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Original Article

Geographic Distribution and Estimating the Childhood Cancer Incidence in Iran: Three-Source Capture-Recapture Analysis on National Registries Data

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Abstract

Background: Cancers seldom happen in childhood age and awareness of accurate cancer incidence is essential in order to preventive programs. This study aimed to estimate the childhood cancer incidence in Iran using the three-source capture -recapture method.

Methods: Total new cases of childhood cancer reported by three national data sources of MAHAK charity database, pathology reports and clinical records in Iran were enrolled in this study. The common cases among three sources were determined using data linkage method. The childhood incidence rate per 1 million populations was estimated based on three-source capture-recapture method. We used BIC, G2 and AIC statistics to select the best-fit model. Arch GIS was used to determine geographic distribution.

Results: Overall, 2567 childhood cancer was included by three sources of registries. The total estimated number of childhood cancer was 5388 (95% CI: 4742.15-6228,14). The higher estimated incidence rate was Leukemia, Lymphoma by 94.91 and 24.80 per 1 million populations and the lower incidence was liver and retinoblastoma with 2.35 and 7.01 per 1 million populations. Provinces of Ardabil and Kohgiluyeh with an incidence rate of 420.01 and 404.61 per 1 million populations had a higher incidence rate and Mazandaran and Ilam with an incidence rate of 60.87 and 66.88 per 1 million populations had the lowest incidence. The overall completeness of the childhood cancer registry based on three-source was 48%.

Conclusion: The low-quality childhood cancer registration system highlights the needs for urgent screening programs for early detection in the high prevalent area in Iran.

Keywords: Pediatrics; Cancer; Childhood; Capture-recapture; Geographic distribution

Introduction

Cancers seldom happen before age of 20 years; they enhance a range of medical, psychological, ethical, and societal concerns (1). In global, childhood cancer is a main cause of death in children. About eighty percent of childhood cancers occurred in low and middle-income countries (2, 3). Nevertheless, children are often overlooked in their efforts for cancer control planning effort, contrary to a disproportionately high number of person-years of life lost due to missed chance to distinguish and remedy cancer in low and middle-income countries (4).

Because of weakness in collecting data about cancer incidence, the situation of this issue is unfamiliar in many low-and middle-income countries (1). Somewhat about sixty percent of countries around the world, do not have population-based cancer registries and they frequently cover only a small deduction of the population (2).

In this condition, up-to-date and exact epidemiological data are necessary to support health policy decisions, and to expand meaningful cancer control projects or strategies for any nation.

Estimating resource needed such as health workers, infrastructure, etc. for effective planning for delivery of health services depends on realizing how many children will develop and survive cancer (5). Also reporting incidence patterns and recognizing geographical differences can supply useful signs for probable etiological associations and observed geographical incidence diversity has been used to help several suppositions of the dependence among exposures related to modern lifestyle and the risk of childhood cancer (6).

One of the main problems in developing countries such as Iran is lack of the up-to-date population-based childhood cancer registries to monitor the trends and geographic variations over time and to provide a unique database for epidemiologic researches (7, 8). Evaluation of the completeness, timeliness, reliability and accuracy of available cancer databases is essential for the policymakers regarding how much they can rely on this information which forms their planning and policies basis (9). The capture-recapture (CRC) method is one of the epidemiological methods for estimating the completeness of registries and to estimate the more accurate incidence rate of disease when various incomplete data sources are available in the same geographic area (10).

In recent years, efforts have been made to establish a population-based cancer registration system in the general population as well as in children (11). However, studies evaluating the registration system have shown that the completeness of cancer registries in the general population has been reported between 24% to 72% for lung cancer and 36% to 66% for gastrointestinal cancers in different provinces of Iran (11-13). The various data sources on childhood cancer are available in Iran including pathology reports, hospital records, mortality data and MAHAK charity database.

The CRC method was used previously in Iran to estimate the number of prevalent cancers in the general population in Tehran metropolitan, Ardabil and Khuzestan provinces (11, 12, 14). However, there is no evidence for estimating childhood cancers using available data sources in Iran. This study aimed to estimate the more accurate of childhood cancers and their geographic distribution using the three-source CRC method in Iran.

