Childhood Cancer in Pakistan, with Special Reference to Retinoblastoma

Pages with reference to book, From 66 To 70

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Abstract

International differences in rates and types of cancer serve as clues to its etiology. To study such variations of childhood cancer, we compared the frequencies of malignancy in the 220 children, age 0-14 years, diagnosed at the Jinnah Postgraduate Medical Center (JPMC), Karachi, Pakistan, 1974 - 1978, to the 1, 938 pediatric cancers in the U.S. Third National Cancer Survey (TNCS), 1969-1971.

TYPE	JPMC		TNCS
	≠	%	%
Retinoblastoma (RB)	36	16	3
Non-Hodgkin's Lymphoma	27	12	6
Leukemia	26	12	33
Hodgkin's Disease	20	9	4
Brain	19	9	20
Wilms' tumor	18	8	6
Soft tissue sarcoma	18	8	4
Bone	18	8	5
Gonadal, germ cell	8	4	4
Neuroblastoma (NB)	8	4	6
Other	22	10	9

Introduction

Epidemiologic studies which expose geographic differences in cancer rate and types have served to increase existing etiologic hypotheses and delineate clues to the origins of cancer. Such studies have identified important differences which appear to be environmentally induced, as endemic Burkitt's lymphoma in Africa (Morrow et al., 1971) and those that are genetically influenced, as the deficiency of Ewing's sarcoma in blacks (Fraumeni and Glass, 1970). In areas where population-based tumor registeries do not exist, the relative frequencies of specific types of cancers can be used for comparisons. In addition, because Wilm's tumor is said to occur with the least geographic variation of the more frequent childhood tumors, it may be used as a standard reference against which the frequency of other childhood cancers can be estimated (Editorial, 1973).
We report the occurrence of childhood cancer at a large state hospital in Karachi, Pakistan, and contrast it to that in the United States, looking for differences possibly related to environmental or genetic factors.

Material and Methods

The data presented in this report concerns children under 15 years of age with malignancy seen at the Jinnah Postgraduate Medical Center (JPMC) from 1974 through 1978. All persons diagnosed with malignancy were reported to the Tumor Registry and the following information was abstracted from hospital records: name, father's name, present and permanent address, sex, age, year of birth, duration 'of symptoms, diagnostic criteria, histopathologic diagnosis and final diagnosis. The Manual of Tumor Nomenclature and Coding of the American Cancer Society was used for coding the histopathological diagnoses and the Eighth Revision of the World Health Organization International Classification of diseases was used for coding final diagnosis. From the data available on registry form, use was made of the child's age, sex, residence, diagnoses according to the cell type and method of diagnosis in this study.

The relative frequencies of cancers were contrasted to that reported from the United States Surveillance Epidemiology End Results Program (SEER) 1973-1976 (Young et al., 1976) and the Bombay (Grovers) registry.

Results

Two hundred twenty children were diagnosed with malignancy during the five year period under study (Table 1).

Table 1.

Distribution of Childhood Cancer in Pakistan, India (Grover's Data) and United States by Cell Type

	JPMC Age Group (Yr)						Seer	Grover
Cell Type	0–4	5–9	10–14	Total	Male/Female	%	%	%
Retinoblastoma	30	6	0	36	(24/12)	16.4	2.5	11.8
Non-Hodgkin's Lymphoma	9	8	10	27	(20/7)	12.3	7.6	9.6
Leukemia	5	7	14	26	(19/7)	11.8	30.9	21.8
Hodgkin's Disease	1	10	9	20	(16/4)	9.1	6.2	6.4
Brain	1	4	14	19	(13/6)	8.7	18.3	8.2
Bone	1	6	11	18	(10/8)	8.2	4.7	8.6
Soft Tissue Sarcoma	6	4	8	18	(12/6)	8.2	6.2	8.6
Wilm's Tumor	13	4	1	18	(14/4)	8.2	5.7	5.9
Head and Neck	1	3	6	10	(6/4)	4.5	0.4	1.8
Gonad, Embryonal	2	2	4	8	(3/5)	3.6	3.1	3.6
Neuroblastoma	4	2	2	8	(3/5)	3.6	6.8	1.4
Liver	2	0	0	2	(2/0)	0.9	1.3	1.4
Other	3	6	1	10	(4/6)	4.5	6.3	19.1
Total	78	62	80	220	(147/74)	100.0	100	

