In the name of God

S.U.M.S.

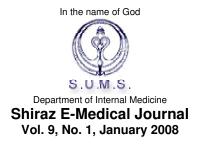Department of Internal Medicine
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A Case Control Study of Acute Leukemia Risk Factors in Adults, Shiraz, Iran.

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Abstract:

Background: Leukemia is one of the most common cancers in Iran. Few studies have focused on identifying the causative factors for leukemia. This implies the necessity of this case-control study. This study was undertaken to identify possible risk factors associated with leukemia.

Materials and Methods: In a case-control study matched by age and sex. 100 leukemic patients admitted in hematology wards in Namazee Hospital affiliated to Shiraz University of Medical Sciences were enrolled. Control group compromised 100 hospitalized patients whose diseases were unrelated to leukemia, and another 100 individuals selected from the general population. Questionnaires were completed by trained medical students.

Results and Discussion: The most significant risk factors were: place of birth and residence during the past 10 years, jobs related to agriculture/animal husbandry, contact with chemical products, history of contact with animals, family history of cancer among 1st degree relatives, and cigarette smoking for more than 10 years.

Conclusion: This epidemiologic study has encountered several restrictions that had effect on our statistics. Future studies should be conducted to achieve a more accurate result.

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Introduction:

With the development of medicine, epidemiologic pattern of diseases changed from infectious to chronic diseases. In this category, cancers still pose a big problem threatening health in societies. By the end of 20th century, cancer has been the subject of most epidemiological studies. These studies have focused on the frequency and distribution of cancer diseases [1]. Prevention and promotion of public health are the foremost objectives of epidemiology. Hence, knowledge of possible risk factors associated with the different types of cancer is necessary in an effort to determine the etiology of the disease [2].

Among the different types of cancers, leukemia appears to have greatly increased in frequency. Leukemias are diseases characterized by malignant proliferation of the blood cells of the blood and bone marrow (and of the lymph nodes in the case of the lymphocytic varieties). The types of leukemia are grouped by how quickly the disease develops and gets worse. Leukemia is either chronic (gets worse slowly) or acute (gets worse quickly). Furthermore, the types of leukemia are also grouped by the type of white blood cell that is affected. Leukemia can arise in lymphoid cells or myeloid cells. Leukemia that affects lymphoid cells is called lymphocytic leukemia. Leukemia that affects myeloid cells is called myeloid leukemia or myelogenous leukemia. There are four common types of leukemia: acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) [3,4]. According to World Health Organization (WHO),

leukemia has proliferated worldwide. The cancer registry has recorded about 250,000 new cases annually [5] and a case fatality rate of 76% [2]. In about 100,000 new cases of cancer, AML accounts for about 2.5% , while ALL is about 1.3%. The incidence of leukemia is more prevalent in men than in women. Higher incidence rates are seen among Caucasians; however, Blacks have higher fatality rates. At the time of the diagnosis, the median age is 10 years in AML and 65 years in ALL.

In Iran, there is diversity in frequency and distribution of cancer diseases. Factors such as ethnicity, environmental, geographical and exhaustive economic and psychological reserves may have contributed to these differences throughout the country.

In 1996, leukemia was ranked 9th among 10 common cancers in Iran. In 1998 and 1999, leukemia and lymphoma increased and caused changes in this ranking [6]. In 2001, leukemia placed 6th after gastric, breast, and skin cancers and lymphoma in a study conducted in Mazandaran [7]. In 2000, some studies in Fars revealed an increase in the prevalence of this cancer and it was ranked 5th after skin, breast, gastric and bladder cancers [2]. Also in 2001, leukemia reached 4th rank after skin cancer, breast cancer and bladder cancer. The most fatal cancers in Iran were gastric cancer, lung cancer, leukemia, and liver cancer [2]. The rapid increase of cancer causes the patient and his family exhaustion of their financial and psychological reserves due to high expenditures on therapeutic drugs and long duration of admission in hospitals. Such condition

creates economic and social burden to the country.

