RESEARCH COMMUNICATION

Primary Malignancies of Bone and Cartilage in Karachi

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Abstract

Introduction: Primary sarcomas of bone and cartilage (BS) are a group of rare neoplasms, with limited information from Pakistan. The present population-based study was conducted with the objective of examining descriptive epidemiological characteristics of BS in Karachi. Materials and methods: Epidemiological data of 68 BS registered at Karachi Cancer Registry for Karachi South during 1st January 1995 to 31st December 1997 were reviewed. Results: Forty six (66.7%) cases were diagnosed in males and 23 (33.3%) in females. BS accounted for 2.2% and 1.1% of all cancers in males and females, respectively. The age standardized rate (ASR) world per 100,000 was 1.75 in males and 1.00 in females. Microscopic confirmation was 99.0%. The mean age of male and female patients were 26.7 years (SD ±17.4) and 24.3 years (SD ±16.0) respectively. In males 14 (30.4%) BS were diagnosed in the 0-14 year age group and 23 (50.0%) cases in the below 20 years age group. The distribution in females was 31 (67.4%) and 8 (34.8%) cases, respectively. Approximately half the cases (34.8% males; 47.8% females) were observed in the lower limbs. The most common morphology was osteosarcoma (30.5% males; 43.4% females), followed by Ewing's sarcoma (23.9%) in males and giant cell tumor (13.0%) in females. Age-specific curves showed a gradual increase in risk from the first until the fifth decade in males, and second to fourth decade in females. The age-specific curves were bimodal. In both genders the first peak was observed at 10-14 years but a second peak was observed at 70-74 years in males and 65-69 years in females. The cardinal symptoms that lead to the diagnosis of bone tumors were pain (22 cases; 32.4%) and spontaneous fractures (45 cases; 66.2%). Conclusion: Karachi falls into a high risk region for BS, which were observed in a relatively younger population, with a male predominance and a high frequency of osteosarcoma. The underlying factors for BS in Karachi need to be addressed considering the overwhelming proportion of youngsters at risk and the late presentation.

Key words: Bone, cartilage - sarcoma - incidence - Karachi - Pakistan

Asian Pacific J Cancer Prev, **10**, 891-894

Introduction

Primary sarcomas of bone and cartilage (BS) are a group of rare neoplasms, comprising 0.2 - 0.5% of all malignancies, with a higher involvement in children (Dorfman et al., 1995; Ries et al., 1999). They constitute 3% of all cancers in the 15-29 year age group and 6% of all childhood cancers below 20 years of age (Mascarenhas et al., 1998; Ries et al., 1999).

The incidence of BS has remained stable in most countries with no tendency to increase or decrease. In the US during 1973-87 the incidence fluctuated around ASR 0.8 per 100,000 (Dorfman et al., 1995) and continued such till 1993-7, the study period (Parkin et al., 2002). Despite the low incidence, it is estimated that 2,570 men and women will be diagnosed with and 1,470 men and women will die of cancer of the bones and joints in 2009 in the US (Horner et al., 2009).

It is likely that the burden of BS may be higher in developed countries but the incidence of cancer is not accurately assessed either because the health care systems are unavailable or are inaccessible. Moreover, there is limited documentation of diagnosed cases which do enter the health-care system, a result of apathy or financial constraints.

Pakistan is a developing country in South-Central Asia. Like other developing countries there is limited population-based cancer data from Pakistan. The only available data is from Karachi South the southern-most district of Karachi, the largest city of Pakistan. It includes all ethnicities of the country, namely Sindhis, Punjabis, Pathans, Baluchs and Mohajirs with a fair representation of all socio-economic categories. Mohajirs are a multiethnic migrant group of Indian origin, subcategorized on the basis of language viz. the urdu, gujrati and memoni speaking Mohajirs. In the absence of a national cancer

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registration system, KS qualifies as a sample population of the country.

The present study was conducted with the objective of examining descriptive epidemiological characteristics and pathology of BS in Karachi. The data is a population-based cancer registry data.