Most of these were residents of Karachi (204, 93%). Histologic confirmation of malignancy varied with the anatomic site involved, but overall was 82%. All cases of leukemia, Hodgkin's disease, nasopharyngeal malignancy and carcinoma were confirmed by histologic examination. The diagnoses of brain tumor, soft tissue sarcoma and non-Hodgkin's lymphoma were more frequently based on

clinical presentation. Biopsy was performed in 74%, 67% and 59% of cases respectively.
There was no distinct age peak by 5 year age group, 78 children were under five years of age, 62 five to nine years, and 80 ten to fourteen years. Only 8 children were under one year of age. Retinoblastoma, Wilm's tumor and non-Hodgkin's lymphomas predominated in the younger children. Among the older children the distribution was less skewed: lymphomas, brain tumors, leukemia, sarcoma of bone and soft tissue were all common. The patients were unequally distributed by sex: 146 boys, 74 girls (Sex ratio 1.97). Only neuroblastoma (sex ratio 0.6) and gonadal and embryonal tumors (sex ratio 0.6) were more common in girls. Hodgkin's disease was four times more common in boys Wilm's tumor three times so.
The most frequent tumor was retinoblastoma, affecting 24 boys and 12 girls. The average age at diagnosis was 3.5 years. Only 3 of the 36 children (8%) had bilateral disease and their ages at diagnosis were younger: 3 months, 2 years and 3 years. Two other tumors of neural origin, primary brain tumors and neurobla.stoma, were much less frequent than in the U.S.
Non-Hodgkin's lymphoma was more common than leukemia. Lymphosarcoma was diagnosed in 6 children, reticulum cell sarcoma in 5 (4 bone and 1 abdomen) and Burkitt's lymphoma in 3. In the remaining cases, the diagnosis of lymphoma was not subclassified. Twenty children, 15 boys and 5 girls, were diagnosed with acute lymphatic leukemia; four children had acute myelogenous leukemia and two chronic myelogenous leukemia. Hodgkin's disease was also common and histologies were those with less favourable prognosis.
Malignant tumors of the bone comprised 8% of the stries. Ewing's sarcoma was diagnosed in five children. Tumors of the head and neck were also frequent. Ten children had such malignancies, 4 with nasopharyngeal carcinoma, 2 with tumor of the parotid gland, and 1 with each squamous cell carcinoma of the tongue, epithelioma of the left eyelid, sarcoma of the maxillary antrum, and epidermoid carcinoma of the external auditory canal.

Discussion

Several differences of interest exist in the relative frequencies of childhood tumors in Pakistan as compared with those in the U.S. Importantly, the relative frequencies we report are similar to those previously published from India (Grover and Hardas, 1972) and are consistent with the incidence rates of the Bombay Cancer Registry, a population based registry in the region.
Earlier enumeration of childhood cancers in the Indian subcontinent reported an increased relative frequency of retinoblastoma, such as we observed. The occurrence of this tumor at JPMC varied from that in the U.S. in three ways: (a) As in India, it is much more commonly diagnosed (Grover and Hardas, 1972). Yet, bilaterality was observed in only 3 of 36 patients, that is 8% vs. 25-30% in western countries (Knodson, 1971). (b) Because bilateral retinoblastoma is inherited as an autosomal dominant disorder, it is said to occur among all people at the same rate (Miller, 1977). Thus, an excess of sporadic retinoblastoma should account for the additional cases and, if a true excess, should be due to the form of disease in which both mutations are postzygotic and environmentally induced (Miller, 1977). (c) The sex ratio is also different from that observed in the U.S. Among white children with retinoblastoma in the U.S., the sex ratio (male/female cases) is 0.93 (Young, 1976). In our series, it was 2.0. Similarly, the ratio is 1.9 in India (Grover and Hardas, 1972). An undifferentiated histopathologic subtype of retinoblastoma. which is usually moderately or 1975). Cases of this more primitive cell type of retinoblastoma may account for the excess in Pakistan, perhaps secondary to an environmental exposure occurring during fetal life.
Other tumors of the nervous system, neuroblastoma and brain tumors, are less commonly observed in Pakistan than in the U.S. The occurrence of neuroblastoma varies considerably by geographic region. There is substantial deficit in Central Africa where it is just 10% of the rate in U.S. blacks. The rate is