Identification of risk factors associated with leukemia is foremost for its prevention and control [5]. Many epidemiological studies about leukemia conducted in other countries have examined and identified a number of possible risk factors (e.g., environmental and genetic) in an effort to determine the etiology of this disease. Among the environmental risk factors identified included exposure to benzene, ionizing radiation, electromagnetic fields (EMFs), and cigarette-smoking. However, only ionizing radiation has been significantly linked with AML or ALL. Other environmental exposures have been found to be weakly or inconsistently associated with leukemia. Due to paradoxes in different studies, they are still done in greater scales. Although leukemia is relatively prevalent in Iran, few studies have been conducted for identification of its risk factors. This implies the necessity of further studies to gain advance information on most significant leukemia risk factors and people at risk. Positive identification and knowledge of these risk factors associated with leukemia can be used to support measures to alleviate potentially harmful exposures and reduce the risk of the disease.

Materials and Methods:

This is a case-control study that is matched by age and sex. Cases involved 100 leukemic patients above 15 years old who were admitted in Hematology ward in Namazee Hospital (the only center affiliated to Shiraz University of Medical Sciences for admission of leukemic pa-

tients in Fars and nearby provinces in southern Iran). Leukemic patients were selected by sequential convenient method. For controls, 2 groups were considered. Both control groups involved 100 people. The first was drawn through random selection of 100 hospitalized patients whose diseases didn't have any relation to leukemia. On the other hand, 100 individuals gathered through stratified sampling from the general population represented the second control group. The required number for cases and controls was 100 and 200, respectively, considering á=5%, (1- â)=80% and OR=2. This study was implemented through dissemination of questionnaires verified by competent hematologists. The reliability of this instrument was estimated to be 80% using á- Chorenbach test. Questions were presented in multiple choices and dealt specifically with exposure to known risk factors. In addition, questions relating to Iran-Iraq war were included.

Medical students who were trained and oriented in two classes about the ongoing study accomplished the questionnaires. For each case, 2 age and sex matched controls were selected and considered in the questionnaire.

The collected data were analyzed by SPSS version 11.5 software. The statistical test applied was Pearson correlation. As in most case-control studies, bias may be introduced in conducting this study depending on how exposure to risk factors is measured, reported and assessed in the questionnaires presented. To mitigate, if not eliminate, bias, 2 groups of controls from community and hospital were selected and compared with each

other. Since there was no significant difference between 2 groups (0.05), both groups were used for estimating OR. To estimate OR for two level variables like sex or contact with animals, we considered p<0.05 as significant difference.

Results and Discussion:

Our study of leukemia incidence in Iran revealed environmental and genetic risk factors, and other important variables that were consistently associated with leukemia.Other factors were found to have contributed weakly or to have no association to the prevalence of leukemia.

The average age of patients was 34.4±7.6 years in men and 31.9±5.5 years in women. The average age of ALL patients was 27.8±4.2 years and 39±7.8 years in AML patients. The most prevalent age group was 16-25 years old accounting for 42% of all the age groups. Other studies noticed a higher average of age for leukemia, particularly AML [9-12]. So the population at risk in Iran belongs to the younger age groups. Further, we were able to determine and confirm previous statistics that leukemia incidence was more prevalent in men, which accounted for 71% of the cases, than in women, accounted for only 29%,while 57% were ALL and 43% were AML cases.

The most significant risk factors were:
a. place of birth and residence for the past 10 years
b. jobs relating to agriculture/animal husbandry
c. contact with chemical products
d. history of contact with animals
e. family history of cancer among 1st degree relatives
f. cigarette-smoking for more than 10 years

Place of birth and residence. Fars Province was the birthplace of 60% of the patients and also the place of residence of 69% of patients. The rest of the patients were from the provinces of Bushehr, Kerman, Kohkilooye, Hormozgan, Sistan, and Khoozestan. Three patients were from Afghanistan. The most prevalent ethnic groups were Persians accounting for 76%, Lor (11%) and Turk (4%). For estimation of odd's ratio (OR), the provinces were divided into 3 groups. Fars province was the basic one. The provinces of Bushehr, Hormozgan and Khoozestan were placed in group 1 for having similarity in climate, presence of refineries, oil and other chemical products, and involvement in Iran-Iraq war. Group 2 was composed of Kerman, Kohkilooye and Sistan provinces.

Comparison of OR between Fars and 2 groups of provinces showed that there was a higher relative risk for leukemia in people born and residing in group 1 provinces. Causal relationship has been established between ALL, in particular, and place of birth and residence. However, place of residence has not shown any significant increase in the risk for AML (Table 1). A simultaneous study in children also revealed that birthplace and residence increased the risk of developing childhood leukemia. Although previous studies have noted same results, further study should be done in these provinces for verification of this finding.

Table 1, Estimate of OR for province of birth and residence in acute leukemic patients.

