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Research Paper

Trends in incidence of Ewing sarcoma of bone in India – Evidence from the National Cancer Registry Programme (1982–2011)

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ABSTRACT

Background: Ewing sarcoma is a malignant tumour found mainly in childhood and adolescence. The present study aims at analyzing the data on Ewing sarcoma cases of bone from the National Cancer Registry Programme, India to provide incidence, patterns, and trends in the Indian population.

Materials and Methods: The data of five Population Based Cancer Registries (PBCR) of Bangalore, Mumbai, Chennai, Bhopal and Delhi over 30 years period (1982– 2011) were used to calculate the Age Specific and Age Standardized Incidence Rates (ASpR and ASIR), and trends in incidence was analyzed by linear and Joinpoint Regression.

Results: Ewing sarcoma comprised around 15 % of all bone malignancies. Sixty-eight percent were 0–19 years, with 1.6 times risk of tumour in bones of limbs as compared to other bones. The highest incidence rate (per million) was in the 10–14 years age group (male −4.4, female −2.9) with significantly increasing trend in ASpR observed in both sexes. Pooled ASIR per million for all ages was higher in male (1.6) than female (1.0) with an increasing rate ratio of ASIR with increase in age. Trend of pooled ASIR for all ages was significantly increased in both sexes. Twelve percent cases were reported in ≥30 years of age.

Conclusion: This paper has described population based measurements on burden and trends in incidence of skeletal Ewing in India. These may steer further research questions on the clinical and molecular epidemiology to explain factors associated with the increasing incidence of Ewing sarcoma bone observed in India.

1. Introduction

Ewing sarcoma is a malignant small round blue cell tumor of bone, first described by James Ewing as an endothelioma of bone in 1921 [1]. It is the third commonest primary malignant bone tumor in all age-groups following osteosarcoma and multiple myeloma. Among children and young adults, it is the second frequently occurring bone malignancy [2–4]. Studies have shown lower incidence of this tumour among the African and East Asian population as compared to the Whites [5,6] with a male preponderance [6,7]. Most studies in the Asian population are hospital or laboratory based and focussed on treatment outcomes with no recent population based evidence of bone sarcoma incidence from India [8–12]. The Bombay Cancer Registry, the oldest population based registry in India, had reported Ewing sarcoma as the commonest bone malignancy in the late part of the 90s [13].The Population based Cancer registry reports of the National Cancer Registry Programme,India provided incidence of all bone malignancies but description by specific histologic types was not presented [14]. This paper provides a detailed analysis of the magnitude of incidence and burden of Ewing sarcoma of bone in the Indian population based on thirty years' data from the Population based cancer registries (PBCR) of the National Cancer Registry Programme (NCRP), India.

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2. Material and methods

The Population based cancer registry data from five urban places – Bangalore (1982–2010), Mumbai and Chennai (1982–2011), Bhopal (1988 – 2011) and Delhi (1988–2009) have been used for the analysis. A total number of 8394 bone malignancies (C40 and C41codes of the International Classification of Disease, 10th revision (ICD-10) [15] constituting approximately 1.2% of all cancers were registered in the NCRP. Among these, cases with morphology code M-92603/6 of the International Classification of Disease, Oncology – third edition (ICD-O-3) [16] were considered as Ewing sarcoma of bone. Peripheral neuroectodermal tumour (PNET) and Askin tumor also of the Ewing sarcoma family of tumours were not included as they had a different morphology code. Variables like age, sex, method of diagnosis, morphology, topography were extracted. Population estimations and quality checks on the data were based on the methods used by the NCRP, India [14].

Proportions of cancer type and site of cancer by age and sex groups were calculated. Unpaired t-test (continuous data) and odds ratio with 95% confidence limits (categorical variables) were calculated using SPSS version 22. Age Specific and Age Standardized (to world standard population) Incidence Rates (ASpR and ASIR) per million populations were calculated by age group and sex for each of the five PBCRs and the pooled data of five PBCRs. Standardized Rate Ratio of ASIR by sex group with its 95% confidence interval was also calculated.

Trends in ASpR and ASIR were calculated by five year periods from 1982 to 2011 using linear regression(IBM SPSS statistics for windows, version 22.0, Armonk, New York), and Joinpoint regression(Joinpoint Regression Program 4.0.1 January 2013,SEER) and expressed as Annual Percentage Change (APC) with significance at $p < 0.05$.

