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Statistical study of environmental factors involved in incidence and emergence of blood cancers: retrospective clinical studies

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Summary. *Aim of study:* Blood cancers (BCs) are diseases that are hard to handle and can easily cause death. The statistics show that about 245,000 people have some form of BC. There are many factors affecting BC where preventing BC entails controlling these factors. The purpose of this retrospective study is to find which genetic and environmental risk factors in cancer have led to increased leukaemia over time. *Materials and Methods:* 762 patients with various BCs in haematology and oncology A and B sections of Shari'ati Hospital, who met the inclusion criteria, were enrolled in this retrospectively study from 2009- 2011. Patients' information was collected using a researcher-made questionnaire from the moment patients arrived. Age, gender, ABO and Rh blood group, patient's occupation, climate type (where patients live), Systolic and Diastolic Blood Pressure (SBP & DBP), Platelet (Plt) and hemoglobin (Hb) Count were carefully analyzed. Information questionnaires were processed in open source R software. Frequency and probability table, classification tree, correlations, χ^2 and logistic regression, regression models were calculated so as to achieve a wide and clear perspective of impacting factors. A regression model was prepared and studied for possible influences. This study considered all probability less than 0.05 significant. Some factors were normalized or adjusted for data missing from questionnaires. *Results:* Results showed that the disease in men was 1.5 times higher than in women. Blood types (43%) along with positive Rh (76%) have the highest risk of BC. Low platelet count correlates more than 80% with BC. Patients who work in administration (32.7%) and services (28.7%) are more susceptible to leukaemia and most of the leukaemia patients were from warm dry regions (50.0%). The role of fatness in BC emergence is statistically ignorable. BC cases increase during the second decade of human life (48.7%), a fact which might be attributed to maturation processes. *Conclusions:* By due consideration of these environmental factors, we can make a proper evaluation of leukaemia and its prevention.

Key words: blood cancer (BC), statistical approach, gender, climate type, occupation

«Studio statistico dei fattori ambientali coinvolti nell'incidenza ed emergenza dei tumori del sangue. Studi clinici retrospettivi»

Riassunto. *Scopo dello studio:* I tumori del sangue (BCs) sono malattie difficili da gestire e possono facilmente causare la morte. La statistica indica che circa 245.000 persone hanno una qualche forma di BC. Ci sono molti fattori che influenzano i BC; la prevenzione dei BC comporta il controllo di questi fattori. Lo scopo

di questo studio retrospettivo è di trovare quali fattori di rischio di cancro genetici e ambientali abbiano portato ad un aumento di leucemia nel tempo. *Materiali e metodi:* 762 pazienti, con vari BCs ricoverati nei reparti A e B di ematologia e oncologia dell'ospedale di Shari'ati, che ha deciso i criteri di inclusione, sono stati inseriti in questo studio retrospettivo dal 2009-2011. Le informazioni sui pazienti sono state acquisite tramite questionario compilato dal ricercatore al momento dell'arrivo dei pazienti. L'età, il genere, il gruppo sanguigno AB0 e Rh la professione, il tipo di clima (dove il paziente vive), la pressione sanguigna sistolica e diastolica (SBP & DBP), la conta delle piastrine (Plt) e dell'emoglobina (Hb) sono stati attentamente analizzati. I questionari informativi sono stati analizzati tramite software R gratuito. La tabella di frequenza e probabilità, il grafico ad albero di classificazione, le correlazioni, il test χ^2, la regressione logistica e i modelli di regressione, sono stati calcolati in modo da raggiungere una più ampia e chiara prospettiva dei fattori coinvolti. Un modello di regressione è stato approntato e studiato per le possibili interazioni. Questo studio ha considerato significative le probabilità con $p< 0.05$. Alcuni fattori sono stati normalizzati o aggiustati a causa di dati mancanti nei questionari. *Risultati:* i risultati hanno dimostrato che il tasso di malattia negli uomini è 1,5 volte più alta rispetto alle donne. I gruppi sanguigni (43%) correlati con Rh positivo (76%) hanno un più alto rischio di sviluppare BC. Una bassa conta piastrinica è correlata per più dell'80% con BC. I pazienti che lavorano nel settore amministrativo (32.7%) e nei servizi (28.7%) sono più suscettibili a leucemia e la maggior parte dei pazienti con leucemia provengono da regioni calde e secche (50.0%). Il ruolo del sovrappeso nell'insorgenza del BC è statisticamente non significativo. I casi di BC aumentano durante la seconda decade di vita (48.7%), un fatto che può essere attribuito a processi di maturazione del sistema emopoietico. *Conclusioni:* attraverso una giusta considerazione di questi fattori ambientali, possiamo fare una valutazione più appropriata di leucemia e della sua prevenzione.

