### **RESEARCH PAPER**

## Patterns and Trends of Childhood Cancer Incidence (0-14 Years) in Delhi, India: 1990-2014

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**Objectives:** To investigate the patterns and temporal trends of childhood cancer incidence (0-14 years) in Delhi from 1990 to 2014.

**Methods:** The new childhood cancer cases diagnosed between 1990 and 2014 were extracted from the Delhi population-based cancer registry (PBCR). Joinpoint regression analysis was performed to assess the temporal behaviour of new childhood cancer. The magnitude of temporal trend was assessed by estimated annual percentage changes (EAPCs).

**Results**: The Delhi PBCR registered 12,637 cases (8484 boys and 4153 girls) during 1990-2014. The overall childhood cancer was twice in boys than girls (5.62% vs. 2.78%). The agestandardised incidence rates (ASIRs) of childhood cancer adjusted to the WHO World standard population distribution (year

hildhood cancer incidence is increasing worldwide; developing countries have higher incidence and mortality as compared to developed countries [1]. Globally top-five childhood cancer sites are leukaemia, lymphoma, central nervous system (CNS), kidney and liver, with boys showing a higher proportion of cancer than girls [2,3]. Age standard incidence rate (ASIRs) in India for childhood cancer were 91 per one million and 65 per one million in boys and girls respectively [3].

According to a recent report based on 28 population based cancer registries (PBCRs), the proportion of new childhood cancer to total cancer varied from 0.8% - 4.7% in boys and 0.5% - 2.6% in girls during 2012-2016. This may be due to variation in environmental exposures or biological susceptibility within Indian regions [4]. Delhi showed the highest proportion of childhood cancer for both boys (4.7%) and girls (2.6%) compared to other region of the country. Delhi observed highest ASIRs among boys (203.1 per one million) as well as among girls (125.3 per one million) based on 2012-2014 data. 2000) was 163 per one million in boys and 92 per one million in girls; median age at diagnosis being 6 and 7 years, respectively. Five-top childhood cancer sites was leukaemia, lymphoma, central nervous system (CNS), bone and retinoblastoma. A decreasing linear trend in proportion of new childhood cancer cases to total all age-group cancer was observed in both sexes during this period. The percentage increase in childhood cancer is similar in both sexes from 1990-94 to 2010-14 (97% vs. 93%). Increasing trend in ASIRs of childhood cancer cases observed. **Conclusion**: The new childhood cancer cases observed increasing trend during 1990 to 2014. Boys had nearly double the number of childhood cancer cases than girls while population ratio of boys and girls during the same period was 1.14:1.

**Keywords:** Age-standardized incidence rate, Annual percentage change, Epidemiology.

The various studies have been conducted to study the temporal trend of different cancer sites other than childhood cancer in Delhi [5,6]. We examined the patterns and temporal trend of childhood cancer in urban Delhi from 1990-2014.

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#### METHODS

The study is based on data extracted from Delhi PBCR, one of the oldest cancer registries of India established in 1986, for all new childhood cancer cases diagnosed between 1990 and 2014. The new cases of top five childhood cancers – Leukaemia (C91-C95), Lymphoma (C81-C85, C96), Central Nervous System (C70-C72), Bone (C40-C41), and Retinoblastoma (C69) were summarized according to gender into five 5-year period (1990-1994, 1995-1999, 2000-04, 2005-2010, 2010-2014). This registry fulfilled the IARC data quality standards and the data was published in cancer incidence in five continents volumes IX and volume X [7,8]. The

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international classification of disease for oncology (ICD-O) code 9th revision was used for the period 1988-2000 and  $10^{\text{th}}$  revision was utilized for the period 2001-2014.

According to the 2011 census, the total population of Delhi was 1,67,53,235 with 97.5% of people living in urban areas. Out of these, 0-14 years population was 45,65,319 and about 97.1% of 0-14 them live in urban areas of Delhi.

The target population for 0-14 years used in determining the incidence rates of respective years was estimated from the 1991, 2001, 2011 census reports of India using difference distribution method [9,10]. These estimates were not adjusted for immigration and fertility changes over the period due to non-availability of adequate data. ASIRs were calculated by the direct method using WHO World standard population distribution, year 2000 [11].

Joinpoint regression model using joinpoint regression programme [12] was applied to assess the magnitude of time trends on the ASIRs of top five childhood cancers and total childhood cancer during 1990-2014 according to gender. ASIR was determined using the formula: Number of new childhood cancer cases in a specific agegroup during a period\*1000,000/Estimated population of a specific age group during the period.

