

Determinants of survival of common childhood cancers in Iran

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Background: Cancer is the second most common cause of morbidity and mortality in children. This study aimed to epidemiologically and demographically assess common cancers in children in Iran. **Materials and Methods:** This cohort study was conducted on children registered in Mahak Hospital and Rehabilitation Complex (which is a non-governmental organizations (NGO)-related hospital for only malignant diseases). A total of 2232 questionnaires were filled out for cancer patients between 2007 and 2016. The factors including age, gender, race, family history, type of treatment, and type of cancer were entered into Cox regression model to examine their effect on mortality of children diagnosed with cancer. **Results:** The Cox regression model showed that age, race, type of cancer, family history of cancer, and type of treatment had a significant effect on mortality of children diagnosed with cancer ($P < 0.05$). The hazard ratio (HR) of mortality in 10–15 years old was higher than that of 1–5 years old ($P = 0.03$, HR = 1.3). The HR of mortality in patients with brain tumor ($P < 0.01$, HR = 2.24), sarcoma ($P < 0.01$, HR = 2.32), and neuroblastoma ($P < 0.01$, HR = 2.56) was twice the value in patients with leukemia. The HR of mortality in patients who had a family history of cancer was higher than that of patients without it ($P < 0.01$, HR = 1.33). Patients who had undergone chemotherapy along with surgery and radiotherapy ($P = 0.02$, HR = 0.68) and patients who received chemotherapy along with surgery ($P = 0.01$, HR = 0.67) had a lower HR of mortality compared to the chemotherapy group. **Conclusion:** Young age, multidisciplinary approach, and absence of family history were associated with lower hazard of death in children diagnosed with cancer; brain tumor, leukemia, and sarcoma had higher hazard of mortality compared to leukemia. Children with a family history of cancer should be under regular follow-up. Treatment should be multidisciplinary and comprehensive.

Key words: Cancer, childhood, Cox models, epidemiology, survival

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INTRODUCTION

Cancer is the second most common cause of morbidity and mortality in 1–14 years old.^[1]

Leukemia accounts for 30% of childhood cancers followed by brain tumor and other cancers of nervous system (26%), soft-tissue sarcoma (7%), neuroblastoma (6%), non-Hodgkin lymphoma (6%), renal tumors (5%), and Hodgkin lymphoma (3%).^[2]

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The incidence of cancer in developed countries is higher than that in developing countries (<40/100,000 children). However, in the recent years, the incidence of cancer in developing countries such as Iran has greatly increased, exceeding the rate in developed countries.^[3]

In Iran, death due to cancer ranks first in terms of morbidity and mortality of children (14.2%, 23,300 cancer deaths). From 2002 to 2012, 9795 Iranian children were diagnosed with cancer.^[4] Cancer in children is considerably different from adult malignancies in terms of type, distribution, and prognosis and follows a unique epidemiological pattern. The 5-year survival in cancer children is higher than that in adults (78% vs. 62%).^[5]

Cancer in children better responds to chemotherapy and radiotherapy. However, these treatments can cause long-term complications in children. Thus, children who survive cancer are in need of constant monitoring.

Higher success in the treatment of cancer in children may be attributed, in part, to the biological differences of cancers in adults and children.^[6] About 90% of cancers in adults arise from the epithelial tissue. In contrast, cancers in children often originate from nonectodermal tissues such as the bone marrow, lymph nodes, bones, and muscles. However, in most cases, the cause of cancer in children remains unknown.^[7]

Further regional studies on different subpopulations and racial groups and people of different socioeconomic classes can help identify the risk factors for cancer in children. This study aimed to epidemiologically and demographically assess common cancers in children in Iran and make a comparison with neighboring countries.

MATERIALS AND METHODS

Study design and participant

This cohort study was conducted on children registered in Mahak Hospital and Rehabilitation Complex (which is a NGO-related hospital for only malignant diseases) from 2007 to 2016 with definite diagnosis of cancer. Research Project Code is IR.SBMU.RETECH.REC.1396.294.

Variables assessment

To collecting data, first, a questionnaire was designed by the researchers. Examined variables included age, gender, country, family history, type of treatment, and type of cancer. A total of 2232 questionnaires were filled out for children from 2007 to 2016.