Parole chiave: tumori del sangue (BC), statistica, genere, tipo di clima, occupazione

Introduction

Blood cancer (BC) is an extremely dangerous disease that can lead to death within a very short time. It is estimated that about every 4 minutes someone is diagnosed with some form of BC. BC statistics also indicate that roughly every 10 minutes, someone in the United States dies of BC (1).

There are three main types of BCs. Lymphoma is a type of BC that affects the lymphatic system, which removes excess fluids from the body and produces immune cells. Myeloma is a type of BC that specifically targets plasma cells. Leukaemia, a type of cancer found in blood and bone marrow, is caused by the rapid production of abnormal white blood cells and the most common kind of cancer in children (2, 3). Leukaemia is a common BC and the most problematic form in certain countries, for example about 2.5% of all UK cancers are leukaemia and of these, about 39% are acute leukaemia (3-5). The four main types of leukaemia are: Acute Lymphoblastic Leukaemia (ALL), Acute Myelogenous Leukaemia (AML), Chronic Lymphocytic Leukaemia (CLL), Chronic Myelogenous Leukaemia (CML) (6). AML may give rise to solid tumours consisting of myeloid leukemic blasts called granulocytic sarcomas or chloromas (7). Acute Leukaemia (AL), both myeloblastic and lymphoblastic, is more common in males in every age-group, with the exception of infant ALL (1). AML is most common in individuals older than 50 years of age whereas ALL is more common in children and young adults. Approximately one third of patients with either ALL or AML achieve long-term survival, however the outcome is closely dependent upon the cytogenetic profile. Leukaemia is the most common cancer in children and teenagers, accounting for almost 1 in 3 cancers. Overall, however, childhood leukaemia is a rare disease.

Most of the remaining cases are AML. ALL is most common in early childhood, peaking between 2 and 4 years of age. Cases of AML are more spread out across the childhood years, but it is slightly more common during the first 2 years of life and during the

teenage years. ALL is slightly more common among white children than among African-American and Asian-American children, and it is more common in boys than in girls (1-8). Other BCs include: Burkitt's lymphoma, a cancer of the lymphatic system (in particular, B lymphocytes); Hodgkin's lymphoma (a cancer originating from lymphocytes), non-Hodgkin lymphomas (NHLs), a disparate group of BCs that include any kind of lymphoma except Hodgkin's lymphomas; Myelodysplastic syndrome (MDS) is a group of myeloid (bone marrow) stem cell disorders (9-10).

Some risk factors of leukaemia have been identified and include: Down syndrome, Li-Fraumeni syndrome, Klinefelter syndrome, and other genetic disorders, inherited immune system problems**,** previous treatment with chemotherapy, chronic exposure to chemicals, smoking and exposure to radiation, including radiation to treat other forms of cancer. Lifestyle-related risk factors for some adult cancers include being overweight, smoking, drinking excessive amounts of alcohol, and getting too much sun exposure (11). Most times, BC is diagnosed among older folk and therefore they are more at risk of developing it than younger people. Acute leukaemia is more common in males at almost every age. Studies have shown that race and ethnicity, and regional climate are involved in BC; for example leukaemia rates are higher for white children than black children (12, 13).

The blood group type also has an important role in causing leukaemia. Bone cancers show the strongest association with blood type B, and a weaker association with blood type A, in which blood type individuals are more predisposed to leukaemia. Similarly, blood type O appears to grant a degree of resistance especially in acute leukaemia. Usually Rh+ blood types are more prone to leukaemia in both sexes (14).

Several studies have shown that some environmental factors may have an important role in the development of leukaemia. In such cases circumstantial prevention not only decreases therapy costs but also enhances the health level of society and life expectancy (15).

The aim of this retrospective study is to identify the genetic and environmental risk factors that relate to increased leukaemia over time. We are hoping, by identification and control of environmental factors, to prevent BC and treatment of it, as well as to reduce the high cost and side effects of treatment (16). This study thus focuses on analysis of some statistically important factors in various types of BCs, such as age, gender, ABO and Rh blood group, patient's occupation, climate type that patients live in, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), platelet (Plt) and haemoglobin (Hb) count. and how these may relate to generation or stimulation of BC.