Simple linear regression was performed to assess the trend of relative proportion of new childhood cancer cases to all age-group cancers. The percentage increase in top-five new childhood cancer cases was calculated by: (childhood cancer cases during 2010-2014 minus childhood cancer cases during 1990-1994) \*100 / Childhood cancer cases 1990-1994. The median age was determined using the median formula for group data on combined 25-years data.

The estimated annual percentage changes (EAPCs) in cancer incidence rates was calculated by fitting a jointpoint regression model, assuming a constant rate of change in the logarithm of the annual ASIRs in each segment. The significance of EAPC was tested using asymptotic t-test and considered significant at 5% if 95% Confidence interval (CI) of EAPC does not include zero. The connecting points of the jointpont segment was treated as break. For 25-data points, joinpoint software recommended a maximum 4 joinpoints. This started with a minimum zero i.e straight line. Monte Carlo permutation test with 4499 randomly permuted data sets was applied to test the additional requirement of joinpoint, the obtained P-value was adjusted according to Bonferroni correction due to multiple comparisons [13]. ASIRs show a rising trend when the point estimate and

lower limit of 95% CI are >0. In contrast, a decreasing trend can be seen when the point estimate and upper 95% CI are <0. Else, the ASIRs are deemed to be stable over the time period. The multiple comparisons, asymptotic t-test and Monte Carlo permutation test are part of joinpoint software [12].

#### RESULTS

In 1990-2014, Delhi PBCR registered 12,637 new childhood cancer cases (8484 boys and 4153 girls). The proportion of childhood cancer was 4.2% relative to total cancers of all-age groups. Childhood cancer amongst boys relative to all age-groups cancer was almost double than in girls (5.62% vs. 2.78%) while the ratio of population of boys and girls was 1.14 to 1 during this period. The combined five top childhood cancer during 1990-2014 were leukemia [C91-C95], lymphoma [C81-C85], CNS tumors [C70-C72], bone tumors [C40-C41] and retinoblastoma [C69] (Table I). The boys observed a similar sequence of top-five childhood cancer during the recent three five-year intervals. While, girls observed different sequence, (leukemia, CNS tumors lymphoma, bone tumors and retinoblastoma). Top five childhood cancers contributed nearly 80% among boys and 70% among girls respectively. Leukemia was a prominent cancer in both gender and contributed 36.1% (approximate one-third) of total childhood cancer cases (Table I). The proportion of childhood cancer to total cancer of all age groups revealed a significant linear decreasing trend in both boys and girls. This percentage of childhood cancer decreased from 6.6% to 4.7% in boys and 3.6% to 2.6% in girls respectively from 1990 to 2014 (Suppl. Fig. 1). Median age at diagnosis of childhood cancer for boys was 6 years and for girls 7 years while in combined it was 6 years.

Over the period of 1990-94 to 2010-14, the percentage increase in new childhood cancer cases was almost similar for both the gender (97% vs. 93%). The

Table I Proportion of Childhood Cancer Cases During	g 1990-
2014 in Delhi	

Type of Childhood Cancer	Boys n=8484	Girls n=4153	Total n=12637
Leukemia	3127 (36.9)	1438 (34.6)	4565 (36.1)
Lymphoma	1517 (17.9)	376 (9.0)	1893 (15.0)
Central nervous system	997 (11.8)	498 (12.0)	1495 (11.8)
Bone	570 (6.7)	351 (8.4)	921 (7.3)
Retinoblastoma	434 (5.1)	232 (5.6)	666 (5.3)
Other types <sup>a</sup>	1839 (21.7)	1258(30.3)	3097 (24.5)

All values in no. (%). <sup>a</sup>Other types of childhood cancer.

girls observed higher percentage change in leukemia, retinoblastoma, and other cancers sites, while lymphoma, and CNS tumors was more in boys during 2010-14 relative to 1990-94. The percentage increase of bone cancer was almost similar in both genders (**Fig. 1**).

The age specific (0-4,5-9,10-14, and 0-14 year) distribution of top-five childhood cancer over the 25-year period (1990 to 2014) was similar in boys and girls except for lymphoma which was more frequent in boys. Retinoblastoma was more common in children <10 years. Although girls had higher counts under five-year compared to the remaining two five-year age groups albeit in boys under 5-year and 5-9 years age-group had similar number of cases. The age-specific incidence rate per one million of childhood cancer was higher in 0-4 years as compared to two subsequent 5-year intervals among both gender (**Suppl. Fig. 2**).

