

## The Incidence of Childhood Cancer in Iran: A systematic review and meta-analysis

Soheil Hassanipour<sup>1, 2</sup>, Mohammad Fathalipour<sup>3</sup>, Hamed Delam<sup>4</sup>, Mohammad Ghorbani<sup>5,6</sup>, Elham Abdzadeh<sup>2</sup>, Morteza Arab-Zozani<sup>7,8</sup>, Shirin Riahi<sup>9</sup>, Hamid Salehiniya<sup>8, 10 \*</sup>

1. Gastrointestinal and Liver Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran.

2. GI Cancer Screening and Prevention Research Center, Guilan University of Medical Sciences, Rasht, Iran.

3. Department of Pharmacology and Toxicology, Faculty of Pharmacy, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

4. Student Research Committee, Larestan University of Medical Sciences, Larestan, Iran.

5. Department of Public Health, School of Health, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran.

6. Health Sciences Research Center, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran

7. Iranian Center of Excellence in Health Management, School of Management and Medical Informatics, Tabriz University of Medical Sciences, Tabriz, Iran.

8. Social Determinants of Health Research Center, Birjand University of Medical Sciences, Birjand, Iran

9. Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran.

10. Department of Epidemiology and Biostatistics, Tehran University of medical sciences, Tehran, Iran.

\*Corresponding author: Dr Hamid Salehiniya, PhD, Social Determinants of Health Research Center, Birjand University of Medical Sciences, Birjand, Iran. E-mail: [alesaleh70@yahoo.com](mailto:alesaleh70@yahoo.com). ORCID ID: 0000-0001-7642-5214

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### Abstract

**Background:** Childhood cancer (ChC) is very rare and occurs between birth and 14 years of age. There are several reports about ChC incidence from various regions of Iran, but with conflicting results. The present study aimed to do a systematic review to estimate the accurate incidence rate of ChC among Iranian people.

**Materials and Methods:** This systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist in 2018. A literature search was conducted using international databases (Medline/PubMed, Scopus, ISI/Web of Knowledge, and Google Scholar) for English papers, and national databases (Scientific Information Database, MagIran, IranMedex, and IranDoc) for Persian papers which estimated the incidence rate of ChC in any geographical location in Iran. The incidence rate of ChC was calculated using random-effect model.

**Results:** Out of 157 papers in the primary searches, 12 studies were included by advanced screening and refinement. The crude incidence rate (CIR) of ChC in 0-14 years was 16.8 per 100,000 (95% CI: 9.04-24.56) for boys and 16.56 per 100,000 (95% CI: 10.51-22.62) for girls.

**Conclusion:** The incidence of ChC in Iran is higher compared to other parts of the world. Considering this issue, holding some interventional programs on tackling potential risk factors, including air pollution, in different regions of Iran is suggested.

**Key words:** Childhood cancer, Incidence, Iran

### Introduction

Childhood cancer (ChC) is very rare and occurs between birth and 14 years of age (1). Malignant neoplasms are considered as one of the main causes of death in children younger than 14 years old (2, 3), and it is the second leading cause of death in the United States after unintentional injuries in children less than 14 years of age (4).

In developed countries, the most common types of cancer diagnosed in children are leukemia and central nervous system cancers (5). The incidence of cancer varies among different communities and races, and it depends on genetic predisposition, early or late exposure to infectious agents, and other environmental factors (5, 6). Approximately 75–150 new cases of ChC

are identified annually per million people (4, 7).

Worldwide, the number of new cases of ChC exceeds 200,000 each year and more than 80% of these cases are from the developing countries (8). According to the World Health Organization, the annual incidence rate of ChC is 100 per million children worldwide (9). In general, cancer is more common in boys than in girls (10, 11).

Proper diet along with physical activity is one of the best modifiable risk factors to prevent diseases, including cancer. Many kinds of food have important role in protecting people against cancers due to the presence of some micronutrients. Many studies have shown that healthy nutrition can reduce the incidence of cancers in adults and even children (12).