Type of leukemia	Acute leukemia		AML		ALL	
Province of birth	CI	OR	CI	OR	CI	OR
Fars		1				
Group 1	1.61-8.09	3.6	1.33-8.85	3.44	1.37-10.45	3.81
Group 2	0.75-2.89	1.47	0.98-4.52	2.11	0.25-2.29	0.77
Province of residence						
Group 1	2.02-15.81	5.25	2.3-22.43	7.1	0.99-14.73	3.87
Group 2	1.29-6.86	2.96	1.51-10.08	3.9	0.56-6.3	1.94

OR: Odd's Ratio, CI: Confidence Interval.

Occupation. Many studies have suggested a link between occupational exposure and leukemia. In examining this relationship, patients included students, clerks, housewives, farmers and workers in other fields. Among the patients, 26% were student, 19% were housewife, and 17% were farmer. In a study conducted in Japan, most cases were from households and clerk groups [9]. However, it is expected for students to be the most common group because of the age distribution of the disease. Our study showed that people employed in agriculture or animal husbandry had high risk of leukemia with estimated OR =2.35, CI=1.0-5.19, and PV=0.01. Our findings were confirmatory of previous studies that implied an increase in leukemia incidence in farm workers due to frequency of chemical exposures and contact with animals.

Contact with chemicals. In studying chemical exposures, chemicals were divided into 2 groups. Group 1 consisted of dyes, pesticides, insecticides, and benzene. On the other hand, Group 2 consisted of lubricating oil, wood glue, petroleum, and laboratory products. Group 1 working with chemicals had a positive exposure-response relationship with leukemia, particularly ALL with OR=2.26 and CI=1.17-4.37. Exposure to benzene is a clear but risk factor for developing AML [14]. Other studies confirmed the same result [3, 4, 15-17]. No relation was attributed to duration of contact (continuous or intermittent).

Workers in other fields of exposures such as refineries, shoes and rubber industries, and printing companies were also found to have an increased risk of developing leukemia, specifically AML, with OR=3.04 and CI=1.13-8.07 (Table 2).

Viral diseases. Among viral diseases, chicken pox was found to have decreased the risk of leukemia. Patients who had previously acquired chicken pox are unlikely to develop the disease. This association was more significant for AML with OR=0.412 and CI=0.244-0.698 (Table 3). A study by Cooper in the United States didn't imply any significant relation between chicken pox and leukemia [18]. Other studies have shown decreased risk of leukemia in children who had previously acquired common infections or

those who had any febrile eruptive disease during their first year of life [4, 18, 19]. Our study also established that chicken pox and mumps were protective factors in childhood leukemia. Although inconclusive, it is possible that early childhood exposure to viral diseases can strengthen the immune system against developing leukemia.

History of contact with animals. History of contact with animals like sheep, cow, and poultry was considered as continuous occupational or non-occupational contact. Results yielded a statistically significant association of leukemia with history of contact with sheep (OR=3.146, CI=1.68–5.86) and contact with cow (OR=3.036, CI=1.52–6.03) (Table 4). Nordstorm and Metayer studies noted same results in which contact with animals and working in meat factory were risk factors [17, 22]. Same results were also achieved in our study in children. It can be reasoned out that the risk may be due to the presence of bovine leukemia virus and the possibility that this disease is common in animals and human.

Table 2, Estimate of OR for employment in acute leukemic patients.

Type of leukemia	Acute leukemia			ALL			AML		
Employment status	PV	CI	OR	PV	CI	OR	PV	CI	OR
Clerk	0.05	0.14-0.61	0.29	0.0	0.03-0.42	0.12	0.01	0.17-0.33	0.41
Household	0.5	0.9-3.89	1.9	0.3	0.6-3.75	1.52	0.031	0.98-6.06	2.45
Farmer husbandry	0.01	1.07-5.19	2.35	0.07	0.82-5.5	2.16	0.16	0.69-5.01	1.88
	0.5	0.38-1.72	0.81	0.7	0.49-2.69	1.16	0.07	0.07-1.09	0.3
Worker	0.16	0.74-3.97	1.72	0.8	0.23-2.93	0.87	0.01	1.3-8.07	3.04
Student	0.1	0.5-1.79	1	0.06	0.92-3.48	1.79	0.002	0.06-0.66	0.21

PV: P Value, OR: Odd's Ratio, CI: Confidence Interval.

Table 3, Estimate of OR for viral illness in case and control groups.

