RESEARCH COMMUNICATION

Retinoblastoma: An Epidemiological Appraisal with Reference to a Population in Mumbai, India

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Abstract

Reliable data on incidence and mortalityfor childhood cancers are available from only a few areas in the developing countries. Neoplasia in children is rare as compared with adult cancer. In Europe, North America and Australia, retinoblastomas account for 2-4 percent of the total and the relative frequency is similar in Asia. In contrast, in African countries retinoblastomas account for 10 to 15% of cancers in children. The data collected at Bombay Cancer Registry for the latest 13 years, 1986-1998, were used for the present study. Analyses were carried out on retinoblastomas by sex, age, religion and laterality, based on differences in rates and proportions.

In Mumbai, during the 13-year period in question, there were only 211 cases of malignant tumors of the eyes. Of these, 147 were retinoblastomas, 84 in males and 63 in females, with crude incidence rates per million population of 4.0 and 3.1, respectively. The corresponding age adjusted incidence rates per million population were 4.2 and 3.3. The crude values were found to be higher in Muslims as compared to Hindus and other religious groups, in both sexes. Out of the total retinoblastomas, 105 were localized, 24 demonstrated regional spread and 16 had metastasized or were very advanced. Some 23 patients had bilateral disease. In a total of 60 patients, retinoblastomas developed on the right side and in 58 in the left eye.

The highest annual age standardized incidence rates for retinoblastomas, in excess of 7 per million population have been observed in the Fortaleza area of Brazil, Nigeria (Ibadan) and Uganda-Kampala. Retinoblastomas have the lowest median age of all childhood malignancies, approximately 15 months. The male to female ratio generally fluctuates around unity but our data indicated a higher proportion in males. Ethnic differences in the frequencies of unilateral and bilateral retinoblastomas are apparent. There is little evidence that any significant change in the incidence of retinoblastoma over time has occurred in any part of the world. Knudson proposed a 2-mutation hypothesis to explain the occurrence of retinoblastoma in both hereditary and sporadic forms with differing frequencies of bilaterality, and this model has become a paradigm for considering the role of genetic factors in the etiology of cancer in general.

Key Words: retinoblastoma - epidemiology - etiology - laterality - mutation,

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Introduction

Reliable data on childhood cancers in incidence and mortality are available from a few areas in the developing countries (Little, 1999). Analysis of specific tumor type show more striking geographic variation of rates that are not readily explained by deficiencies in the data. The childhood cancer is rare compared with adult cancer. The incidence is only 2% of that in adults in developed countries and about 3% of that in developing countries (Parkin et al, 1998). In Europe, North America and Australia, retinoblastoma accounts for 2-4 percent of neoplasms in children. The relative frequency is similar in Asia (Ajiki et al, 1994; Yeole et al, 2001). In contrast, in African countries, retinoblastoma represents 10 to 15% of tumors (Parkin 1988). In adults, the majority of malignant tumors of the eye are malignant melanomas, but estimated rates of this cancer do not show geographic variation or striking time trends (Hakulinen et

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al, 1978, Strickland and Lee, 1981). It is also likely that genetic predisposition has a greater role in the etiology of childhood tumors and particularly for retinoblastomas. Keeping all these points in mind, an attempt was made have to make an epidemiological assessment of retinoblastomas in a Mumbai childhood population.

Materials and Methods

The data collected at Bombay Cancer Registry for the latest 13 years, 1986-1998, were used for this study. The analysis was carried out on retinoblastomas by sex, age, religion and laterality, based on various rates and proportions.

Mumbai, a densely populated urban metropolis on the west coast of India, occupying an area of 603.0 km^2, is the smallest administrative district in the Maharashtra state. It is situated between latitudes 18^0 54‘ and 19^0 18‘ north and longitudes 70^0 43‘ and 70^0 00’ east. The population count of Mumbai at the 1991 census was 9,908,547 persons with a sex ratio of 819 females per 1000 males and a density of 16,432 inhabitants per square kilometer. Mumbai is the industrial heart of India and had a multilingual population, representing every state in the union.