In Iran, the most common cancers among children are leukemia, brain, central nervous system tumors, and lymphoma, accounting for more than half of new ChC cases (13). Studies have shown that the incidence rate of ChC in Iran is 48 to 112 per million among girls and 51 to 144 per million among boys (14). In 2008, the incidence of this cancer in Tehran, the Capital of Iran, was 176 per million children (15).

Over the past 30 years, few epidemiological studies have been carried out in Iran on the incidence and prevalence of cancer, especially ChC (2, 16-18). These studies are conducted at different times and places. Regarding the fact that it is necessary to be aware of the incidence rate of ChC for health planning purposes, this study aimed to investigate the incidence of cancer in children under 14 years of age in Iran.

## Materials and Methods

The study was planned and conducted in January 2018. The review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist (19).

## Search strategy

A comprehensive literature search of published studies was carried out using Medline/PubMed, Scopus, Embase, ISI/Web of knowledge, and Google Scholar for international papers, and Scientific Information Database (SID) (www.sid.ir), MagIran (www.magiran.com), IranMedex (www.iranmedex.com), and IranDoc (www.irandoc.ac.ir) for national papers. The keywords included “cancer”, “cancers”, “tumor”, “tumors”, “carcinoma”, “neoplasm”, “child”, “childhood”, “infants”, “adolescents”, “children”, “pediatric”, “incidence”, “epidemiology” and “Iran”. No time and language limitation was considered. EndNote X5 software (Thomson Reuters, Carlsbad, CA, USA) was used to check and manage the citation results.

## Inclusion and exclusion criteria

In the present study, all papers contained clear description of CIR of ChC, and obvious reports of Iranian population were included. Additionally, the papers with the following criteria were excluded: duplicated studies, those which reported prevalence rate, and the poster and conference papers.

## Quality assessment

In order to assess the quality of the articles, we used a checklist prepared by Joanna Briggs Institute (JBI) (20). The purpose of this appraisal was to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, procedure, and analysis.

## Statistical analysis

All the analyses were performed using STATA software, version 12 (StataCorp, College Station, Texas, United States). Cochran's Q (significance level of  $p \leq 0.1$ ) and  $I^2$  tests (significance level of  $\geq 50\%$ ) were used to assess the statistical heterogeneity. A random-effects model

was conducted for meta-analysis of heterogeneous cases.

### **Risk of bias across studies**

Random-effect model was used for minimizing the risk of bias across the studies (21, 22).

## **Results**

### **Description of literature search**

The primary searches in the literature yielded 157 potentially relevant studies. After title and abstract screening, 42 studies met the inclusion criteria and entered the second stage of evaluation. Some studies were excluded by full-text reviewing for the following reasons: duplicate studies (n=4), lack of relevance to the aim of the study (n=52), and incorrect study population (n=35). Subsequently, the review used 12 unique studies. The search process and study selection according to the PRISMA flowchart in the present systematic review has been summarized in Figure I.

### **Description of the included studies**

Based on the geographical locations, two studies were conducted in Fars province (23, 24), three in Ardabil province (25-27), one in Kerman province (28), one in Golestan province (29), one in East Azerbaijan province (30), one in Tehran metropolis (31), one in Shahroud city (32), one in Khuzestan province (33), and one in all states of Iran (34). The basic characteristics of the included studies are demonstrated in Table I.

### **The results of enclusion studies**

The highest CIR for 0-4 year old boys and girls was reported from Fars province (27.8per 100,000 for boys in 2006 and 21.2 per 100,000 for girls in 2007). The highest CIR for 5-9 year old boys and girls

was reported from Fars province (32.6 per 100,000 for boys and 22.7 per 100,000 for girls in 2006). The highest CIR for 10-14 years among boys and girls was reported from Fars province (27.4 per 100,000 for boys and 20.1 per 100,000 for girls in 2006). The reported crude incidence rate of childhood cancer in the review is presented in Table II.