Patients were divided into two groups of Iranian and non-Iranian (Afghan, Iraqi, Azerbaijani, Kuwaiti, Saudi

Arabian, Emirati, and Pakistani patients). In terms of age range, patients were divided into five groups of <1 year, 1–5 years, 6–10 years, 11–15 years, and >15 years. Based on the type of cancer, the patients were divided into nine groups of leukemia, retinoblastoma, brain tumor, histiocytosis, lymphoma, renal cell carcinoma, sarcoma, neuroblastoma, and others. Treatment modalities included surgery, chemotherapy, radiotherapy, and all three.

Statistical analysis

Census was used to collect the data in this study. Data of 2232 children with cancer were followed up and analyzed using the stratified Cox model. First, age, sex, country, family history, type of treatment, and type of cancer were entered separately into the crude Cox model, and effect of each variable was estimated with hazard ratio (HR). Then, significant variables in crude Cox model were entered into the multiple Cox model. For applying Cox model to the survival data, proportional hazard (PH) assumption must be satisfied which assumes that the HRs are constant over time.

The PH assumption was tested by Schoenfeld residuals. Because this assumption was not met for our dataset, stratified Cox model was used in which the model was stratified by the variables which do not satisfy PH assumption. HR for stratification variable cannot be calculated, and HR for other variables was estimated in different stratum of the stratification variable.

RESULTS

The median survival time of children was 137 months (range: 0–254 months). Because of high number of censorship and missing values in some categories of variables, it was impossible to calculate median for each variable separately, and instead, we reported the mean survival time for variables. It is shown in Table 1.

Table 2 shows the results of crude Cox model and stratified Cox model (adjusted model).

The crude Cox regression model showed that the factors including age, country, type of cancer, family history, and type of treatment had significant effect on mortality of children diagnosed with cancer ($P < 0.05$). Schoenfeld residual test showed that the assumption of equality of HR in the Cox model for the type of treatment (in chemotherapy plus surgery plus radiotherapy and also chemotherapy plus radiotherapy groups) was not met. It means that the HR of mortality in different treatment groups was not constant and could not be determined. Thus, the multiple Cox model was stratified according to the type of treatment. The

Table 1: Summary of survival time of children with common cancers

Variables	Number	Death (%)	Mean survival time (SE)
Age (years)			
1-5	909	237 (26.1)	34 (1.27)
6-10	552	149 (27)	29.13 (1.58)
11-15	478	156 (32.6)	29.66 (1.57)
<1	230	63 (27.4)	33.36 (2.9)
>15	55	22 (40)	24.8 (3.87)
Country			
Iran	2058	575 (27.9)	32.35 (0.84)
Afghanistan	49	20 (40.8)	23.98 (4.97)
Iraq	74	19 (25.7)	18.91 (3.19)
Azerbaijan	33	9 (27.3)	22.04 (5.82)
Other	6	2 (33.3)	43 (17.22)
Sex			
Female	973	27 (27.9)	30.92 (1.19)
Male	1259	356 (28.3)	32 (1.09)
Consanguinity			
No	1446	357 (24.7)	32.19 (0.96)
Yes	584	180 (30.8)	30.17 (1.44)
Treatment*			
Ch	849	205 (24.1)	29.94 (1.29)
R & S & R+S	37	8 (21.6)	18.12 (4.11)
Ch+S+R	474	15 (432.5)	31.77 (1.60)
Ch+R	186	72 (38.7)	29.77 (2.68)
Ch+S	666	181 (27.2)	34.94 (1.55)
Type of cancer			
Leukemia	650	184 (28.3)	36.46 (1.62)
Retinoblastoma	239	40 (16.7)	44.04 (2.52)
Brain tumor	609	190 (31.2)	25.02 (1.21)
Langerhans cell histiocytosis	18	1 (5.6)	29.94 (7.51)
Lymphoma	167	26 (15.6)	39.58 (2.86)
Kidney disease	66	16 (24.2)	39.46 (5.42)
Sarcoma	311	112 (36)	28.44 (1.80)
Neuroblastoma	87	32 (36.8)	26.17 (3.31)
Other	85	26 (30.6)	24.63 (3.32)
Total patients	2232	627 (28.1)	32.44 (0.76)