Methods

Three Sources Data Collection

All new cases of childhood cancer registered by three sources including clinical records, pathology reports from all medical universities in Iran that reported to cancer registries office in Iran Ministry of Health and Medical Education (MOHME) and MAHAK database (Mahak Society to Support Children with Cancer) were enrolled in the study. We used the last updated and cleaned data that existed in MOHME in the year 2016. All data were enrolled in the same time interval and geographic locations by three sources of registries in order to adhere to the capture-recapture assumptions.

Data linking among three-sources

SQL capacity of Microsoft Office Access was used to identify and remove duplicate records between the three data sources. First, data were linked through the national ID codes. Thereafter, those records that did not have the national ID codes were identified and common cases among three sources were identified by matching other variables such as cancer type (based on ICD code), patient's name and surname, date of birth and father's name.

Statistical analysis

Three sources capture-recapture (CRC) method was applied using log-linear models in order to estimate more accurate of childhood cancer in Iran. We considered all possible combinations of three sources of registries in the capture-recapture analysis in which patients do or do not register in each data source. The general model uses eight parameters: the common parameter (the logarithm of the number expected to be in all lists), three 'main effects' parameters (the log odds ratios against appearing in each list for cases who appear in the others), three 'two-way interactions' or second-order effect parameters (the log odds ratios between pairs of lists for cases who appear in the other), and a 'three-way' interaction parameter.

We used the goodness of fit criteria such as Akaike's Information Criterion (AIC), log likelihood-ratio test (G2) and Bayesian Information Criteria (BIC) to select the best fitting model.

The log likelihood-ratio test ($G^{2)}$ statistical formula was calculated as below:

$$G^2 = -2\sum Obs_j \ln[Obs_j/Exp_{ji}]$$

In this formula, the Obs_j is defined as the observed number of individuals in each cell of j, and Exp_{ji} is the expected number of individuals in each cell j under model i.

$$AIC = G^2 - 2[df]$$

G2 is a log likelihood-ratio test that indicated that how the model is fitted to the data and the second term, 2(df), and is due to additional parameters and also the complexity of the model.

$$BIC = G^2 - [\ln N_{obs}][df]$$

In this formula, the df is the number of freedom and N is the total number of observed individuals (11, 15).

The best log-linear model with a lower amount of AIC was selected (15). All statistical analysis was performed in STATA software version 12 (StataCorp, Texas, USA). ArcGIS 10 was used for the geographic distribution of childhood cancer in Iran. The updated electronic topographic map of Iran and related provinces was used in this study. The data estimated based on three sources of the registry by capture-recapture was linked to every provinces using the unique code corresponding to each province in the map data tables using the Excel software. The Getis-Ord Gi spatial statistics were used to determine the provinces with a high incidence of childhood cancer.

Ethics approval

The methodology and ethical considerations of this study was assessed and approved by the National Institute for Medical Research Development (IR.NIMAD.REC.1396.220).

Results

Overall, 2567 childhood cancer records were identified after removing duplicate records among three sources of registries of them 1360 (52.98%) were male. The details of common childhood cancer records between the MAHAK database, clinical records and pathology reports were shown in the Venn diagram (Fig. 1).

The pathology reports and clinical records were reported 1136 and 1326 childhood cancer records, respectively. MAHAK database with 419 records indicated lower numbers of childhood cancer. The common records between the MAHAK database with pathology and clinical were 80 and 55, respectively. Moreover, the number of 105 patients was registered both in the pathology report and clinical records and 37 records were common among three sources (Fig. 1).

