case-control study conducted in our center, the risk of NHL and multiple myeloma was shown to be the highest for exposure to pesticides, among them, insecticide's risk was confirmed (Costa et al., 2010).

In our case-control study, more emphasize was on the dose of pesticide exposure by asking more detailed questions from adult cases and the parents of pediatric cases. In pediatric cases, 15% did not report any exposure and 85% had exposure to pesticides. In the control group, these figures were 31% and 69%, respectively. In the adult population, the exposure rate was 83% for the cases and 75% for the controls.

In our study, the dose of exposure was intermediate in 15% and high in 72.5% of pediatric cases. It was 18.5% and 11% in controls respectively (OR=16.7, 95% CI: 7.2-38.4) (Table 1). In the adult cases it was 41% for intermediate and 49% for high exposures. In the control group, it was 22% and 13% respectively (OR= 17.3, 95%CI: 9.6, 30.9) (Table 2).

In the pediatric group, 49% reported exposure to spray from of pesticides, 73% to home powders, and 38% to farm/garden types. It was 54%, 82% and 21% in the pediatric control group, respectively. In the adult cases, exposure to spray forms was 19%, to home powders was 45%, and to farm/garden exposures was 34%. It was 31%, 59%, and 7% for adult control cases, respectively. It should be mentioned that most of the cases used different forms of pesticide, at the same time or at different times. When the dose of exposure was high, the latent period to develop leukemia was short, even in weeks.

Farmers and their children were at a significantly more increased risk of developing acute leukemia in comparison to others jobs ($p \leq 0.001$). This can be due to exposure to higher doses of pesticides in this group of people (OR=14.7 for parents of pediatric cases and 5.4 for adult cases). Two of our pediatric cases (13 years old, each) and 12 of adult cases were students and reported working in farms while 5 subjects were housekeeper.

The mutation of xenobiotic (exogenous) transport and metabolizing enzymes can increase the susceptibility to leukemia by exposure to pesticides (which were not studied in our cases), but when the dose is intermediate or high, the individuals without mutation are at elevated risk of leukemia development too.

Not only acute leukemia but NHL, multiple myeloma, pancreatic cancer, soft-tissue sarcoma, childhood brain tumor, solid tumors, germ cell tumors, Ewing's sarcoma and Wilm's tumor can be due to pesticides exposure (Buckley et al., 1989). So exposure to pesticides can be one of the most important causes of acute leukemia as 70-90% of our population of study reported using these pesticides to control indoor ants, flies, etc., and outdoor plant/tree insects, weeds, etc. It seems that there is a need to educate the people on public health importance of exposure to pesticides especially during school time to reduce the risk of malignancies during childhood.

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