The age-period graphs for top-five cancers as well as total childhood cancer according to gender are included as **Suppl. Fig. 3** and **4**. In boys, total childhood cancer and leukemia had an upward incidence pattern in recent two periods than the remaining three periods in nearly all the three childhood age groups. In girls, total childhood cancer, leukemia and bone cancers showed increasing trend in all childhood age groups from 2005 to 2014 (**Suppl. Fig. 2** and **3**). Lymphoma was more frequent in 5-9 years age-group, bone in 10-14 years age-group, and retinoblastoma in 0-4 year age groups among the boys, similar pattern of these sites was observed among the girls.

The ASIRs of childhood cancer was 163.2 per one million (95% CI:159.8-166.7) in boys and 91.6 per one million (95% CI:88.8-94.4) in girls. (**Table II**). The trend analysis showed a significant increase in ASIRs of childhood cancer, EAPC 1.53% (95% CI: 0.87 to 2.13) in boys and observed one break among girls, the trend remained stable between 1990-2005, but increased more rapidly with 6.0% per year these after (**Fig. 2, Table II**).



Fig. 1 Comparison of relative percentage change in top-five childhood incidence cases from 1990-94 to 2010-2014 between boys and girls.

For pooled data, no change in ASIRs trend was seen till 2004, but a significant rise was observed with EAPC 4.0% per year in recent decade (2004-2014) [data not shown].

The childhood cancer trends varied according to cancer site as well as by gender. In boys, upward trends were observed for lymphoma (EAPCs= 1.25% per year), and for bone tumors (EAPC 2.51% per year). However, leukemia and CNS tumors observed no change between 1990 and 1999, but found a positive significant trend with EAPC of 4.6% per year and 3.1% per year from 1999 to 2014. The girls showed a different trend than boys; one break was observed in CNS tumors with a 2.6% decrease in EAPC from 1990 to 2007 and remained stable since then (Table II). Leukemia also observed one break with a stable incidence trend between 1990-2004 and a sharp upward trend in recent decade with EAPC of 7.0% per year. Bone tumors had a significantly rising with EAPC of per year during 1990-2014. Lymphoma, 3.2% retinoblastoma and other childhood cancers sites depicted a consistent flattening trend over the period.

#### DISCUSSION

The percentage of new childhood cancer cases to total cancer cases were significantly decreasing in both genders. This may due be to the falling trend of fertility rate and growing trend of expectancy of age in Delhi as well as in India [14]. The total fertility rate decreased from 4.83 in 1980 to 2.3 in 2015 as per United Nation websites [15]. In Indian urban areas, life expectancy at birth increased from 65.4 during 1990-94 to 71.5 during 2010-2014. The life expectancy at birth in Delhi during 2010-14 was 73.5 [16].

ASIRs of childhood cancer showed an increasing trend during 1990-2014 in boys and in girls during 2005-2014.



Fig. 2 Trend of age-standardized (world population, per one million) incidence rates for childhood cancer in Delhi urban area between 1990 to 2014 (trend modelled using joinpoint regression).