3. Results

Among all bone malignancies (8394) registered, 1301(15.5%) cases were Ewing sarcoma of bone in the five PBCRs. In the childhood (0–14 years) group, Ewing sarcoma accounted for 577 (38.8%) of all bone malignancies in the PBCRs. The highest proportions were observed in 10–14 years age group (25.2%) followed by 15–19 years (23.3%), with 68% cases in the 0–19 years age group. The proportion of cases in ≥ 30 years age was 11.6% ($n = 150$) in PBCRs. The M:F ratio was 1.8:1. Microscopic diagnosis was available in 99.4% of all registered cases.

The Age Standardized Incidence Rate (ASIR) per million (pooled) for all ages were 1.6 (male) and 1.0 (female) with a Rate Ratio (RR) of 1.54. Pooled ASIR was the highest in 0 to 19 years (male – 2.8, female – 2.0) and the lowest in ≥ 30 years (male – 0.5, female – 0.2). Rate Ratio of ASIR was 2.46 in ≥ 30 years as compared to 20–29 years(1.65), and 0–19 years (1.41) (Table 1).

The Age Specific Incidence Rate (ASpR) per million varied from 0.5 (male) and 0.4 (female) in 0–4 years age group in Mumbai to 6.5 (male) and 4.4 (female) in the 10–14 years age group in Delhi. In all the PBCRs, the Age specific incidence rate peaked in the 10–14 years age group in both sexes except for females in Bhopal and Mumbai and males in Bangalore (Fig. 1).

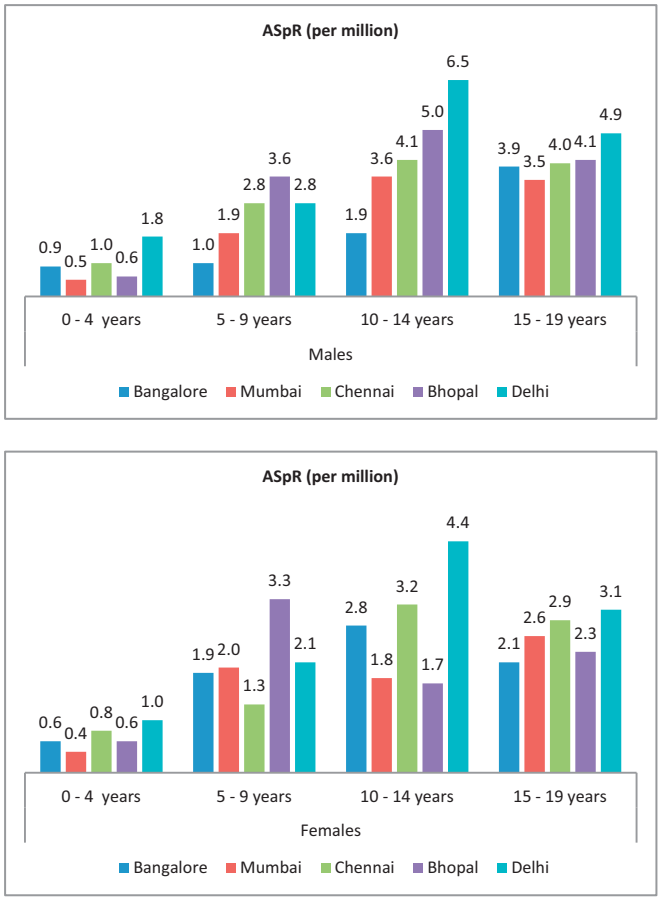


Fig. 1. Comparison of Age Specific Incidence Rate (ASpR) per million of Ewing's Sarcoma of bone by age group (0–19) and sex in five PBCRs (1982–2011), India.

The Age Specific Incidence Rate (ASpR) per million (pooled) was highest in the 10–14 years age group with 4.4 (male) and 2.9 (female) per million.