### **The results of meta-analysis (0-4 years)**

The CIR of ChC in 0-4 years was 15.9 per 100,000 (95% CI: 10.61-19.77) for boys and 10.11 per 100,000 (95% CI: 6.47-13.74) for girls.

### **The results of meta-analysis (5-9 years)**

The CIR of ChC in 5-9 year old participants was 14.82 per 100,000 (95% CI: 10.70-18.94) for boys and 9.91 per 100,000 (95% CI: 7.04-12.77) for girls.

### **The results of meta-analysis (10-14 years)**

The CIR of ChC in 10-14 year old patients was 12.84 per 100,000 (95% CI: 9.38-16.29) for boys and 10.92 per 100,000 (95% CI: 8.43-13.41) for girls.

### **The results of meta-analysis (0-14 years)**

The CIR of ChC in 0-14 year patients was 16.8 per 100,000 (95% CI: 9.04-24.56) for boys and 16.56 per 100,000 (95% CI: 10.51-22.62) for girls. Moreover, the results of the random-effect model for CIRs of ChC are represented in Figures 2, 3 and 4 for boys, girls, and total, respectively.

### **Test(s) of heterogeneity**

The results on the heterogeneity of the studies are presented in Table III.

### **Publication Bias**

Publication bias was assessed, using Egger's tests (35). Results of Egger's tests showed lack of publication bias (bias; 4.52, P=0.452). Additionally, publication bias was assessed by funnel plot (Figure 5).