Material and methods

This retrospective statistical study analyzes patients referred to haematology and oncology units at *Shariati* hospital, Tehran during 2009- 2011. For this study, we randomly selected 762 patients suffering from various BCs, including AML, ALL, CML, CLL, Lymphoma, post-BMT, Burkitt, NHL, MDS, and Hodgkin. 17 volunteers were excluded from the study on grounds of inadequate resources. The subjects were selected according to certain inclusion and exclusion criteria. Patients over 10 years of age were selected. Patients' BC was confirmed by biochemical and serological tests. Ethical consent was obtained from patients before the study and all volunteers participated in this study with full consent and full knowledge; where participants were not present at the hospital, verbal consent was obtained. During the study patient information was protected and all data were collected as pre-defined codes.

For this study two researcher-made questionnaires (A and B) were designed, consisting of several parts. Questionnaires were sent to ten oncology specialists and the material was revised and improved according to their feedback. In order to check the collection of data from medical records, a peer researcher sampled the data and verified their consistency (all data were collected by one researcher).

Questionnaires included demographic characteristics, age, gender, and weight, climate where patient lives, patient's occupation, and initial reason for referral. Questionnaire A collected data via interviews. Clinical information in questionnaire B included medical information extracted from medical records at the hospital, such as systolic blood pressure (SBP), diastolic

blood pressure (DBP), ABO and Rh blood group, type of cancer, platelet (Plt) count, hemoglobin (Hb) count as examined during the treatment period by haematology and oncology specialists.

According to information obtained from the Iranian Meteorological Organization (IMO), the climate type resided in was divided into 5 categories of warm and dry, warm and humid, cold and dry, cold and humid and temperate and humid, the areas being shown in Figure 1. BCs are classified into 5 groups: AML, ALL, Lymphoma, Post-BMT and "Others," a category including rare, less severe cancers such as Burkitt, NHL, MDS, and Hodgkin. Occupation factors were divided into 7 categories: self-employment, administrative, employees, housewives, unemployed, and service work. The study complies with current ethical considerations and was approved by the BMSU Ethics Committee (registration code: 730215).

The information questionnaire data, duly modified by Excel software, were processed in open source R (version R2.12.2) software. The correlation coefficient was calculated to be 85%. Frequency and probability tables, classification tree, correlations, χ^2, logistic regression and regression model were calculated so as to achieve a wide and clear perspective of impacting factors. Some of factors were normalized or adjusted for data missing from questionnaires. This study took all probability less than 0.05 as significant.

Figure 1. Various types of Iranian city climate (From IMO website: http://www.irimo.ir).

Results

Patient profiles and information on adjusted frequencies of all factors are summarized in Table 1. A total of 762 patients suffering from various BCs were referred for interdisciplinary evaluation during 2009-2011, and their data were included in the database. The mean age of all participants was 48.93±12.6 years (range 18-90 years), the majority of cases being in group II (16-30 years). Of the 762 patients who entered the study, 433 (58.1%) were male and 312 (41.9%) were female. Our results showed that AML was the most common histopathological type of BC (44.6%). Most of the leukaemia patients were from warm dry regions (50.0%). Classification tree analysis also confirm these results: in each age and weight range, sex and blood group type (ABO and Rh) the commonest type of leukaemia is AML. As the tree shows, the types of leukaemia in areas with different climates varies according to age and gender. But in every situation AML cancer prevails. Therefore, to control this type of cancer one needs to monitor other non-environmental factors. A and Rh+ blood groups have most cases of leukaemia: 244 (32.7%) and 560 (70.2%) respectively. Blood group AB had the highest percentage of ALM cancer. The mean systolic and diastolic pressures in patients were 10.98±1.59 and 6.60±1.51, respectively.

Platelets are one of the most important elements in the blood clotting system; there must be more than 2×10^5 in normal cases and more than 61% of patients suffer from severe platelet deficiency (result not shown) (13). Patients' weights were classified into 7 groups (I-VII). As shown in Table 1, the majority of cases (23.5%) were in group V (mean 61-70 kg). It was also shown that patients who have administrative (32.7%) and service-work (28.7%) occupation are more susceptible to leukaemia (Table 1). Figure 2 shows the classification tree results with respect to all parameters.