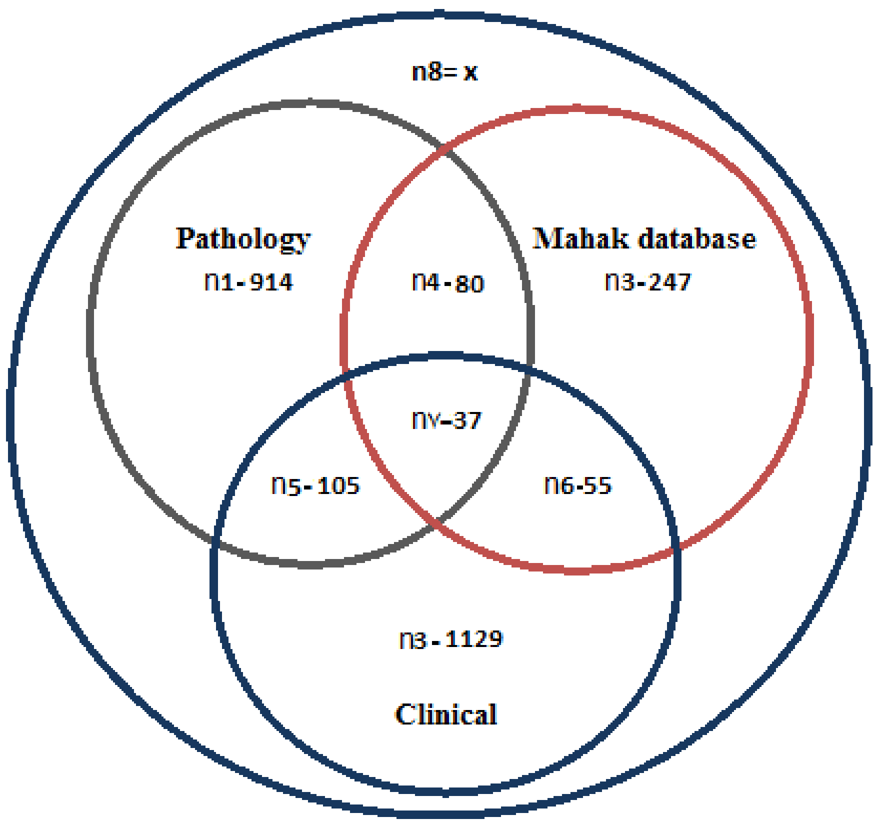

Fig. 1: Venn diagram for the common records of childhood cancers between Pathology, Clinical and Mahak charity institute databases

Moded selection in log-linear analysis

In three source capture-recapture analysis, a model in which two sources C and A and also two sources C and B are mutually interdependent and two sources A and B are independent (CA/CB) were selected based on lower amount of Akaike's Information Criterion (AIC=69.31), Bayesian Information Criterion (BIC=68.98) and G2 Index(G^2=8.85) (Table 1).

Childhood cancer estimation Using CRC Method

Total estimated number of childhood cancer was 5388 (95% CI: 4742.15-6228,14) and also in male and female were 5388 (95% CI: 4742.15-6228,14) and 5388 (95% CI: 4742.15-6228,14), respectively. The overal completeness of childhood cancer registry based on three source was 48% (Table 2). In cancer type subgroup,the higher estimated was Lukemia 1821 (95% CI: 1240.33-3272,41), Lymphoma 476 (95% CI: 312.87-960,19), Renal tumor 385 (95% CI: 233.70-910,69) and Central nervous system (CNS) 274 (95% CI: 295.86-317,67) and the lower number was liver 45 (95% CI: 34.87-148,75) and retinoblastoma 134 (95% CI: 75.88-268,63).

Table 1: Model selection in log-linear analysis by AIC, BIC and G^2 statistics

Model	*X* [c]	*N* [d]	*95% CI for N*	*DF* [b]	*G²* [a]	*BIC* [a]	*AIC* [a]
✦C/A/B	5258.68	7825.68	(7163.82-8582.82)	4	131.58	164.13	164.34
CA/B	5891.59	8458.59	(7609.93 -9450.01)	5	116.73	156.65	156.92
CB/A	3084.62	5651.62	(5094.52 -6331.52)	5	85.70	120.08	120.35
AB/C	7112.12	9679.12	(8620.03 -10923.52)	5	46.93	98.79	99.06
CA/CB	2821.97	5388.95	(4742.15 -6228.14)	6	8.85	68.98	69.31
CA/AB	9827.67	12394.68	(10531.41 - 14693.86)	6	90.02	121.01	121.34
CB/AB	5070.23	7637.23	(6330.65 -9397.42)	6	43.61	94.53	94.85
CA/CB/AB	20412.53	22979.53	(14575.81- 37264.17)	7	0.00	0.00	0.00