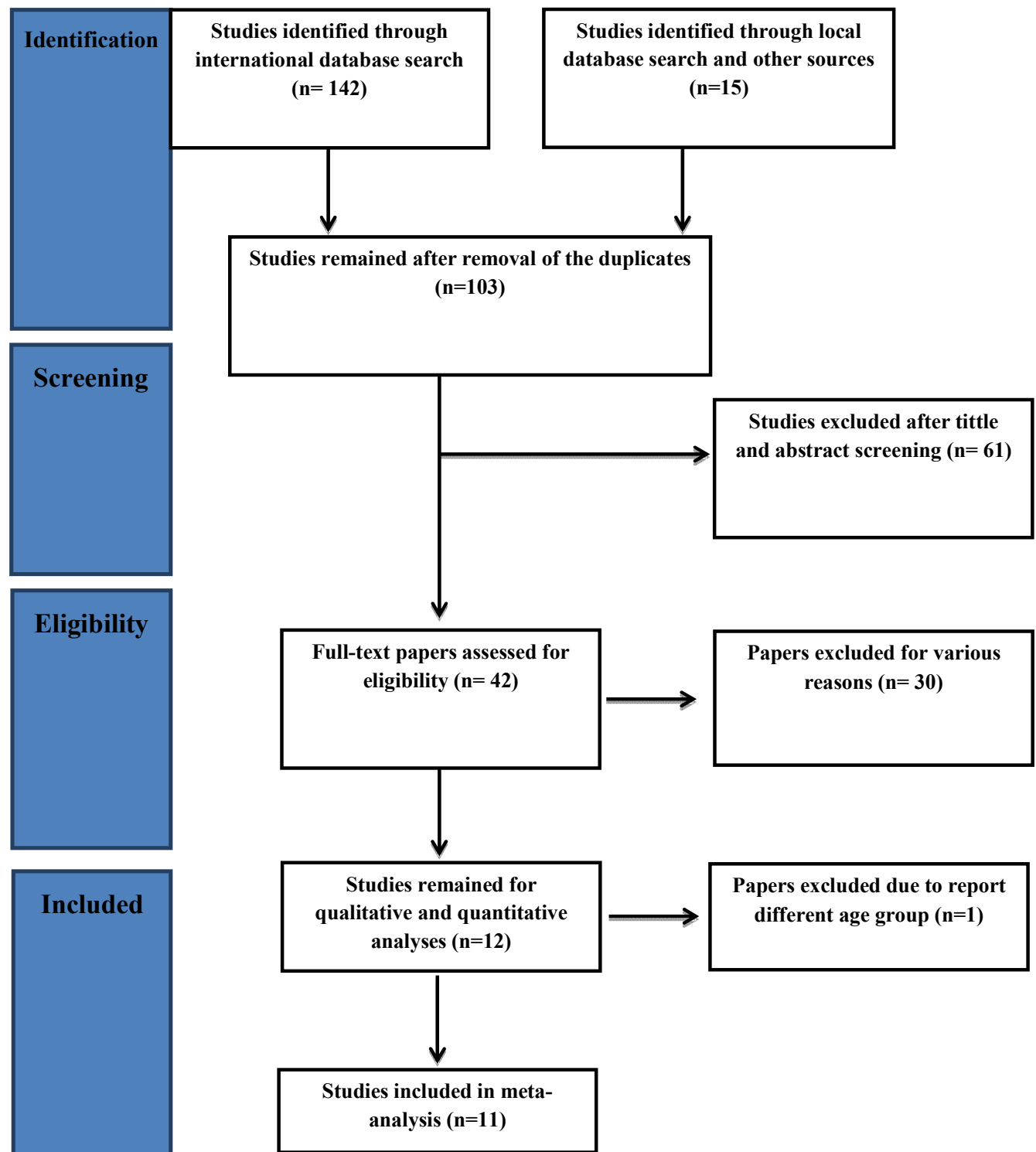


Figure 1. Flowchart of the included eligible studies in systematic review

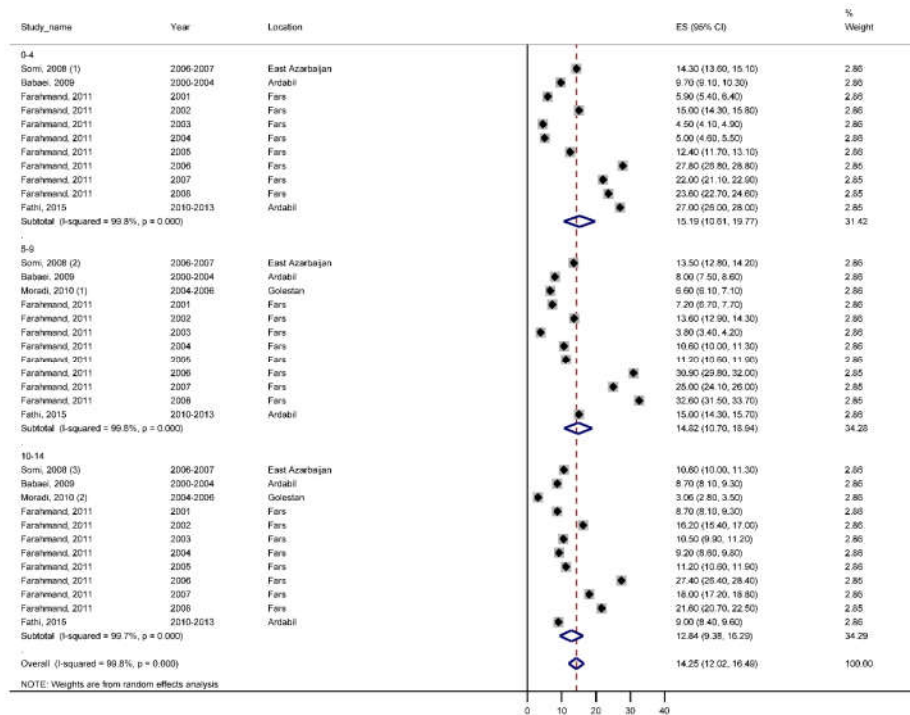


Figure 2. Forest plot of the random-effect meta-analysis for CIRs of ChC among boys in the Iran