The test showed that the clearest correlations by age group were groups I (1-15) and II (16-30). The

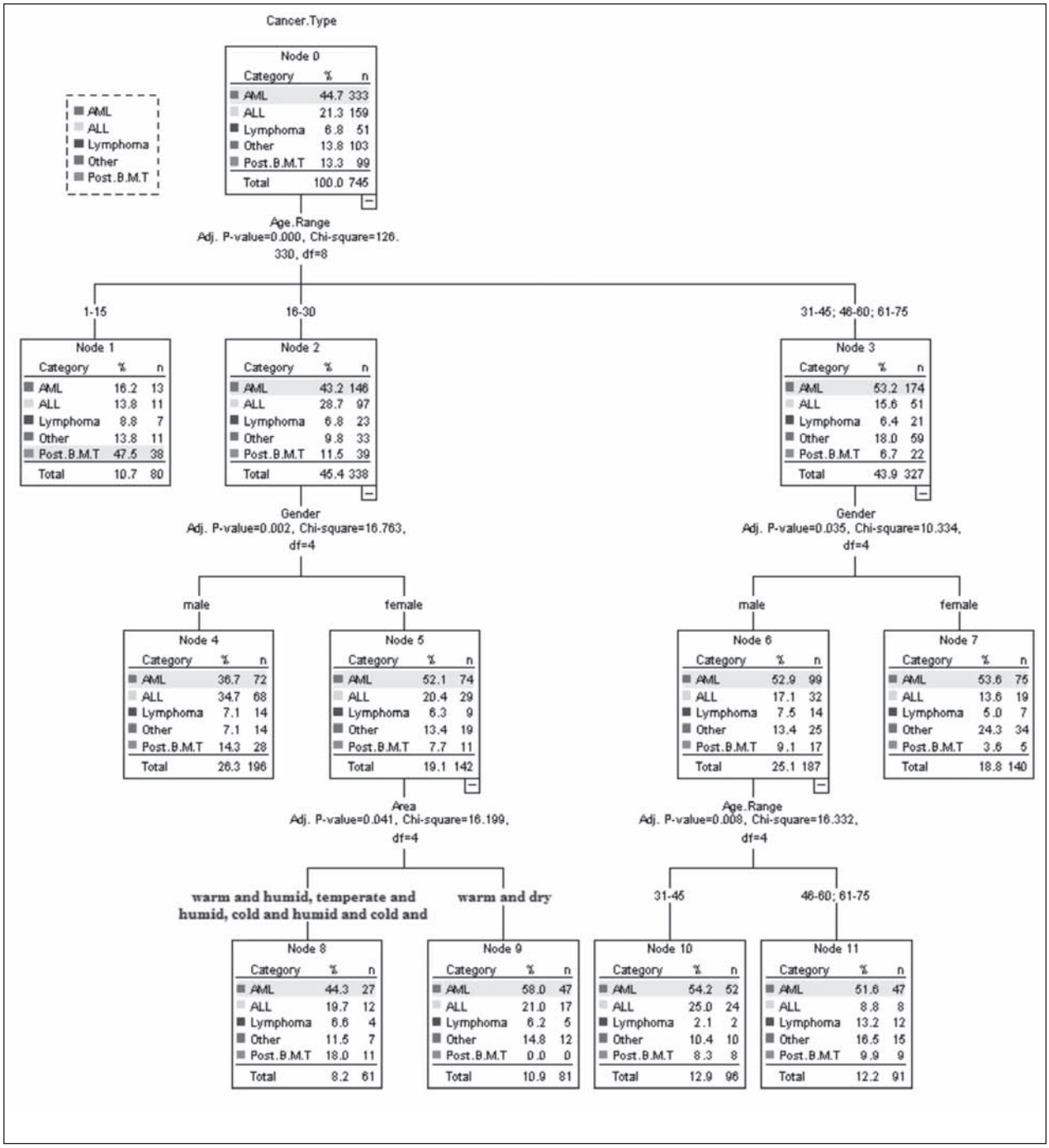

Figure 2. Classification tree results with respect to all parameters.

percentage of patients with ALM has increased considerably (429.1%) from group I to group VI ($p<0.001$). While the prevalence of ALM in age group I was significantly higher than in the other age groups, the prevalence of ALL in age group II was significantly higher than in the others. We also observed that the percentage of ALL cancer in male patients was significantly ($p=0.005$) higher than in female patients;

Table 1. Adjusted frequencies of all factors.