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Та	ble II Age	-standar(	lized Rate	es and Tin	ne Trend o	of Five Top-Childhood (	Cancers in Delhi Urban Area by Sex	1990-2014
Cancer type	Age-stai	ndardized	incidence	rate/mill	ion populd	ution/year <sup>b</sup>	Estimated annual percentage change	[EAPC(95%CI)]
	1990-94	i 1995-99	2000-04	2005-09	2010-14	1990-2014 (95% CI) <sup>b</sup>	Trend-1	Trend-2
Boys								
Leukemia [C91-C95]	50.8	46.0	50.1	65.7	82.1	60.2 (58.0 to 62.3)	$-1.27 (-5.06 \text{ to } 2.67)^a [1990 \text{ to } 1999]$	$4.58(3.16 \text{ to } 6.01)^{b}[1999-2014]$
Lymphoma [C81-C85,C96]	27.5	23.2	27.4	31.4	31.9	28.5 (27.1 to 30.0	1.25 (-0.006 to 2.3) $^{a}$	
CNS [ C70-C72]	20.3	16.6	16.1	21.2	21.2	19.1 (17.9 to 20.3)	$-3.20 (-8.1 \text{ to } 1.90)^{a} [1990-2000]$	$3.10 (6.5 \text{ to } 5.6)^c [2000-2014]$
Bone [ C40-C41 ]	8.3	8.7	10.1	12.0	12.8	10.6(9.8 to 11.5)	$2.51 (0.88 \text{ to } 4.16)^c$	
Retinoblastoma [C69]	8.5	9.1	7.5	9.0	9.6	8.8(8.0 to 9.64)	1.09 $(-0.73 \text{ to } 2.94)^{d}$	
Other CC	35.2	40.3	36.5	32.8	35.8	36.1 (34.41 to 37.7)	$0.41 (-0.53 \text{ to } 1.36)^a$	
Total	150.5	143.9	147.8	172.2	193.6	163.2 (159.8 to 166.7)	$1.53 (0.87 \text{ to } 2.13)^b$	
Girls								
Leukemia [C91-C95]	23.8	29.1	23.23	34.4	45.0	32.1 (30.1 to 33.4)	0.37 (-3.06 to 3.92) <sup><i>a</i></sup> [1990-2004]	$7.06(2.7 \text{ to } 11.6)^{c}[2004-2014]$
Lymphoma [C81-C85,C96]	9.1	7.4	7.1	8.3	9.2	8.0 (7.4 to 9.01)	$0.41 (-1.29 \text{ to } 2.14)^{a}$	
CNS [C70-C72]	13.3	10.1	10.2	8.3	13.0	10.9 (9.9 to 11.9)	-2.6(-4.7 to -0.44) <sup>c</sup> [1990-2008]	10.3 (-0.27 to 21.96); <sup>a</sup> [2008-2014]
Bone [C40-C41]	6.8	5.3	6.2	7.8	10.9	7.5 (6.7 to 8.3)	$3.2 (1.61 \text{ to } 4.79)^b$	
Retinoblastoma [C69]	5.2	5.0	3.4	5.3	7.5	5.3 (4.6 to 6.0)	1.92 (-0.76 to 4.80) <sup><i>a</i></sup>	
Other CC	30.2	28.4	27.5	24.1	30.0	28.0 (26.4 to 29.5)	$-0.16 (-1.32 \text{ to } 1.02)^a$	
Total	88.3	85.3	<i>T</i> . <i>T</i>	88.1	115.6	91.6 (88.8 to 94.4)	-0.99 (-2.65 to 0.71) <sup>a</sup> [1990-2005]	$6.04 (2.87 \text{ to } 9.31)^{d} [2005-2014]$
<sup>b</sup> age-standardized to the WHO	World stana	lard popule	ttion. vear	2000/111:	CNS = Cen	tral Nervous System. <sup>a</sup> P>0.	$05: ^{b}P < 0.001: ^{c}P < 0.05: ^{d}P = 0.001.$	

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Our results of rising trend of new childhood cancer cases was akin to Canada [17], Australia, and Taiwan [18,19] (Suppl. Table I). To the best of our knowledge, no Indian study has assessed the time trend analysis of new childhood cancer cases, albeit one study reported rising trend in childhood cancer among the Indian PBCRs comparing three time periods [20]. Leukemia contributed to 36.1% of total childhood cancer cases as also seen in Canada [32.4%; 1992-2010], Australia [32.4%; 1983-2006], Taiwan [33.9%; 1996-2010], Estonia [31.1%; 1970-2016], Thailand [36.1%: 1990-2011]. [17-19,21-22]. Globally, the next two commonest childhood cancers are CNS tumors with range 13.9%-22.7%, followed by lymphoma with range 10%-11.2%, albeit in urban Delhi lymphoma and CNS tumors account for with a percentage of 15.0% and 11.0% of all the childhood cancer cases respectively [17-20]. However, in Chennai lymphoma and CNS tumors account for 20% and 11% of all childhood cases respectively [23].

ASIR for childhood cancer in Delhi was 129.8 per one million [95% CI: 127.6-132.1] from 1990-2014 which is closer to the Taiwan (125.0 per one million from 1996-2010) [19] and lower than United States (172.8 per one million between 2007 and 2011) [24] and Australia (157.5 per one million from 1997-2006) [18].

The etiology of childhood cancer is still limited, some of the factors like environmental exposure, genetic, parental smoking, higher birth weight, and high maternal age are associated with most childhood cancers [25,26]. A large US case-control study reported an increase of 8% in overall childhood cancer risk for each 5-year increase in maternal age [27]. Likewise, an increasing trend in median marriage age was observed in India [28]. The main reasons for increasing median age are rise in female workforce and higher education enrolment of females especially in urban India [28]. Indirectly, the median age of first-time mother showed an increasing trend but exact magnitude cannot be estimated.