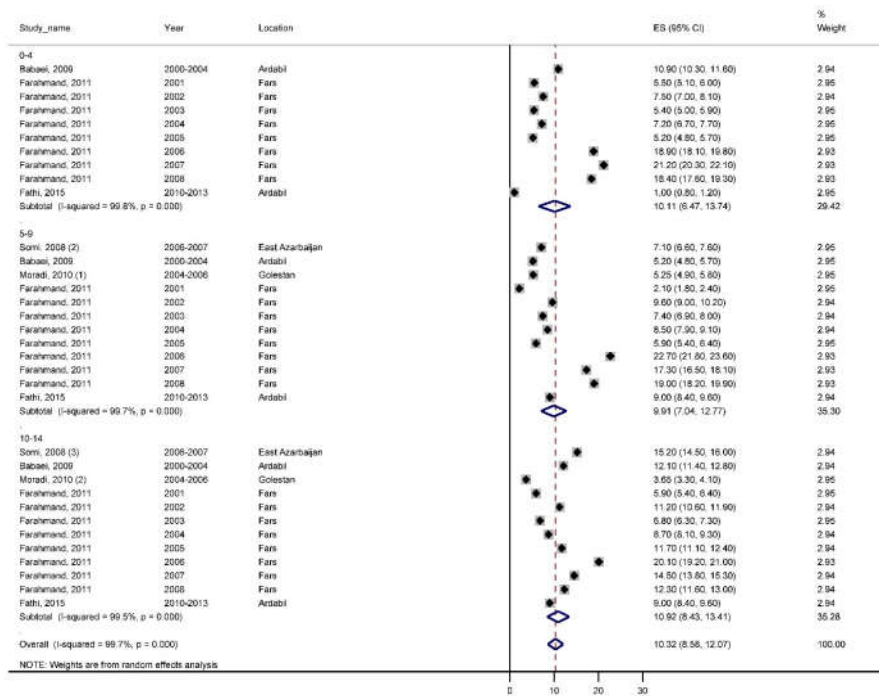


Figure 3. Forest plot of the random-effect meta-analysis for CIRs of ChC among girls in the Iran