Factors	Frequencies	(%)
Gender		
	Male	58.1
	Female	42.9
ABO Blood Group		
	A	32.7
	B	16.4
	AB	25.5
	O	24.4
Weight (kg)		
	I (0-20)	3.9
	II (21-40)	5.6
	III (41-50)	11.0
	IV (51-60)	22.1
	V (61-70)	23.5
	VI (71-80)	17.3
	VII (81-100)	16.6
Cancer Type		
	AML	44.6
	ALL	21.3
	Lymphoma	7.0
	Post B.M.T	13.3
	Others	13.8
	Rh-	20.9
SBP (M±SD)		10.98±1.50
Climate		
	Warm & Dry	50.0
	Warm & Humid	18.1
	Cold & Dry	9.0
	Cold & Humid	11.7
	Humid & Temperate	11.3
Age (Years)		
	I (1-15)	10.6
	II (16-30)	45.6
	III (31-45)	24.9
	IV (46-60)	14.9
	V (61-80)	4.1
Occupation		
	Administrative	32.7
	Self-employment	10.5
	Employees	6.4
	Housewives	9.8
	Service-work	28.7
	Unemployed	11.9
Rh		
	Rh+	75.1
	Rh-	20.9
DBP (M±SD)		6.60±1.51

however the prevalence of ALM cancer in women was significantly ($p<0.05$) higher than in male patients.

Chi-square, logistic linear regression and likelihood ratio test analysis for various different factors is shown in Table 2. This test result demonstrates a significantly positive correlation ($p<0.001$) between cancer types with gender, age and occupation.

In this study, we performed logistic regression testing to verify the effects of individual variables on the dependent variable (type of cancer). In logistic regression testing, AML is selected as the reference category while changes in other classes (i.e. other types of cancer) are investigated using various factors. The changes probably occurring from ALL to AML, from Lymphoma to AML, from other to AML and POST BMT to AML, investigated using independent variables and only significant variables, were reported as less than 0.05. Our results show that only male gender has an effect on the model (0.002). Rh and ABO blood group and weight have no effect on the model. The age variables, age class I (1-15 years) and II (16-30 years) have the greatest impact on the model. Service-work is the occupational variable that has the greatest impact on the model. Most women diagnosed with AML and men with ALL cancer, also by changing gender from male to female, 80.8% increased AML cancer risk. In age variable, by changing class less than 15 years to 61-75 years, AML cancer risk increased (approximately 429.1%). By changed from 16-30 to 61-75 years of age, AML more likely to develop cancer (359.9%). So AML cancer risk is high than ALL in class under 15 years of age is 16-30 years. In occupation variable, by change from administrative to unemployed, to change the type of cancer from ALL to AML increased (118.7%). Also, by Change from service-work to unemployed increases the risk of AML (123.4%). So the risk of AML than ALL cancers in Service-work is more than administrative.

Discussion

This study analyzes some statistically important factors - such as age, gender, ABO and Rh blood group, patient's occupation, climate type that patients live in, Systolic Blood Pressure (SBP), Diastolic Blood

Table 2. Dependency tests for cancer types and other factors.

Factor Analysis	Pearson Chi-Square			Likelihood Ratio			Linear-by-Linear Association		
	Value	df	Asymp. Sig.	Value	df	Asymp. Sig.	Value	df	Asymp. Sig.
Gender and Cancer Type	24.990	4	.000	25.170	4	.000	0.870	1	.351
Rh Blood Group and Cancer Type	2.027	4	.731	2.030	4	.730	0.065	1	.798
ABO Blood Group and Cancer Type	12.526	12	.404	13.097	12	.362	0.271	1	.603
Age and Cancer Type	151.546	16	.000	125.424	16	.000	22.687	1	.000
Climate and Cancer Type	18.807	16	.279	19.911	16	.224	0.921	1	.337
Occupation and Cancer Type	30.305	20	.006	31.325	20	.011	1.113	1	.029
Weight and Cancer Type	11.136	24	.988	11.463	24	.985	0.453	1	.501

Pressure (DBP), platelet (Plt) and haemoglobin (Hb) count on various types of BCs - which could be related to generation or stimulation of BC. Here sophisticated statistical tests are used in order to determine the exact role and effect of the factors mentioned. Most BCs in Iran are ALL and AML which seem to have the same origin. Cancers may be cautiously classified into 5 groups according to their severity and predominance (16).