Materials and Methods

Epidemiological data of malignant tumors of the bone, ICD-10 (International Classification of Diseases, 10th edition) categories C40-41, registered at Karachi Cancer Registry (KCR) for Karachi South (KS), during 1st January 1995 to 31st December 1997 were reviewed. Malignancies arising in the bone marrow (ICD C42) were not included in the study.

The study included clinically diagnosed and microscopically verified cases. Histologically verified cases were initially evaluated on hematoxylin and eosin (H&E) stained sections. Special stains and immunohistochemistry were selectively used. Manual and computerized validity checks for the cancer data were performed as per recommendations of the International Agency for Research on Cancer (IARC) and International Association of Cancer Registries (IACR) (Parkin DM, 1994), these included checks for multiple primaries and duplication. Cases were categorized by tumor site, age and sex of the patients. Variables recorded were the hospital patient-number, date of incidence, name, age, sex, address, ethnicity, topography, morphology, grade and stage. Data were classified using ICD-O3 (International Classification of Diseases-Oncology, 3rd edition) and computerized using a customized version of CANREG-4 software (WHO, 2002).

Crude, age standardized incidence rate (ASR) and age-specific incidence rates were calculated using the person years of population at risk by sex and 5-year age-groups, based on the 1998 census; population of 893,684 males and 794,920 females, assuming an annual growth rate of 1.94%, as calculated by the Federal Bureau of Statistics. Standardized incidence rate was calculated with an external reference population, the 'world' population with a given 'standard' age distribution (Segi M, 1960). The methodology applied was direct standardization, using 5-year age groups. The rates given are the annual incidence per 100,000 population averaged over the number of years for which data are presented'. Incidence tables were based on ICD-10 (WHO, 1992). Data were analyzed using SPSS 16.0.

Results

A total of 68 BS were registered at KCR for KS, during a 3 year period, 1st January, 1995 to 31st December 1997. Of these 46 (66.7%) were diagnosed in males and 23 (33.3%) in females. BS accounted for 2.2% and 1.1% of all cancers in males and females respectively (Bhurgri Y et al, 2002; Bhurgri Y et al, 2000). The male, female ratio was 2:1 and the adult, childhood ratio was 1:3.

The age standardized rate (ASR) world per 100,000 and crude incidence rate (CIR) were 1.75 (1.21 to 2.29) and 1.72 (1.22 to 2.21) in males and 1.00 (0.50 to 1.50) and 0.96 (0.56 to 1.36) in females respectively. Microscopic confirmation was 99.0%. The cumulative rates 0-64 and 0-74 years were 0.11% and 0.15% in males and 0.06% and 0.09% in females.

The mean age of male patients was 26.7 years (95% CI 21.5, 31.9; SD ±17.4); the age range was 68 years (4-72 years). The mean age of the female patients was 24.3 years (95% CI 17.4; 31.2; SD ±16.0) with an age range of 55 years (10-65 years). In males 14 (30.4%) BS were diagnosed in the pediatric age group (0-14), 23 (50.0%) cases were observed in the below 20 years age group and 31 (67.4%) cases were observed below 29 years of age (table 1). In females the distribution was 8 (34.8%), 13 (56.5%) and 15 (65.2%) for the below 14, below 20 and below 29 years of age, respectively. Only 8.7% male and 4.3% female cases were older than 60 years of age.

Approximately half the cases (34.8% males; 47.8% females) were observed involving the lower limb in both genders (table 2). The most commonly affected bones were femur, tibia and humerus in that order. Histological stratification indicates that the most common morphology was osteosarcoma (30.5% males; 43.4% females) followed by Ewing's sarcoma (23.9%) in males and giant cell tumor (13.0%) in females. Majority of the cases of osteosarcoma were observed below 20 years of age (70% males; 80% females). The mean age of osteosarcoma cases in males and females was 19.5 years (95% CI 14.6, 24.4; SD±9.4; range 11-40 years) and 22.8 years (95% CI 8.5, 37.1; SD±19.9; range 10-65 years) respectively. The mean age of Ewing's sarcoma cases was 15.2 (95% CI 8.8-21.5; SD±9.5; range 8-40 years) in males. No second primary tumor was reported.