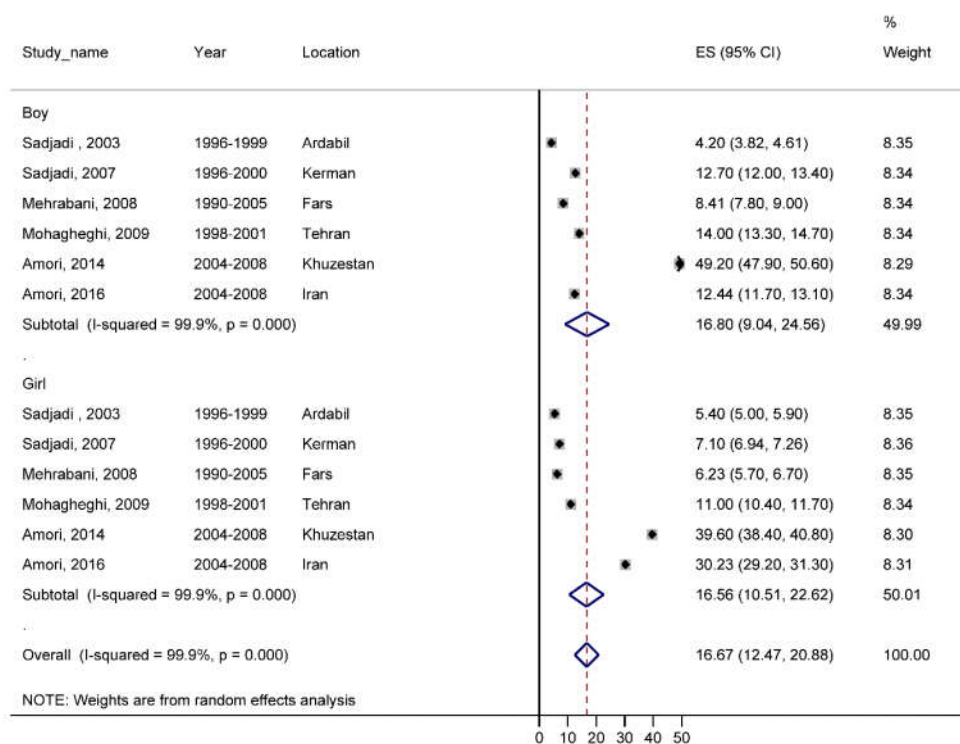


Figure 4. Forest plot of the random-effect meta-analysis for CIRs of ChC among 0-14-year children in the Iran

Table I. Basic characteristics of the studies included in the review

Order	Author/Year	Time period	Location	CIR (Males)				CIR (Females)			
				0-4	5-9	10-14	0-14	0-4	5-9	10-14	0-14
1	Sadjadi, 2003	1996-1999	Ardabil	-	-	-	4.2	-	-	-	5.4
3	Sadjadi, 2007	1996-2000	Kerman	-	-	-	12.7	-	-	-	7.1
4	Mehrabani, 2008	1990-2005	Fars	-	-	-	8.41	-	-	-	6.23
5	Somi, 2008	2006-2007	East Azerbaijan	14.3	13.5	10.6	-	15.1	7.1	15.2	-
6	Babaei, 2009	2004-2006	Ardabil	9.7	8.0	8.7	-	10.9	5.2	12.1	-
7	Mohagheghi, 2009	1998-2001	Tehran	-	-	-	14	-	-	-	11
8	Moradi, 2010	2004-2006	Golestan	-	6.60	3.06	-	-	5.25	3.65	-
9	Farahmand, 2011	2001	Fars	5.9	7.2	8.7	-	5.5	2.1	5.9	-
		2002		15	13.6	16.2	-	7.5	9.6	11.2	-
		2003		4.5	3.8	10.5	-	5.4	7.4	6.8	-
		2004		5	10.6	9.2	-	7.2	8.5	8.7	-
		2005		12.4	11.2	11.2	-	5.2	5.9	11.7	-
		2006		27.8	30.9	27.4	-	18.9	22.7	20.1	-
		2007		22	25	18	-	21.2	17.3	14.5	-
		2008		23.6	32.6	21.6	-	18.4	19	12.3	-
10	Amoori, 2014	2004-2008	Khuzestan	-	-	-	49.2	-	-	-	39.6
11	Fathi, 2015	2010-2013	Ardabil	27	15	9	-	1	9	9	-
12	Amori, 2016	2004-2008	Iran	-	-	-	12.44	-	-	-	30.23

Table II: The reported crude incidence rate of childhood cancer in the review

Order	Author/Year	Time period	Location	CIR (Males)	CIR (Females)	Quality level
0	Sajadi, 2003	1996-1999	Ardabil	0-14 years: 4.2	0-14 years: 5.4	Medium
1	Sadjadi, 2007	1996-2000	Kerman	0-14 years: 12.7	0-14 years: 7.1	Medium
2	Mehrabani, 2008	1990-2005	Fars	0-14 years: 8.41	0-14 years: 6.23	Low
3	Somi, 2008	2006-2007	East Azerbaijan	0-4 years: 14.3 5-9 years: 13.5 10-14 years: 10.6	0-4 years: 15.1 5-9 years: 7.1 10-14 years: 15.2	Medium
4	Babaei, 2009	2004-2006	Ardabil	0-4 years: 9.7 5-9 years: 8.0 10-14 years: 8.7	0-4 years: 10.9 5-9 years: 5.2 10-14 years: 12.1	Medium
5	Mohagheghi, 2009	1998-2001	Tehran	0-14 years: 14	0-14 years: 11	High
6	Moradi, 2010	2004-2006	Golestan	<1 year: 12.36 1-4 years: 3.28 5-9 years: 6.60 10-14 years: 3.06	<1 year: 7.47 1-4 years: 3.02 5-9 years: 5.25 10-14 years: 3.65	Medium
7	Farahmand, 2011	2001	Fars	0-4 years: 5.9 5-9 years: 7.2 10-14 years: 8.7	0-4 years: 5.5 5-9 years: 2.1 10-14 years: 5.9	Medium
		2002		0-4 years: 15 5-9 years: 13.6 10-14 years: 16.2	0-4 years: 7.5 5-9 years: 9.6 10-14 years: 11.2	
		2003		0-4 years: 4.5	0-4 years: 5.4	