The change in trends could also be influenced due to shift in coding or registration practices and improvement in diagnostic advancement during the period. The immigrants might also contribute to increase in new childhood cancer cases. Immigration in Delhi steadily increased from 6.34 lakhs during 1961-1971 to 22.2 lakhs during 2001-2011 [29]. However, effect of this increase on

#### WHAT THIS STUDY ADD?

- There is approximate 100% increase in incidence of reported childhood cancer cases from 1990-94 to 2010-2014 in urban Delhi.
- Median age at diagnosis of childhood cancer in Delhi is 6 years.

childhood cancer cannot be ascertained due to non-availability of data.

The main strength of Delhi PBCR is almost complete coverage and collection high-quality data. The Delhi PBCR data is also included in the International Agency for Research on Cancer scientific publications [7,8]. Although Delhi PBCR collects the data of only those patients who have been residing for at least one year in Delhi but veracity cannot be confirmed. The projected population of each year to calculate the ASIRs does not adjust for immigration and fertility changes over the years which may over-estimate the incidence rate. The subgroups of leukemia and lymphoma trend could not be observed due to a small number of cases. Age-periodcohort (APC) model that assess the effect of age, effect of period, and effect of cohort on the incidence, was not performed in the present study. The join point analysis developed by National cancer Institute, USA, is a robust method to assess the trend analysis especially for cancer incidence and mortality data [12,13].

The trend of overall new childhood cancer cases showed a significant increase especially in the latest decade in Delhi for boys and girls. The contribution of childhood cancer to total cases showed a decreasing trend during this period. Compared to girls, boys had doubled childhood cancer cases during 1990-2014. Leukemia is the most common cancer site and contributed to one-third of total childhood cancers during the 25-year period. The trend and knowledge of present status of childhood cancer helps the public health policy makers as a baseline for future planning and allocation resources.

**Note**: Supplementary material related to this study is available with the online version at *www.indianpediatrics.net* 

*Contributors:* All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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Country Name	Study	*APC(95	1% CI)	Age-standardized
	period			incidence rate
		Trend-1	Trend-2	
Canada [17]	1992-2010	0.45 (0.08-0.81)	-	$157.9^{b}$
Australia [18]	1983-2006	1.7 (0.9 to 2.5)	-0.1(-0.7 to 0.06)	$157.5 (153.6-161.5)^a$
		1983-1994	1995-2006	
Taiwan [ 19]	1996-2010	1.21 (0.6 to 1.7)	-	$125.0 (122.3 - 127.7)^a$
Estonia [21]	1995-2016	0.5 (0.1-0.9)	-	138.1 <sup><i>a</i></sup>
Thailand [22]	1990-2011	1.2 (0.8-1.7)	-	$98.5^{c}$
Present Study	1990-2014	-0.22 (-1.75 to 2.21)	4.05 (1.85-6.29)	129 (127.6-132.4) <sup>a</sup>
(Delhi, India)		1990-2004	2005-2014	

# Supplementary Table I Comparison of Incidence Trend and Age-standardized Incidence Rate of Childhood Cancer Among Various Countries

\* Annual percentage change in incidence rate using Joinpoint regression analysis Incidence rates were age-standardised using <sup>a</sup>WHO world standard population distribution, year 2000 <sup>b</sup>Canadian population distribution, year 2011, <sup>c</sup>Segi's et als. World standard population estimates, year 1960



Supplementary Fig. 1 Trend of percentage of new childhood cancer cases to total all-age group cancer cases. (Girls: slope =-0.05; *P*=0.002 and Boysslope=-0.092 *P*=0.013)



□ Leukaemia □ Lymphoma □ CNS □ Bone ■ Retnioblastoma ■ Other CCs

\*The rates were standardized according to WHO World population distribution, year 2000 using direct method [11]

Supplementary Fig. 2 Childhood cancer (0-14 years) distribution by gender and age-groups, Delhi, 1990-2014.



Supplementary Fig. 3 Age-period diagram of age-specific incidence rate in girls during 1990-2014 in Delhi urban, India



Supplementary Fig. 4 Age-period diagram of age-specific incidence rate in boys during 1990-2014 in Delhi urban, India.