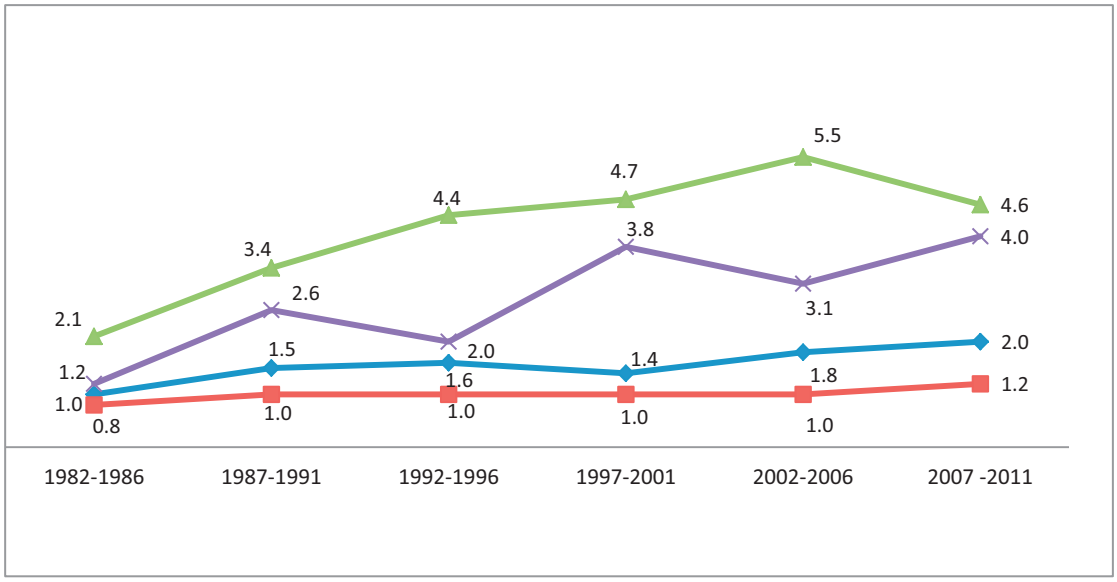
Pooled ASIR per million for all ages increased from 1.0 in 1982–86 to 2.0 in 2007–11, ($p = 0.019$) in males and from 0.8 to 1.2 ($p = 0.034$) in females with a five-year Annual Percentage Change (APC) of 2.24% (males) and 1.17% (females). A statistically significant increase in ASpR was observed in 10–14 years age group in both sex groups (Fig. 2).

Bones of extremities were more commonly involved compared to other bones (includes axial skeleton) in PBCRs (69.2%).The risk of

Table 1
Number, proportion (%), age–group specific (ASpR) and age standardized (ASIR) Incidence rate per million with Rate ratio and 95% Confidence Interval of Ewing Sarcoma of bone by sex in different age groups in five PBCRs (pooled) (1982 – 2011), India.

Age group (years)	Total *n*(%)	Male *n*(%)	Female *n*(%)	ASpR per million		ASIR per million		Rate ratio of ASIR (95% CI)
	1301 [100.0]	838 [64.4]	463 [35.6]	Male	Female	Male	Female	
00–04	70 (5.4)	44 (5.3)	26 (5.6)	1.1	0.7	2.8	2.0	1.41 (1.38–1.45)
05–09	181 (14.0)	99 (11.9)	82 (17.7)	2.2	2.0			
10–14	326 (25.2)	203 (24.4)	123 (26.6)	4.4	2.9			
15–19	302 (23.3)	196 (23.5)	106 (22.9)	4.1	2.7			
20–24	171 (13.2)	113 (13.6)	58 (12.6)	2.1	1.3	1.7	1.0	1.65 (1.53–1.78)
25–29	95 (7.3)	64 (7.7)	31 (6.7)	1.3	0.7			
> =30	150 (11.6)	114 (13.7)	36 (7.8)	0.6	0.2	0.5	0.2	2.46 (2.19–2.76)
All ages[a]	1295 (100.0)	833 (100.0)	462 (100.0)	1.7	1.1	1.6	1.0	1.54 (1.49–1.60)

[a] Age not known for 6 cases.



	All ages (ASIR)		10 -14 years (ASpR)	
	Male	Female	Male	Female
APC0	2.24*	1.17*	3.15*	4.19*
* P< 0.05				

Fig. 2. Trend of Incidence Rate per million by sex in all ages (ASIR) and 10–14 years age groups (ASpR) in five PBCRs (pooled), India from 1982 to 2011.

Table 2
Association of anatomical site of involvement in Ewing sarcoma of bone with age groups in pooled data of five PBCRs (1982–2011), India.