				5-9 years: 3.8	5-9 years: 7.4	
				10-14 years: 10.5	10-14 years: 6.8	
				0-4 years: 5	0-4 years: 7.2	
				5-9 years: 10.6	5-9 years: 8.5	
				10-14 years: 9.2	10-14 years: 8.7	
				0-4 years: 12.4	0-4 years: 5.2	
				5-9 years: 11.2	5-9 years: 5.9	
				10-14 years: 11.2	10-14 years: 11.7	
				0-4 years: 27.8	0-4 years: 18.9	
				5-9 years: 30.9	5-9 years: 22.7	
				10-14 years: 27.4	10-14 years: 20.1	
				0-4 years: 22	0-4 years: 21.2	
				5-9 years: 25	5-9 years: 17.3	
				10-14 years: 18	10-14 years: 14.5	
				0-4 years: 23.6	0-4 years: 18.4	
				5-9 years: 32.6	5-9 years: 19	
				10-14 years: 21.6	10-14 years: 12.3	
8	Amori, 2014	2004-2008	Khuzestan	0-14 years: 49.2	0-14 years: 39.6	Medium
9	Fathi, 2015	2010-2013	Ardabil	0-4 years: 2.7	0-4 years: 1.4	High
				5-9 years: 1.5	5-9 years: 0.9	
				10-14 years: 0.9	10-14 years: 0.9	
10	Amoori, 2016	2004-2008	Iran	0-14 years: 12.44	0-14 years: 30.23	Medium

Table III: The results of the heterogeneity of studies

Age group/Gender	Q-value	df	I-square	Tau-squared	P-value
0-4 Boy	5586.2	10	99.8%	59.89	<0.001
0-4 Girl	5239.5	9	99.8%	34.27	<0.001
5-9 Boy	5631.9	11	99.8%	52.82	<0.001
5-9 Girl	3872.6	11	99.7%	25.54	<0.001
10-14 Boy	3987.6	11	99.7%	37.10	<0.001
10-14 Girl	2233.0	11	99.5%	19.27	<0.001
0-14 Boy	4322.9	5	99.9%	93.86	<0.001
0-14 Girl	4762.9	5	99.9%	57.08	<0.001
Total	9276.8	11	99.9%	55.16	<0.001

## Discussion

The aim of this study was to investigate the incidence of cancer in children younger than 14 years old in Iran. Few epidemiological studies have been conducted on ChC in Iran; the published ones are limited to leukemia and brain tumors (14, 29, 36).

The results of this study showed that the incidence of ChC among Iranian boys and girls, aged 0 to 14 years old, was higher than other countries (CIR=16.8 per 100,000 in boys and 16.5 per 100,000 in girls). According to the studies, the incidence rate of ChC in various countries is as follows: Pakistan 10 per 100 thousand, India 6.4 per 100 thousand, Japan 10.7 per 100 thousand, Finland 14.8 per 100 thousand, America 13.8 per 100 thousand, and Uganda 18.3 at 100 thousand (37-42).