The Mumbai Cancer Registry was established in June 1963 as a unit of the Indian Cancer Society, at Mumbai, with the aim of obtaining reliable morbidity and mortality data on cancer from a precisely defined urban population. The actual compilation of data could only begin in 1964. Until then, no continuing surveys have ever been undertaken anywhere in India.

The Indian Council of Medical Research, realizing the importance of information on the incidence of cancer for planning for cancer control programs, established the National Cancer Registry Project (NCRP) in 1982. Mumbai Cancer Registry joined this network program at its com. Other than Mumbai the registries at Chennai, Banglore, Delhi, Bhopal and Barshi are members of this network.

The Mumbai Registry today, covers more than 120 hospitals and private nursing homes in the metropolitan area. Staff members personally visit the wards of the cooperating hospitals regularly; to interview all identified cancer patients and also those under investigation. The record files maintained by the various departments of these hospitals (pathology, hematology, radiology) and the various specialized surgical and medical wards are, also examined. As a result of such data collection from different hospitals, one and the same patient is found to be registered at two or more hospitals. Care is taken to see that multiple entries for the same patient are not made in the records.

As per 1991 census, the child population count for Mumbai was 3165000 (29.7%) out of 10651000 total count.

For Population Based Cancer Registries, the indicators ‘Proportion of deaths in period’, ‘Proportion of death certificates only’ and ‘Stability of age adjusted incidence rates can determine the completeness of coverage of data. Indicators like ‘Proportion of cases registered after histological verifications’, ‘Proportion of cases where age is not known’, ‘Flattening of age incidence curve’, and ‘ Proportion of other and unspecified neoplasms’ can throw some light on the quality of the data collected by the registry. In Mumbai Cancer Registry data the proportion of deaths in period is 52%, the proportion of death certificates only is about 6%, which is quite low, and comparison of age adjusted incidence rates over the recent years does not show any statistically significant change. These facts indicate that the Mumbai registry data is complete. At present in Mumbai Cancer Registry data, the percentage of histological confirmation is about 85% - which is quite high, the proportion of age not known is only 0.02% - which is quite low and proportion of other and unspecified site is only 1% - which is also very low, these indicators show that the quality of Mumbai Cancer Registry data is reasonably good.

Results

In Mumbai, during the 13-year period (1986-1998), 10,000 total cancer cases were registered, of which only 211 cases (0.2%) were malignant tumors of eye. Out of these 211 eye tumors, 147 were retinoblastomas and remaining 64 belonged to non-retinoblastoma the types. Almost all non-retinoblastoma tumors were belongs to adult age group while out of 147 retinoblastomas, 145 (98%) belonged to the child bearing age group.

Out of total 147 retinoblastoma, 84 (57.1%) were males and 63 (42.9%) were females. The proportion for males was 54% and for females was 46% of the general population from which these retinoblastomas were diagnosed. The proportion of boys and girls was 52% and 48% respectively in corresponding childhood population.

The average age specific, crude and age adjusted incidence rates (World) per million populations by sex for retinoblastomas for the period 1986-1998 are presented in Table 1.

Crude incidence rate per million populations was 4.0 for males and 3.1 for females. The corresponding age adjusted incidence rate per million populations were 4.2 and 3.3. Age specific, crude and age adjusted incidence rates were little higher for males as compared to that of females. Cancer incidence rates were found to decrease sharply with age. The maximum numbers of cases (75%) were occurred

Table 1. Number, Age-specific, Crude and Age-adjusted (World) Incidence Rates per Million Population by Age and Sex for Retinoblastoma, Greater Mumbai, 1986-1988

Age group	Male		Female		Total	
	Number	Rate	Number	Rate	Number	Rate
00-04	64	9.4	47	5.9	111	8.2
05-09	15	2.1	12	1.7	27	1.9
10-14	3	0.4	4	0.6	7	0.5
Total	82	4.0	63	3.1	145	3.5
AAR		4.2		3.3		3.8

in the age group 0-4 in both the sexes. In the remaining groups, 20% cases were occurred in 5-9 age group and remaining 5% in 10-14 age group. As almost all retinoblastomas were occurred in childhood age group, only 30% have enrolled in primary school.