*R & S & R+S=Only radiotherapy, or only surgery, or combination of radiotherapy and surgery; Ch+S + R=Combination of chemotherapy and surgery and radiotherapy; Ch+R=Combination of chemotherapy and radiotherapy; Ch+S=Combination of chemotherapy and surgery; SE=Standard error

HRs for other variables were calculated in each stratum of stratification variable using the stratified Cox model. The results of stratified Cox model are as follows:

The HR of mortality in different age groups was compared to that in 1–5 years old. The HR of mortality in 10–15 years old was higher than that of 1–5 years old ($P = 0.02$, HR = 1.32).

The HR of mortality was compared between the Iranian and non-Iranian children. The HR of mortality in Afghan children with cancer was twice the rate in Iranian children ($P = 0.01$, HR = 1.91). Children of other countries were not significantly

different from Iranian children in this respect. The HR of mortality due to different types of cancer was compared with that of leukemia. The HR of mortality in brain tumor ($P < 0.001$, HR = 2.24), sarcoma ($P < 0.001$, HR = 2.32), neuroblastoma ($P < 0.001$, HR: 2.56), and other cancers ($P < 0.001$, HR = 2.70) was more than twice the rate for leukemia.

In children who had a family history of cancer, the HR of mortality was higher than that of children without a family history of cancer ($P = 0.003$, HR = 1.33).

DISCUSSION

In this study, the HR of mortality in Afghan children with cancer was about twice the value in Iranian children. Previous studies showed that one important predictor of cancer prognosis is access to health-care system for diagnosis and treatment and follow-up of disease.^[8,9]

Treatment of cancer in children is complex, and several factors affect the success of treatment including type of cancer, its stage and histology, child's condition, age, sex, race and primary health status of the child, access to health care, having insurance coverage, and follow-up of disease. A previous study showed that of factors affecting the survival of patients, access to medical facilities for diagnosis and treatment is the most important factor determining the final prognosis.^[10] Our study also showed that patients who received chemotherapy plus surgery plus radiotherapy and chemotherapy plus surgery had a lower HR of mortality than the chemotherapy group.

The treatment approach for cancer was recently changed, and combination therapy has increased the survival rate of cancer patients.^[11,12] The chemoradiation treatment protocols increased the survival of patients with many common types of cancer as well as pediatric cancers. For treatment of high-grade glioma, addition of radiotherapy to chemotherapy yielded significantly different results.^[13]

Loeffler *et al.*^[14] in a meta-analysis showed that addition of radiotherapy to chemotherapy for treatment of patients with Hodgkin lymphoma improved the complete 10-year remission by 11% compared to chemotherapy alone.^[14] It seems that considering the invasive nature of most pediatric cancers, combination therapy, various chemotherapies, radiotherapy, and alternative treatments such as immunotherapy in most cancers can improve the survival of children. However, follow-up is also essential, and the long-term effects of more invasive treatments along with the use of different treatment modalities should also be taken into account.

Table 2: Hazard ratio estimated in Cox (crude) model and stratified Cox (adjusted) model