It was also shown that patients who have low mobility and daily activity or patients who have free and critical tasks (e.g. administrative (32.7%) or critical (28.7) jobs) are more susceptible to leukaemia. Annually in the United States approximately 21% of cases are (14) ALL. Leukaemia (non-CLL) is a cancer type suitable as an indicator of health effects of ionizing radiation since it has a high relative excess risk and few confounders. Excess incidence of leukaemia has earlier been observed among different populations of medical workers (17). In a cohort of Chinese medical diagnostic X-ray workers, the RR of leukaemia was 2.4 among those who were employed before 1970 (18). The average cumulative dose was estimated to be 551 mGy, i.e., notably higher than average cumulative doses calculated for a Nordic cabin crew where over 90% of cumulative doses were below 35 mSv. However, since approximately 40% to 80% of cosmic radiation consists of neutrons, which are more effective in inducing biological damage than x-radiation, the studies among medical workers and cabin crew cannot be straightforwardly compared. In this study we have shown that patients who have administrative (32.7%) and service work (28.7%) are more susceptible to leukaemia.

The annual US incidence rate for ALL under the age of 20 years is 35.0 per million populations, with males having a higher incidence than females (13-14).

The age-specific incidence for childhood ALL was characterized by a peak between the ages of 2 and 5 years. Internationally, there was considerable variation in the incidence of childhood and adolescent ALL, with annual rates ranging from 9 to 47 per million for males and from 7 to 43 per million for females (16-19). Children may do better because of differences between childhood and adult ALL in the disease itself, differences in treatment (children's bodies can often handle strong treatment better than adults), or some combination of these. Approximately 21,780 deaths (12,740 males and 9,040 females) in the US were attributed to leukaemia in 2011. Estimated deaths for the four major types of leukaemia in 2011 were AML – 9,050 deaths, CLL – 4,380 deaths, ALL – 1,420 deaths and CML – 270 deaths. For other unclassified forms of leukaemia, an additional 6,660 deaths in 2011 were estimated (1).

Incidence rates for all types of leukaemia are higher among men than among women. In 2011, males were expected to account for nearly 57 percent of the new cases of leukaemia. Our result was comparable with other studies. In our study the percentage of all types of leukaemia in male patients was significantly higher than those in female patients. Recent studies have shown that leukaemia is the tenth most frequently occurring type of cancer in all races or ethnicities (15). ALL incidences are higher in children and adolescents from 0 to 14 years than it is in people aged 15 years through young adulthood. AML incidence is

lower in children and adolescents from 0 to 14 years than it is in people aged 15 years through young adulthood (9-19).

Weight scaling was first intended to be each 20 kilograms but analysis proved the same as now, so for better monitoring of this datum we used the Howlader *et al.* and Ferlay *et al.* scaling (20-21). In the original Oxford Study of Childhood Cancer (Hewitt, 1966) unaffected and siblings in familial cases of childhood leukaemia have a low male-to-female ratio (0.71). Association of childhood leukaemia with high birth weight is more pronounced in a subgroup of female children with older mothers enjoying high socioeconomic status (22). Previous weight scaling might have a better correlation with 15-year age brackets. In this research we found no correlation between weight and the prevalence of cancer type. Hence weight and its impact on BC can be ignored because of its low significance in the chi-square test.

In one study by Zand *et al.* (13) they found that both blood typing of Rh and ABO have a moderate-to-high impact on proneness to BC because both of these factors are strictly connected with the blood and its characteristics. Jackson (1999) reported the ABO blood groups of leukaemia patients divided by sex. The proportion of females with blood group O is about half the proportion seen in males, and this is statistically significant (p=0.03) (23). The type of leukaemia and RH status were recorded by McMahon (1958). There was no significant difference between the percentages of Rh negative patients in this study (24). Jackson (1999) reported that ABO blood group frequencies differ between male and female patients in leukaemia (23). We in our turn observed that leukaemia prevalence in warm and dry climate type is higher than in other areas, about 50%.

In this research we showed that blood group AB had the highest percentage of ALM cancer compared with other blood groups. Nowadays new diagnostic experiments make it easier to detect problems as soon as they occur in the human body. It is advisable to check young people every two years and old people every year.

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