The number of retinoblastomas registered by sex and religion along with the incidence rates were presented in Table 2. The crude incidence rates per million populations are found higher (statistically significant) in Muslims as compared to Hindus and other religious group in both the sexes. The crude incidence rate for Muslims is one and half times that of in Hindus and nearly four times of that found in other religious groups in both the sexes. As far as mother tongue is concerned maximum number of retinoblastomas are found to be Marathi speaking followed by Urdu and English speaking.

Out of 147 retinoblastomas registered, two patients were registered through unmatched deaths. From remaining 145 retinoblastomas, 137 (94%) patients have been diagnosed through microscopically; remaining 8 cases were diagnosed clinically as they have reported as an advanced stage disease at the time of registration. All microscopically confirmed cases have retinoblastoma as a histological type classification. Out of 145 retinoblastomas, who were registered through hospitals, 105 (72%) were localized,24 (17%) have regional spread and 16 (11%) were reported as metastasized or very advanced disease. 29 retinoblastoma patients refused to accept any sort of treatment, 54 patients have been treated by surgery alone, 10 by radiotherapy and 6 by chemotherapy alone. 45 patients were treated by combined therapy while 9 patients accepted hormone therapy.

Out of total retinoblastomas registered it was not possible to get laterality information for 6 patients. 23 (17%) patients have bilateral disease, in 60 patients; retinoblastoma was developed on right side and for 58 on left side of the eye (Table 3). As far as survival rates are concerned, the observed survival rates for one year, three year, and five year rates were 78%, 73% and 68% respectively for retinoblastomas.

Table 2. Number of Cases and Crude Rates per Million Population by Religion and Sex for Retinoblastomas, Greater Mumbai, 1986-1988

Religion	Males		Females		Total	
	Number	Rate	Number	Rate	Number	Rate
Hindus	59	4.0	44	3.1	83	3.5
Muslims	20	6.4	15	4.9	35	3.5
Others	3	1.4	4	1.2	7	1.3
Total	82	4.0	63	3.1	145	3.5

Discussion

In adults, the majority of malignant tumors of the eye are malignant melanomas. The estimated rates for these cancers did not show any geographic variation (Hakulinen et al, 1978). In children, almost all eye tumors are retinoblastomas. In Europe, North America and Australia, retinoblastomas accounted for 2-4 % of neoplasms in children (Parkin et al, 1988). The relative frequency is similar in Asia (Ajiki et al, 1994; Yeole et al, 2001). Our data also indicates that 3.5% share of retinoblastomas in total childhood cancers. In contrast, in African population, retinoblastoma represents 10-15% of total tumors (Parkin et al 1988, Mukiibi et al, 1995, Wessels and Hesseling, 1996).

The highest annual age standardized incidence rate for retinoblastomas, in excess of 7 per million population have been observed in the Fortaleza area of Brazil, Nigeria (Ibadan) and Uganda-Kampala (Parkin et al, 1988). The incidence in most of the Europe, North and South America, Oceania and Asia fall in the range 3-6 per million (Drute et al 1990, Mosso et al, 1992, Bernard et al, 1993 and Miller et al,1995). In present series, we have also reported the age standardized rates of the magnitude 3.8 per million population for retinoblastomas (Table 1).

The male female ratio of retinoblastoma fluctuates around unity in most of the population (Parkin et al, 1988). Our data indicates higher proportion for males (1.4:1), which may be due to the higher proportion of boys than girls in childhood population.

Retinoblastoma has the lowest median age of all childhood malignancies, approximately 15 months. Incidence peaks in the first year of life, at between 18 to 26 per million and declines gradually with age thereafter. The tumor is extremely uncommon in children aged 10 and over.

The relative frequency of retinoblastoma is at least as high among the black population of the United States as the white (Parkin et al, 1988). In England, the standardized rate ratio for retinoblastoma for the group as Asian (Indian, Pakistani or Bangladeshi origin) compared with those categorized as white was 2.14 (Powell et al, 1995). Our data shows, Muslim population is 1.5 times are at risk as compared to that of Hindus for retinoblastomas (Table 2).