Viral illness	Case			Control			OR estimate		
	-	+	total	-	+	total	PV	CI	OR
Chicken pox	74	26	100	108	92	200	0.001	-0.698-0.244	0.412
Rubella	97	3	100	197	3	200	0.38	0.4-10.24	2.031
Measles	83	17	100	1.67	33	200	0.91	0.5-1.125	1.032
Mumps	86	14	100	170	30	200	0.81	0.46-1.8	0.92

PV: P Value, OR: Odd's Ratio, CI: Confidence Interval.

Table 4, Table 4-Estimate of OR for contact with animals in case and control groups.

Contact with animals	Case			Control			OR estimate			ALL	AML
	-	+	total	-	+	total	PV	CI	OR	PV	PV
Caw	78	22	100	183	17	200	0.001	-6.03-1.52	3.036	0.608	0.005
Sheep	72	28	100	178	27	200	0.001	-5.86-1.689	3.146	0.006	0.001
Hen	86	14	100	180	20	200	0.3	-3.21-0.66	1.47	0.9	0.1

PV: P Value, OR: Odd's Ratio, CI: Confidence Interval, ALL: Acute Lymphoblastic Leukemia, AML: Acute Myelogenous Leukemia.

Family history of cancer. In our study of family history of cancer, 3 groups were drawn, namely: Group 1 – 1st degree relatives, Group 2 – 2nd degree relatives, and Group 3 – distant relatives. Our Study showed that a positive family history of leukemia among 1st degree relatives has been associated with increased risk for ALL (OR=3.75, CI=1.32-10.99, PV=0.033). Previous studies shared the same views [4,22,23,]. However, no correlation was established between other types of cancer in the family and leukemia.

Cigarette-smoking. To determine cigarette-smoking as a risk factor for developing leukemia, 2 groups were preferred according to duration of smoking. Group 1 consisted those smoking for more than 10 years; while in Group 2, those smoking for less than 10 years. In our study, smoking for more than 10 years had elevated the risk for AML (OR = 3.81, CI = 1.37-10.48, PV = 0.002). Many studies have also shown an increased risk for AML [3, 4, 27- 29].In a study in 2002 at Los Angles ,AML subtype M2 was related to cigarette smoking and other subtypes were not associated to smoking [27]. In another study by Kasim in Canada heavy smoking accompanying by obesity increased the risk of AML [28]. It can be pointed out that prevalence of older age in group 1 had affected on our findings. Overall, cigarette-smoking was a risk factor for developing leukemia depending on its frequency, amount and duration.

Involvement in Iran-Iraq War. 12 of 100 patients included in our study were present in the past war. Among them, 2 patients had exposure to chemical weapons; 1 of them had direct contact with mustard gas, and the other was un-

known. Our assessment revealed no significant relation with leukemia. This finding conflicts with other studies that have shown positive association. In a study conducted by Ghanei and Vosooghi, out of 665 patients who were exposed to mustard gas, 9 of them had acquired CML [29]. In justifying our results, it is important to note that majority of the patients (students and household groups) had not experienced the war. More than a decade had passed since the end of Iran-Iraq war. Many leukemic patients had already died; therefore, they were not involved in this study. Furthermore, our finding is inconclusive of any association between leukemia and factors related to war

Radiation. Radiation is one of the few exposures for which causal relationship with leukemia, particularly AML, has been established [33-35,]. Exposure to radiation is a clear but weak risk factor for AML. Studies have demonstrated the relationship between the degree of irradiation and occurrence of leukemia [36,37]. In our study, radiation has not been found to have significant association with leukemia. The reason could be that some patients failed to recall their exposure. Although other studies noted the same assessment [30], a more accurate result would be achieved depending on the dose of radiation, duration of exposure, and the age of individual at the time of exposure. However, this could not be done in our study.

Also, our study has not observed any significant relation between leukemia and allergy. Some studies demonstrated similar findings [17]; others have shown con-

clusive link of allergy with leukemia [28, 29].

Conclusion:

The prevalence of leukemia incidence has significantly increased throughout Iran. Despite many studies conducted on leukemia, the causative factors of this disease remain unclear. Identifying risk factors for leukemia is an important step in the elimination of the overall burden of the disease. However, in our study, the task of possibly identifying leukemia risk factors is difficult due to several limitations that we encountered. Future studies are needed to overcome these restrictions in order to achieve a more accurate result.

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