also low in India (Grover and Hardas, 1972) and the frequency at JPMC was approximately one-half that in the U.S. (Young, 1976). About 22% of neuroblastoma has been estimated to have a heritable component (Knodson and Strong, 1972). Rather than a lack of non-heritable forms in the low frequency areas, it has been suggested that something inhibits tumor development (Knodson and Meadows, 1972). This is an intriguing hypothesis since clinical neuroblastoma sometimes undergoes spontaneous regression and in situ neuroblastoma is found incidentally at autopsy of children under 3 months of age, but not after. The tumor apparently under-goes regression or maturation (Knodson and Meadows, 1972). Chronic infection and infestation with circulating parasites are among the characteristics of the areas where neuroblastoma is infreouent. PerhaDs a high level of circulating maternal gammaglobulin is transmitted from mother to fetus and inhibits development of the tumor (Miller, 1977). The occurrence of neuroblastoma in four patients with fetal hydantoin syndrome may support this theory (Sherman and Roizen, 1976; Pendergrass and Hanson, 1976; Ramilo and Harris, 1979; Allen et al., 1980). Hydantoin therapy is known to reduce circulating immunoglobulin levels, especially in persons with idiopathic epilepsy (Rausing, 1978).

In highly developed countries, tumors of the central nervous system have been consistently reported as a leading type of childhood malignancy, while this has not been true in less developed countries. Certainly brain tunors may be under recognised in areas where neurosurgeons are not available, but this is not a factor at JPMC. What then accounts for the difference. Both genetic and environmental factors have been identified in the etiology of brain tumors; factors which may influence the geographic variation. Brain tumors are rare in blacks and Asians in Israel (Munoz, 1976) and occur in families and in patients with the autosomal disorders neurofibromatosis, tuberous sclerosis, von Hippcl-Lindau syndrome and nevoid basal cell carcinoma syndrome (Mulvihill, 1977). Environmental factors include radiation and chemical carcinogens (Gold et al., 1979). Further, Hodgkin's disease and non-Hodgkin's lymphoma were observed more frequently in this series, lymphomas consisted of 22% of the total cases compared to 10% in the U.S. Similar observations have been made in Saudi Arabia. Immunosuppression secondary to dietary differences may be responsible.

Tumors of the head and neck arc increased not only in Pakistani children, -but also in adults (JPMC Monogram, 1977). Adults in Pakistan chew betel nuts, a native substance which in a recent Indian study has been proven to be carcinogenic (Ranadive et al., 1979). Their excess of head and neck tumors has been linked to this habit, which may also be operative in the children.

The ratio of Ewing's sarcoma to Wilm's tumor is 0.27, similar to that in the U.S. of 0.22. Thus, Ewing's sarcoma appears to be as common among Pakistani children as in other Caucasian populations, and unlike that in black and Oriental children.

From this study, several intriguing etiologic hypotheses of childhood cancer have emerged which warrant further study. Specific hypotheses, especially as to the occurrence of retinoblastoma, should be tested. Examination of the histopathology of these tumors is already underway.

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