[a] Akaike's Information Criterion /Bayesian Information Criterion/ Goodness of fit.
[b] Degree of freedom.
[c] The estimated number of childhood cancers that were not recorded in any of three sources.
[d] The estimated total number of childhood cancers in Iran .
[e] Pearson Chi^2 for goodness of fit.
✦ C: Pathology source. A: Clinical Source. B: MAHAK charity institute source; Model C/A/B: A model where all available resources are independent; Model CA/B: A model where sources C and A are dependent and independent of the source B; Model CB/A: A model where sources C and B are dependent and independent of the source A; Model AB/C: A model where sources A and B are dependent and independent of the source C; Model CA/CB: A model where two sources C and A and also two sources C and B are mutually interdependent and two sources A and B are independent; Model CA/AB: A model where two sources C and A and also two sources A and B are mutually interdependent and two sources C and B are independent; Model CB/AB: A model where two sources C and B and also two sources A and B are mutually interdependent and two sources C and A are independent; Model CA/CB/AB: A model where all two-way interaction between resources are exist

Table 2: Estimated Number of childhood cancer by Log-Linear Model Based on Three Independent Sources

Subgroups		*Reported number of childhood cancers**	*Estimated number of childhood cancers*	*95% CI for Estimated number of childhood cancers*	*Completeness (%)***	*Incidence rate (per 1 million person)*
Sex	Male	1360	2550.24	(2204.06-3038.40)	53.33	264.81
	Female	1207	2962.87	(2379.16-3837.23)	40.74	324.17
Cancer type	Central nervous system (CNS)	262	274.00	(295.86-317.67)	95.62	14.28
	Childhood liver cancer	34	45.10	(34.87-148.75)	75.39	2.35

	Leukemia	852	1821.50	(1240.33-3272.41)	46.77	94.91
	Lymphoma	230	476.00	(312.87-960.19)	48.32	24.80
	Renal tumor	172	385.50	(1662.38-2636.34)	44.62	20.09
	Retinoblastoma	51	134.60	(233.70-910.69)	37.89	7.01
	Other sites	966	2044.52	(75.88-268.63)	47.25	-
Provinces	East Azerbaijan	80	200.07	(103.51-692.50)	39.99	223.79
	West Azerbaijan	118	143.07	(66.14-44.22)	82.48	170.78
	Ardabil	43	111.42	(62.51-259.52)	38.59	371.09
	Esfahan	258	300.00	(270.24-402.99)	86.00	271.85
	Alborz	64	110.00	(75.08-180.90)	58.18	189.67
	Ilam	4	9.00	(4.50-11.99)	44.44	66.88
	Bushehr	36	52.80	(37.32-205.87)	68.18	172.94
	Tehran	470	893.78	(751.60-1107.73)	52.59	333.18
	Charmahal &Bakhtiari	36	68.50	(41.77-218.88)	52.55	277.91
	South Khorasan	19	37.00	(20.42-104.20)	51.35	170.11
	Khorasan Razavi	183	305.00	(199.20-1013.49)	60.00	176.45
	North Khorasan	24	43.00	(24.83-259.92)	55.81	182.27
	Khuzestan	204	348.00	(250.22-652.59)	58.62	270.20
	Zanjan	53	107.00	(62.00-308.92)	49.53	423.05
	Semnan	16	27.00	(16.45-35.59)	59.26	179.51
	Sistan& Balouch-estan	74	150.00	(81.66-749.99)	49.33	141.01
	Fars	199	300.00	(205.27-1824.92)	66.33	269.55
	Qazvin	31	58.40	(35.25-202.35)	53.08	196.59
	Qom	14	30.00	(14.70-217.14)	46.67	89.49
	Kurdistan	29	55.00	(30.39-407.91)	52.73	143.57
	Kerman	48	108.50	(67.35-234.38)	44.24	126.62
	Kermanshah	43	73.50	(48.94-128.15)	58.50	172.66
	Kohgiloye& Bouyerahmad	79	206.00	(113.24-542.61)	38.35	404.62
	Golestan	47	93.54	(63.93-173.52)	50.24	186.68
	Gilan	46	118.50	(58.60-371.66)	38.82	263.46
	Lorestan	43	103.40	(57.33-294.68)	41.59	238.81
	Mazandaran	18	39.00	(19.49-234.63)	46.15	60.87
	Markazi	131	214.60	(155.31-366.39)	61.04	688.05
	Hormozgan	57	151.00	(67.44-849.78)	37.75	285.63
	Hamedan	37	80.91	(45.96-145.63)	45.73	205.97
	Yazd	61	88.85	(66.49-179.26)	68.65	289.28
Total		2567	5388.97	(4742.15-6228.14)	47.63	280.78