Age-specific curves showed a gradual increase in risk from the first until the fifth decade in males, and second to fourth decade in females. The age-specific curves were bimodal. In males the first peak was observed at 10+ and a second peak at 70+. In females the first peak was observed at 10+ but the second at 65+. Only in our study.

The cardinal symptoms that lead to the diagnosis of bone tumors were pain (22 cases; 32.4%) and spontaneous fractures (45 cases; 66.2%).

Discussion

Karachi falls into a moderate to high risk region for BS with an ASR world per 100,000 of 1.75 in males and 1.00 in females; a male, female ratio of 2:1 and an adult,

Table 1. Distribution of Bone and Cartilage Sarcomas by Gender and Age Group

Age groups (years)	Male N (%)	Female N (%)
0-14	14 (30.4)	8 (34.8)
0-20	23 (50.0)	13 (56.5)
0-29	31 (67.4)	15 (65.2)
15-19	9 (19.6)	4 (17.4)
20-29	8 (17.4)	3 (13.0)
30-59	11 (23.9)	7 (30.4)
60-74	4 (8.7)	1 (4.3)
Total	46 (100)	23 (100)

Table 2. Distribution of Bone Sarcomas by Site and Morphology (Number and % Data)

	Males		Females	
Site				
Upper limb (C40.0- 40.1)	6.0	13.1	2	8.7
Lower limb (C40.2- 40.3)	16.0	34.8	11	47.8
Limb, NOS, (C40.9)	9.0	19.6	-	-
Skull and face (C41.0)	3.0	6.5	1	4.3
Mandible (C41.1)	3.0	6.5	-	-
Vertebral column (C41.2)	1.0	2.2	-	-
Rib (C41.3)	1.0	2.2	4	17.4
Pelvis (C41.4)	5.0	10.9	1	4.3
Bone, NOS (C41.9)	2.0	4.3	4	17.4
Morphology				
Malignant tumor, NOS (M8000)	3.0	6.5	1	4.3
Synovial sarcoma (M9040)	1.0	2.2	-	-
Osteosarcoma (M9180)	14.0	30.5	10	43.4
Chondrosarcoma (M9220)	3.0	6.5	3	13.0
Chondroblastoma (M9230)	1.0	2.2	-	-
Giant cell tumor (M9250)	7.0	15.2	3	13.0
Ewing's sarcoma (M9260)	11.0	23.9	2	8.7
Ameloblastoma (M9310)	3.0	6.5	2	8.7
Others	3.0	6.5	2	8.7

childhood ratio of 1:3.

The incidence of BS in Karachi is high in comparison to most world regions. The highest recorded incidence for BS during the study period (1995-7) was observed in Ferrara, Italy (ASR 2.8 per 100,000 population) in males and Wuhan, China (ASR 1.9 per 100,000 population) in females (Parkin et al., 2002). The incidence of BS in Karachi ranked 11th amongst the 230 contemporary registries listed in 'Cancer Incidence in the Five Continents' volume 8 (CIV 8). This incidence is identical to that observed for Jews in Israel, but lower than the incidence reported by registries in China, Philippines and Viet Nam (Parkin et al., 2002).

The incidence of BS in females is much lower worldwide as compared to the males (Rao et al, 1996; Yeole and Jussawalla, 1998; Katchy et al, 2005). The same was observed in Karachi, the incidence in males was twice that observed in females. In the later, BS ranked 32nd in CIV 8, preceded by registries from China, Philippines, Viet Nam, Thailand and India.

The incidence of BS is high in South East Asia, in sharp contrast to soft tissue sarcoma (STS), which is observed with a lower frequency (Bhurgri et al., 2008). South and Central Asia appear to be a low risk zone for both STS and BS, though some studies have reported a higher incidence of BS in this region, similar to Karachi. These include a report from Rajasthan, India (Sharma et al., 1992) and Kuwait (Katchy et al., 2005).