Age group (years)	Bone of limbs (C40) *n*(%)	Bone of other than limbs (C41[a]) *n*(%)	OR	95% CI	*p*
00–19	523 (72.6)	197 (27.4)	**1.64**	**1.24 −2.16**	**< 0.0-01**
> = 20	204 (61.8)	126 (38.2)			

[a] Cases with code C41.9 (Bone, NOS) are excluded from C41.

Ewing sarcoma in bones of extremities as compared to other bones was 1.6 times in 0–19 years age group as compared to 20 years and above ($p < 0.0001$) (Table 2).

4. Discussion

Bone malignancies constituted 1% of all cancers, and Ewing sarcoma of bone accounted for 15.5% of all bone cancers in population based registries. Skeletal Ewing was the major type [96%], and Ewing sarcoma of soft tissues was only 2.8% in all age groups, Skeletal Ewing proportions reported were higher as compared to a population registry in California (75%) [17].

Maximum cases were in the 0–14 years age group, with highest proportion (25%) in the 10–14 years age group, followed by 5–9 years (14%) and 0–4 years (5%). Almost half of cases (48.5%) were in the 10–19 years age group,similar to studies from Saudi Arabia (43.5%), Pakistan and India. (50% in 11–20 years) [18–20]. Ewing sarcoma has been infrequently reported in the ≥ 30 years age group, as compared to 12% in this analysis [2,6,7].

The pooled Age Specific Incidence Rate per million (ASpR) was the

Table 3
Comparative incidence rates (Crude and ASIR) of Ewing's sarcoma from selected International Registries (Incidence Rate is expressed per million population).

Age group (years)	Male				Female			
	ASpR per million	ASIR per million			ASpR per million			ASIR per million
	00–04	05–09	10–14	00–14	00–04	05–09	10–14	00–14
Reference studies								
4 PBCRs of UK (1981–2002)[22]	1.0	2.0	3.3	1.9	0.9	1.7	3.7	1.9
NCR, Ireland (1994–2000)[26]				3.2				2.6
Singapore Childhood Cancer Registry (1997–2005)[24]	0.6	0.5	0.5	0.5	0.0	1.0	0.5	0.5
PBCR from Chennai, India (1990–2001)[25]	0.5	2.3	2.1	1.5	0.0	0.0	3.9	1.1
Present study								
Chennai (1982–2011)	1.0	2.8	4.1	2.5	0.8	1.3	3.2	1.7
Pooled (1982–2011)	1.1	2.2	4.4	2.4	0.7	2.0	2.9	1.8

Table 4
Comparison of highest ASIR of microscopically verified Ewing sarcoma across continents in the CI5 Volume X (2003–2007).
Source: CI5 X, available from – http://ci5.iarc.fr/CI5-X/PDF/BYHISTO/C40.pdf.

Continent	Male		Female	
	Highest ASIR/ million	Registry	Highest ASIR/ million	Registry
Africa	4.0	Tunisia, North	2.0	Tunisia, North
America, Central and South	3.0	Brazil, Goiania	2.0	Argentina, Cordoba, Brazil, Sao Paulo, Costa Rica, USA, Puerto Rico
America, North	6.0	USA Delaware	5.0	USA, Wyoming
Asia	4.0	India, Bhopal	3.0	Israel, Jews, Turkey, Trabzon
Europe	7.0	Italy- Parma	7.0	Switzerland, Geneva
Oceania	3.0	Australia - NSW, Queensland, Tasmania, New Zealand	3.0	Australia, Queensland
Current study (2002–2006)	1.6	Pooled (2002–2006)	1.0	Pooled
Neighbouring countries				
Asia	1.0	Singapore	1.0	Singapore
Asia	1.0	China, Hong Kong	1.0	China, Cixian County
Asia	2.0	Malaysia, Penang	1.0	Malaysia, Penang

highest in 10–14 years age group, and ranged from 1.9 (Bangalore) to 6.5 (Delhi) in males and from 1.7 (Bhopal) to 4.4 (Delhi) in females. A study of four PBCRs in the United Kingdom reported the highest incidence rate of 3.32 (males) and 3.67 (females) in 10–14 years age group [21], while Cuba reported the highest incidence in the 15–19 years age group (3.0 in both sexes) [22]. In contrast, the Singapore Childhood Cancer Registry found the highest ASpR in the 0–10 years age group in both sexes [23]. In India, Chennai PBCR had earlier reported the highest incidence rate of 2.3 per million among male 5–9 years age group in 1990 − 2001 [24]. In the current analysis (1982–2011), the highest incidence has been shifted to the 10–14 years males. (4.1 per million) (Table 3).