Ethnic differences in the frequencies of unilateral and bilateral retinoblastomas are apparent.. In the series of cases in Britain, the overwhelming majority of which would have been in white children, 40% of retinoblastomas occur bilaterally (Draper et al, 1992). In two African series in which laterality reported, no bilateral cases were observed (Obafunwa et al, 1992, Tijani et al, 1995). In Asian population of Britain, less than one quarter of cases were bilateral (Stillei et al 1991). This is consistent with our finding that in our series, the percentage of bilateral cases is 17% (Table 3).

There is a little evidence that any significant change in the incidence of retinoblastoma over a time in any of the part of the world.

Knudson (1971) proposed a 2-mutation hypothesis to explain the occurrence of retinoblastoma in both hereditary and sporadic forms with differing frequencies of bilaterality, and this model has become a paradigm for considering the role of genetic factors in the etiology of cancer in general.

Knudson postulated that all retinoblastomas occur as a result of two mutations. In hereditary cases, the first mutation is in a germinal cell, while in non-hereditary cases, the first mutation is in a somatic cell. The second mutation always occurs in a somatic cells. In carriers of the germinal mutation, the mutation is present in all the cells of the individual and in consequence a bilateral tumor, or indeed multiple primary neoplasms are more likely to occur. In the non-hereditary form both mutations takes place post-zygotically in the same somatic cell, and as a result the tumors are more likely to be unilateral and univocal with later age of onset.

Between 40 and 50% of retinoblastoma patients have the heritable form of the disease; One quarter of these are familial cases and the remaining three quarters are thought to be sporadic arising from new mutations in the parental germ cells (Bunin et al, 1989, Narod et al 1991). The majority of heritable cases are bilateral and all bilateral cases are heritable. All of the predictions of Knudson's model has been confirmed following molecular cloning and characterization of a candidate retinoblastoma susceptibility gene (Goodrich and Lee, 1990).

As far as occurrence of concordance in twins it was reported that in combined data from five series from four of seven monogygotic twin pares and two of gygotic pares, were concordant for retinoblastoma (Buckley et al, 1996).

Parents with the hereditary form of retinoblastoma have a much higher exists risk of second primary tumors than those with the non-hereditary form (Draper et al, 1985, der Kinderen et al, 1988; Eng et al, 1993). In studies with a short follow-up period, most of the second primary tumors are osteosarcomas and soft tissue sarcomas (Moll et al, 1996). Other types of second primary tumors including melanoma are found in studies with longer follow-up.

In the analysis of 67 sporadic heritable cases, defined as having bilateral disease without family history or unilateral disease associated with a 13q deletion but no family history, a significant association with paternal military service was found. The relative risk was of the order 2.8 (Bunin et al, 1990). The relative risk of eye cancer associated with growth of field vegetable and pesticide purchase as recorded in the Norway- 1969 census was 3.2, based on 4 exposed cases and adjusted for year of birth and calendar year (Kristensen et al, 1996).

Bunin et al (1989) reported an inverse association between retinoblastoma and maternal use of multivitamins during pregnancy. In the same study it was found that there was no association between the non-heritable form of the disease and maternal consumption of tobacco and alcohol during pregnancy, or maternal consumption of tobacco during pregnancy or of alcohol during the preceding month.

Table 3. Number of Cases and Percentage Distribution by Laterality and Sex for Retinoblastomas, Greater Mumbai, 1986-1988

Laterality	Male		Female		Total	
	Number	%	Number	%	Number	%
Right	38	26.2	22	15.2	60	41.4
Left	32	22.1	26	17.9	58	40.0
Both	12	8.3	11	7.6	23	15.9
Unknown	0	0.0	4	2.7	4	2.7
Total	82	56.6	63	43.4	145	100.0

The rational for considering retinoblastoma separately from other childhood cancers as its bilateral occurrence, having lowest median age and substantial proportion of cases are hereditary. Genetic predisposition has a greater value in the etiology of retinoblastoma. Attempts need to be made to carry out special epidemiological studies on retinoblastoma to know its etiology in detail. These studies on retinoblastomas are particularly important in helping to through some light on the genetic component in etiology and possible also regarding the relationship between genetic and extrinsic factors.

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