Comparison of the incidence rate of BS with that of the closely related group of STS indicates that osseous neoplasms occur at a rate approximately one tenth that of their soft tissue counterparts (Higginson et al., 1992; Dorfman and Czerniak, 1995; Mack, 1995). In Karachi the incidence of STS in males and females for the same period as this report was ASR 3.3 and 2.1 per 100,000, in males and females, respectively, indicating that BS are more common than elsewhere occurring at half the rate of STS.

The commonest morphology of BS diagnosed worldwide is either osteosarcoma (35%) or chondrosarcomas (25%), followed by Ewing's sarcoma (16%), chordoma and malignant fibrous histiocytoma/ fibrosarcoma (Dorfman and Czerniak, 1995; ACS, 2008). In the younger age groups BS comprised mostly of osteosarcomas (5.6 per million children below 15 years of age) and Ewing's sarcoma (2.1 per million children in the United States) with chordomas, chondrosarcomas and malignant fibrous histiocytoma contributing towards the second peak occurring in patients older than 60 years. Osteosarcoma occurs predominantly in patients younger than age twenty (Fletcher et al., 2002). It is also reported that in countries and regions with higher incidence rates, the relative fraction of osteosarcomas appears to be larger.

The most common morphology of BS diagnosed in Karachi South was osteosarcoma (30.5% males; 43.4% females) followed by Ewing's sarcoma (23.9%) in males and giant cell tumor (13.0%) in females. This morphology is compatible with the younger population at risk and the higher risk of BS in the population.

There appears to be a racial variation in the morphological distribution of BS when stratified histological cancer registry data is compared. It is reported that unlike osteosarcoma which is more apparent in blacks, Ewing's sarcoma is reported to occur almost exclusively in the white population (Fletcher et al., 2002), which may well explain the preponderance of osteosarcoma in our population. Rao et al in 1996 reported osteosarcoma (45.7%) as the commonest BS in India followed by Ewing's sarcoma (19.4%), but the Bombay Cancer Registry reported Ewing's sarcoma as the commonest BS for the same time period (Yeole and Jussawalla, 1998). In Kuwait too, the most frequent BS in descending order were Ewing's sarcoma, multiple myeloma, osteosarcoma, chondrosarcoma and non-Hodgkin's lymphoma (Katchy et al., 2005). We cannot entirely rule out misclassification, the preponderance of Ewing's sarcoma could also be attributed to the significant number of these malignancies arising from soft tissue.

The bimodal age specific incidence rates (ASIRs) observed globally were also observed in Karachi, moreover the age specific incidence curves presented striking differences according to cell type as reported by Yeole and Jussawalla in 1998. We also observed that the lower limb was the most commonly affected site in our study with the femur, tibia and humerus being involved in that order. This is also reported by other authors (Rao et al., 1996).

Approximately 50% of the BS in Karachi is observed in those below 20 years of age. The figure is higher than reported by Kathy et al in Kuwait, where 42% of the primary tumors occurred below the age of 20 years. Spontaneous fractures were the cardinal presenting sign for BS in Karachi, observed in 45 (66.2%) of the cases. This figure is higher than reported elsewhere probably due to the late presentation of the disease; Kathy in 2005 reported pathological fractures as the presenting sign in 35% of the cases.

The factors contributing towards the development of BS vary and include genetic predisposition as seen in Li-

fraumeni syndrome, Rothmund Thomson Syndrome, Bloom Syndrome, retinoblastoma and Pagets disease. Radiation exposure increases the risk of osteosarcoma (Lorigan et al., 1989, Mascarenhas et al., 1998). Known risk factors for chondrosarcoma include Marfucci's syndrome, Ollier's disease, multiple osteo-chondromatosis and hereditary multiple exostoses (Mascarenhas et al, 1998). Other contributing factors of BS include bone marrow transplantation, injury and possibly viruses and environmental pollution (Larrson et al., 1974).

In conclusion, Karachi falls into a high risk region for BS, which was observed in a relatively younger population, with a male predominance and a high frequency of osteosarcoma. The underlying factors for BS in Karachi need to be addressed considering the overwhelming proportion of youngsters at risk.

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