Variables	Crude Cox model			Stratified Cox model		
	HR	95% CI	P	HR	95% CI	P
Age (years)						
1-5	Ref	-	-	Ref	-	-
5-10	1.11	0.89-1.37	0.33	0.93	0.73-1.19	0.59
10-15	1.38	1.13-1.70	<0.001	1.32	1.04-1.66	0.02*
<1	1.04	0.77-1.41	0.75	1.07	0.75-1.53	0.69
>15	1.86	1.20-2.890	<0.001	1.45	0.88-2.57	0.13
Country						
Iran	Ref	-	-	Ref	-	-
Afghanistan	1.92	1.23-3.01	<0.001	1.91	1.15-3.11	0.01*
Iraq	1.14	0.68-1.90	0.61	1.06	0.60-1.86	0.83
Azerbaijan	1.27	0.66-2.46	0.46	1.57	0.69-3.56	0.27
Other	1.21	0.30-4.85	0.78	0.78	0.10-5.62	0.81
Sex						
Female	Ref	-	-	Ref	-	-
Male	1.01	0.85-1.18	0.94	1.07	0.89-1.28	0.43
Consanguinity						
No	Ref	-	-	Ref	-	-
Yes	1.36	1.13-1.64	<0.001	1.33	1.10-1.61	0.003*
Treatment						
Ch	Ref	-	-			
R & S & R+S	1.29	0.63-2.63	0.47	-PH		
Ch+S+R	1.35	1.08-1.67	<0.001	-PH		
Ch+R	1.68	1.27-2.21	<0.001	-PH		
Ch+S	1.07	0.87-1.33	0.48	-PH		
Type of cancer						
Leukemia	Ref	-	-	Ref	-	-
Retinoblastoma	0.51	0.35-0.73	<0.001	0.76	0.49-1.19	0.23
Brain tumor	1.48	1.20-1.83	<0.001	2.24	1.62-3.10	<0.001*
Langerhans cell histiocytosis	0.25	0.03-1.78	0.16	0.57	0.08-4.18	0.58
Lymphoma	0.49	0.32-0.76	<0.001	0.68	0.41-1.13	0.14
Kidney disease	0.91	0.54-1.52	0.71	1.72	0.93-3.15	0.08
Sarcoma	1.01	1.26-2.04	<0.001	2.32	1.60-3.34	<0.001*
Neuroblastoma	1.71	1.16-2.52	<0.001	2.56	1.52-4.29	<0.001*
Other	1.59	1.05-2.41	<0.001	2.7	1.6-4.55	<0.001*

*Significant at $\alpha=0.05$. HR=Hazard ratio; -PH=Proportional hazard assumption was violated; Ref=Reference category; CI=Confidence interval

Our results showed that family history of cancer significantly affected the survival of children after treatment. Genetic defects have found to be responsible for 15% of children's cancers in general, but they play a more important role in specific types of pediatric cancers such as adrenocortical carcinoma^[15] and a less important role in some other types such as acute lymphocytic leukemia (ALL).^[16]

It appears that regular follow-ups in children with a family history of cancer can be helpful for in-time diagnosis and successful treatment. Moreover, genetic counseling in families with cancers related to genome has shown promising results in detection of cancer genome and subsequent care.^[17]

In this study, the survival rate of cancer patients decreased by an increase in age and the survival rate of 1–5-year-old cancer children was higher than that of older age groups. This finding may be due to different biological and histological factors determining cancer prognosis in different age groups. For instance, favorable attributes of ALL, such as hyperdiploidy and *TEL-AML1* translocations, occur primarily in children diagnosed at 1–9 years of age.^[18,19]

Whereas, unfavorable characteristics, such as L2 morphology, pro-T-cell immunophenotype, and the *BCR-ABL* translocation, are more common in adolescents.^[18] For NHL, adolescents are more likely to be diagnosed with diffuse large B-cell lymphomas, including primary B-cell lymphomas, and other rare histologies than younger patients which are associated with lower survival rates.^[20,21]

Similarly, the proportion of cases with alveolar rhabdomyosarcoma, associated with poorer survival compared with embryonal rhabdomyosarcoma, is greater among adolescents.^[22,23] On the other hand, due to the presence of several psychological and social factors in adolescents, risk of delay in the correct diagnosis of cancer is higher, and they are often diagnosed in higher stages, which affect treatment and prognosis.^[24]

Pollock *et al.* showed that in multiple regression model, all solid tumors except for lymphoma had longer cancer-specific lag times in adolescents than in children.^[25] This difference remained significant even after controlling for the type of cancer, which showed that pediatric cancer, irrespective of its type, is diagnosed earlier at a younger age compared to older ages.^[26-28]

CONCLUSION

In multiple regression analysis of common childhood cancers (brain tumors, leukemia, and sarcoma), young age, multidisciplinary approach, and absence of family history of cancer improve the survival of children. Children with a family history of cancer should be under regular follow-ups, and the treatment of cancer in children should be comprehensive. The HR of mortality in cancer children with different treatment modalities is not constant over time, and long-term complications of multidisciplinary approaches make it difficult to make a decision regarding this modality. Further studies are required to assess the short- and long-term survival of cancer children undergoing multidisciplinary treatments.

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Conflicts of interest

There are no conflicts of interest.

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