The pooled Age Standardized Incidence Rate (ASIR) per million was highest in the 0–19 years age group in both sexes (male-2.8, female–2.0).Similar rates of 2.93 per million in 1–19 years age group [SEER data (1973–2004)] [3] and 2.0 per million (both sexes) in the 0–19 years age group in the National Cancer Registry of Cuba (2001 − 2003) [22] have been reported. The ASIRs in the childhood (0–14) age group (male – 2.4, female – 1.8) was higher than the rates reported by Singapore Childhood Cancer Registry (0.5 each in male and female) [23] and the UK study of four PBCRs among male (1.9) [21], but lower than the incidence rates in the National Cancer Registry of Ireland (male – 3.2, female – 2.6) (Table 3) [25]. Rate Ratio of ASIR by sex increased with age and was maximum in ≥ 30 years (2.46) i.e. almost twice as compared to 0–19 years (1.41).

The pooled ASIRs for all age groups in India (Table 1) was much lower than the highest ASIRs (ranged from 2–4 per million in males and 1–4 per million in females) of microscopically diagnosed cases reported in the Cancer Incidence in Five Continents Vol X(CI5X) [26]. ASIRs were higher for Indians as compared to Chinese and Malay population in Singapore in both sexes (Table 4) [26], that suggest racial and ethnic factors may be associated with disease development.

There is very scant literature available on trends in incidence of Ewing sarcoma globally. PBCR data from the United Kingdom reported a decline in ASIR of Ewing sarcoma of bone in 0 − 14 years age group in males (1.98–1.24 per million) and females (2.58–1.27 per million) from 1981–1988 to 1996–2002 [21]. Few studies that have shown trends in incidence (significant rise in Cuba and a non-significant decline in Canada) for all malignant bone tumours in the childhood age group [22,27], do not provide further data on specific histological types. This study has highlighted the increasing trends in incidence rates of Ewing sarcoma of bone in India in different age groups. Trends in pooled ASIR per million from 1982 to 2011 show a significant increase with Annual Percentage Change (APC) of 2.24 (males) and 1.17 (females) for all ages and specifically APC of 3.15 (males) and 4.19 (females) in the 10–14 year age group. A significant rise in incidence was also observed in males in the 0–4 years and ≥ 30 years age groups by linear regression (data not presented). This increasing trend in Ewing sarcoma for all age groups mirrors the trend of increasing incidence of all cancers due to demographic factors (increase in life expectancy, decrease in childhood mortality) and increase in case detection and registration in India. However, the increasing trend in incidence observed in specific age groups (10–14 for both sexes, 0–4 years and ≥ 30 years for male) merits further investigation.

Most frequently reported anatomical sites of Ewing were long bones of lower limb followed by long bones of upper limb, and data on the specific long bones was not available. Pelvic bone, sacrum and coccyx group of bones were the most commonly affected bones of the axial skeleton. The risk of Ewing sarcoma in bones of limbs as compared to other bones was 1.6 times in 0–19 years age group as compared to those aged ≥ 20 years. California PBCR reported a higher proportion of Ewing sarcoma in the peripheral skeleton in the age group of < 18 years (46.2%) as compared to adults (40.2%) [17]. The possible risk factors of tumorigenesis related to association of anatomical sub-sites and age group needs further research.

The National Cancer Registry Programme in India has not been recording advanced methods like cytogenetics and immunohistochemistry and thus data on type of EWS-FLI translocations is not available. The main findings of peak incidence in 10–14 years age group, an increasing trend in incidence in 10–14 years (males and females), male preponderance of tumour occurrence that is prominent in ≥ 30 years age group, and involvement of peripheral skeleton in childhood and adolescence add to the knowledge on epidemiology of Ewing sarcoma in India. These may steer further research questions on the clinical and molecular epidemiology of Ewing sarcoma of bone. This paper has addressed the gap in paucity of literature on skeletal Ewing in India and globally, especially with respect to population based measurements on burden and trends in incidence.

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