The overall incidence rate of childhood cancer in Iran was 280.78 per 1 million populations and in male and female was 264.81 and 324.17 per 1 million populations. Among all types of childhood cancer, the highest incidence rate belonged to Lukemia 94.91 per 1 million populations, Lymphoma 24.80 per 1 million populations, renal tumor 20.09 per 1 million populations and central nervous system (CNS) 14.28 per 1 million populations and the lower incidence was liver 2.35 per 1 million populations and retinoblastoma 7.01 per 1 million populations (Table 2).

Geographic Distribution of Childhood Cancers

The national distribution of childhood cancers in Iran according to the estimated numbers by CRC method indicated that provinces of Markazi, Kohgiluyeh & Boyer Ahmad, Ardabil and Tehran with an incidence rate of 371.09, 404.61, 420,01 and 333.18 per 1 million population had the higher incidence rate and and Mazandaran, Ilam and Qom provinces with the incidence rate of 60.87, 66.87, and 89.49 per 1 million population had the lowest amount of childhood cancer occurrence (Table 1, Fig. 2). More details about the geographic distribution of childhood cancer in Iran were presented in Table 2 and Fig. 2.

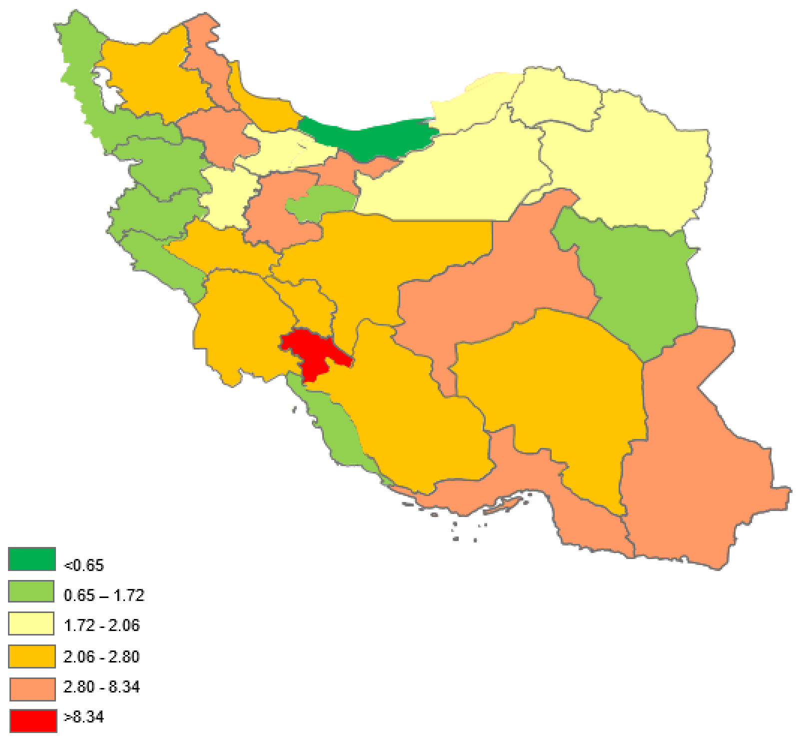

Fig. 2: Geographic distribution of estimated childhood cancer incidence (per 10000 populations) in Iran

Discussion

In the present study, the actual number of children with cancer in Iran was estimated by CRC which is substantially higher than the number reported in available data sources. Estimates obtained through the CRC method indicated that 5389 children aged 0-14 yr have cancer in the country and the existing data banks only show approximately 50% of them. Therefore, many children with cancer were not registered in the banks due to a lack of a centralized and up-to-date registration system. Therefore, we can with more certainty assume that the results of this study are closer to the real number.