The results of this study indicated that, according to different age groups, the incidence of ChC in Iran was higher in boys aged 0-4 years old and in girls aged 10-14 years. On the other hand, the lowest incidence rate of cancer among boys and girls occurred respectively in age groups of 10 - 14 years and 5 - 9 years. One of the reasons for this issue may be the genetic differences between boys and girls and different exposures in different ages (43, 44).

The results of this study showed that the highest incidence rate of ChC in girls, in all age groups, was observed in Fars province (CIR=21.2 per 100,000 in the age group 0-4 years, 22.7 per 100,000 in the

age group 5-9 years, 20.1 per 100,000 in the age group 10-14 years). In addition, the highest incidence rate of ChC in boys, in all age groups, occurred in Fars province (CIR= 27.8 per 100,000 in the age group 0-4 years, 32.6 per 100,000 in the age group 5-9 years, and 27.4 per 100,000 in the age group 10-14 years). The high incidence of ChC in Fars province might be due to more exposure to cancer risk factors such as environmental pollution, infectious agents, and more accurate records of newly diagnosed cancer cases in this province compared to other regions of Iran (45).

The results of our study indicated that the lowest incidence rate of ChC in girls aged 0-4 years and 5-9 years was observed in Ardabil province (CIR= 1 per 100,000 and 5.2 per 100,000, respectively). Moreover, the lowest incidence rate of this cancer among girls aged 0-14 years was observed in Golestan province (3.6 per 100,000). However, the lowest incidence rate of ChC in boys, between 2001 and 2003, in the age groups of 0-4 and 5-9 years, occurred in Fars province (4.5 per 100,000 and 3.8 per 100,000, respectively). Moreover, the lowest incidence rate of this cancer in boys aged 10-14 years was observed in Golestan province (3 per 100 thousand). Possible reasons for this low incidence rate can be lower environmental exposure to cancer risk factors in children in Ardabil and Golestan provinces (46-49). These provinces are less polluted and have some ethnic characteristics. Especially in Golestan province, there is limited genetic diversity and more intra-ethnic marriages (50-52). Moreover, the registration system in Fars province was weaker between 2001 and 2003 than the following years, being one of the main reasons for inaccurate and low reporting of cancers in this province (53). In Fars province, ChC incidence has a significant upward trend (24).

According to the results of this study, the highest incidence rate of ChC among Iranian boys and girls, in the age group of 0 - 14 years, was observed in Khuzestan

province (CIR=49.2 per 100,000 in boys and 39.6 per 100,000 in girls). One of the main reasons for this issue is the high level of pollution in this province in terms of dust pollution and the presence of many environmental exposures for the occurrence of various ChC s, including leukemia and other cancers (54-57). Furthermore, the lowest incidence rate of ChC among boys and girls in 0-14-year age group was observed in Ardabil province (CIR= 4.2 in 100,000 in boys and 5.4 in 100,000 in girls). According to studies, possible reasons for the lower incidence rate of ChC in Ardabil province are fewer residents, ethnic differences, and inaccurate reporting of newly diagnosed cancer cases in this province compared to other areas of the country (58).

In USA, Non-Hodgkin lymphoma showed an increase between 1975 and 2013 in children (59). The AIRTUM working group found an increase in children with all lymphomas up to 1999 and a decline afterwards. In Europe, for the period 1975–1997, the increase in Hodgkin lymphoma was found in both the 10–14 (AAPC (average annual percent change) 1%) and the 15–19 (AAPC 3.5%) age groups (60) Isaevska et al., showed that the incidence rate of all tumor types for children (0–14 years) in Piedmont was 156.9 per 100000 (151.3–161.6). There was a statistically significant increase in the incidence rates of all tumor types in children for the overall period of 1976–2011 (59). This increase might be partly due to introduction of antenatal and perinatal ultrasound imaging (61).

## Conclusion

The incidence of ChC in Iran is higher compared to other parts of the world. Considering this issue, developing some interventional programs such as tackling potential risk factors, including air pollution, in different regions of Iran is suggested.

## Conflicts of interest

There are no conflicts of interest.

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