Based on the estimated results of this study, the incidence of cancer in children aged 0–14 yr was 280.8 per million person-years. However, the overall incidence rate reported in the population-based registry study from 62 countries conducted by the International Agency for Research on Cancer was reported by 140.6 per million in children aged 0-14 years (1). The incidence of children with cancer was reported in the GLOBOCAN database which showed that the incidence per million children is between 50 and 200 cases yearly (16). The previous childhood cancer incidence in Iran was reported by 48 to 112 and 51 to 144 among girls and boys, respectively. In Golestan Province was 99.3 per 1 million between 2004-2006 (17). These reports are consistent with the incidence rate of childhood cancer in neighboring countries of Iran that was reported from 99.8 per million population in Saudi Arabia to 115 per 1 million in Iraq (18-20). However, despite of previous statistics of childhood cancer in Iran, the estimated number of childhood cancer by the CRC method was higher than both previous national reports and the neighboring countries that were only based on the pathology reports.

The age-standardized rate reported by worldwide cancer report for the Western Asia region, which includes Iran, was reported as 140.9 per million person-years (18). These cancers in some countries of North America, in Southern Europe, and in Oceania was more than 150 per million person-years, also in sub-Saharan Africa, Native American, and India was less than 100 per million. However, the incidence rate of all tumor types for children (0–14 years) in Italy was 156.9 (151.3–161.6), the incidence rate for adolescents (15–19 yr) was 281.7 (259.8–305.0) (21). Therefore, the incidence rate of childhood cancers was slightly higher in Iran than in other countries and it seems that it's equal with adolescent cancer and some report states that 84% of childhood cancers occur in the low-income and middle-income countries, where access to care is poor (22). As a middle-income country, cancer is the major cause of mortality and disability in Iran and in early year's studies stated that these countries face an increase in the incidence of non-communicable diseases NCDs, including cancers (23).

Childhood cancer incidence was different in various geographical regions of Iran, and the highest rate of cancer was observed in metropolitan provinces. Based on the frequencies of childhood cancer, about 20% of total cancer incidence in Iran relates to Tehran Province and 51% of total cancer incidence relates to 5 provinces. Incidence rates were lower in low-income areas than in higher-income areas (24, 25). Exposures to carcinogenic chemicals such as air pollution and other environmental factors may contribute to cancer risk (26). In the present study, the central, northeast, and south regions of Iran areas were provinces with high cancer, which located most industrial factories in these provinces. For example in Tehran, the number of vehicles is very high and air pollution is considered as the main problem (27). Another reason could be the centralization of diagnostic equipment in metropolitan areas, so often people who belong to other areas are referred to these provinces, so they are registered in metropolitan provinces.

In this study, incidence rates were slightly higher in girls than in boys (incidence sex ratio was 1.22 in the 0-14 yr age group) which were similar to other studies (21, 28) which are about 1.2 for all incident cancers (29). Physiological differences between males and females may be an assumption to explain why there is a disparity in the incidence of children with cancer (30).

This study subject to some limitations regarding access to a wide range of calendar time of three data sources and only the latest available data sources were enrolled in this study. The CRC estimation may be subject to over- or underestimation and we tried to select the best-fitted log-linear model by considering the interaction between data sources and matching the data sources by time interval and geographic location to meet the CRC assumptions and to minimize the bias in estimations.

Conclusion

This study describes the national childhood cancer incidence patterns in children younger than 15 yr, despite possible some limitation in the quality of data banks related to childhood cancer in Iran. There is a significant difference in the estimated incidence rate of childhood cancers in Iran compare to both previous national reports

and the neighboring countries that were only based on the pathology reports.
Moreover, this study indicated a significant difference between the geographic regions of Iran such as Ardabil, Kohgiluyeh, Markazi and Tehran provinces that need to pay more priority in screening and preventing programs. Finally, the quality of childhood cancer registry in Iran is inappropriate and needs more attention to improve its quality. Some strategies such as the use of population-based online registry using electronic health record (EHR) and using health national code of patients instead of name and surname should be used to improve the quality of the childhood cancer registry system.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that they have no competing interests.

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