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Epidemiology of Retinoblastoma

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1. Introduction

It is widely acknowledged that cancers are disorders of cell growth and behavior and that its cause has to be defined at cellular levels. However, studies have shown that the cause of cancer can be deduced from a study of its epidemiology. Sir Percival Pott is credited with linking chemicals to causing cancer when he observed astutely that Chimney sweeps, because of their chronic exposure to sooth, were prone to scrotal cancers. Subsequently, the Danish Chimney sweeps guild ruled that its members must have their bath daily and this prevented the problem.[1] Prior to this, John Hill had linked nasal polyps to "immoderate use of snuff". Epidemiology has also contributed in linking cervical cancer to human papilloma viruses and radiation to different cancers[1]. It is also important for the purposes of health planning and allocation of resources to know the distribution of any particular disease.

Retinoblastoma, an embryonal tumour originating from retinal cells, is reputed to be the commonest intraocular malignancy in children. Currently, retinoblastoma is the most common solid tumour in children after brain/nervous system tumours and lymphomas in the United Kingdom.[2] Kramarova and Stiller also reported a similar pattern among American children.[3] In Nigeria, retinoblastoma is second only to lymphoma in most studies[4,5,6] and third in some series.[7] Report from other African countries shows that this tumour is the second most common childhood solid tumour.[8]

2. Age distribution

Age has an important influence on the likelihood of beings afflicted with cancer. The incidence of cancer rises with advancing age and most cases occur in people aged 55years and above. The age related rising incidence may be explained by the accumulation of mutations associated with the emergence of cancers. Most cases of retinoblastoma, however, occur in childhood with over 90% being diagnosed before five years of age; only 24 cases have been reported in adults aged between 20years and 74 years.[9] The worldwide incidence rate of retinoblastoma for children aged 0-4years varies from 3.4% per million in Bulgaria[10] to a very high 42.5 per million in Mali.[11] Incidence rates vary greatly in some regions while it varies only slightly in some other regions (table 1).

Region	Incidence
Australia	1.4
Belgium	1
Canada	2
Croatia	0.7
Czech Republic	0.7
Denmark	1.3
Estonia	1.5
Finland	1.1
France	1.6
Germany	2.3
1celand	1.1
Ireland	1.0
Italy	1.4
Latvia	0.2
Lithuania	1.4
Malta	1.9
New Zealand	2.2
Norway	0.7
Poland	0.6
Portugal	3.6
Russia	1.3
Slovakia	1.5
Slovenia	1.0
Sweden	3.5
Switzerland	1.7
The Netherlands	1.2
United Kingdom	1.3
United States White	1.4
United States Hispanic	1.4
Yugoslavia	o.2

Table 1. Average incidence for whites in the United States and Nations with greater than 85% White population *(adapted from J Pediatr Ophthalmol Strabismus 2009 ;46: 288-293)*

A large study in the USA[12] covering a 30year period from1975 – 2004 using the Surveillance Epidemiology and End Results (SEER) programme database of the National Cancer Institute found 658 of retinoblastoma cases over the period. The overall mean

adjusted incidence was 11.3 for males and 12.4 for females. Seventy two per cent (72%) were unilateral while 27% were bilateral. In 1% of cases the laterality was unknown. With increasing age at diagnosis, the bilateral tumours decreased significantly. However, the percentage of unilateral tumours increased with increasing age at diagnosis. The overall incidence of retinoblastoma also reduced with increasing age (Figure 1). Bilateral new cases are not seen after the age of 3years. The peak age of presentation for both bilateral and unilateral retinoblastoma in the USA is before one year of age. Thereafter, the incidence reduced steeply with age. Only 4.3% of new cases of retinoblastoma were seen between the ages of 5-9years in this study.
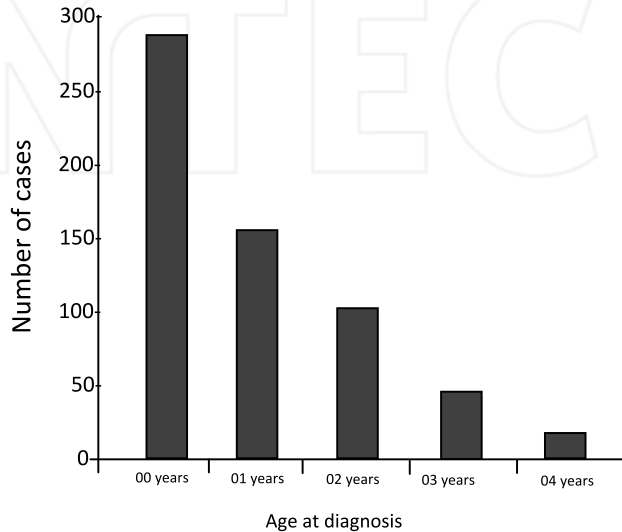

Fig. 1. Distribution of retinoblastoma by age at diagnosis (*Adapted from Br J Ophthalmol 2009; 93: 21-23*)

Another work in the USA[13] from 1993 to 1997 using data from the international agency for cancer found a rate incidence of 4.4 per million for white children with most of the other findings similar to the findings by Broaddus et al.[12]

In Great Britain,[14] retinoblastoma affects approximately 1 in 20000 children. The bilateral cases make up 36% of the total cases. In this study in the UK, using the National Registry for Childhood Tumours (NRCT), the peak incidence was in children below one year, similar to findings in USA studies. After the age of one year, the incidence reduced steadily. Children older than four years made up less than 5% of new cases. The peak age for unilateral cases is in the two year age group while that of bilateral cases is before the first birthday. British studies have shown that unilaterality does not rule out heredity. In this series reported by MacCarthy et al, almost 11% of the unilateral retinoblastoma was heritable cases. All the bilateral cases are usually heritable.

A Swedish and Finish[15] study covering 1958 to 1998 using data from cancer registries and corresponding national referral centers for retinoblastoma found 0-13 and 0-10 new cases per year in Sweden and Finland respectively. The incidence rates per million children under

5years in Sweden and Finland was 11.8 and 11.2 respectively. In this study 90-96% of all retinoblastomas were diagnosed in children less than 5 years.

In Pakistani studies,[16] between 1999 and 2002 found 70 retinoblastoma cases, with 93% of them in children below 5years; 67% of the cases were bilateral. Bilateral cases became less prevalent with increasing age while the unilateral cases peaked in the 2-3year age group with a gradual decline thereafter. The mean at presentation is 28.17 months, unilateral cases having a mean age of 31.81 months. In China,[17] a study covering 1957 to 2006 found that 1234 eyes were enucleated due to retinoblastoma in a specialist eye hospital. The mean age was 2.8years with a range of 1 month to 14years. Bilateral tumours accounted 2.4% of cases, an interesting finding. This was attributed to the nature of their study.

In South Africa,[18] a study by Freedman and Goldberg in 1976 covering a 20-year period in a specialist eye Hospital found 71 cases out of which 82% were unilateral and the other 18% bilateral. The average of the unilateral cases was 3½ years while while for the bilateral, it was 3years, much higher than the findings in western industrialized countries; 80% of cases were diagnosed before the age of 4years.

In a Congolese[19] study carried out in a teaching Hospital on Congolese blacks over a 58month period found 21% bilateral cases. The mean age for all cases was 2.94years with a 4months to 6years. The mean age for the bilateral cases was 1.12years. The mean age in other African studies ranged from 24months to 44months.[20,21,22,23] The relatively advanced age of presentation in African series has been attributed very late presentation. The African patients may seek alternative means of healing before coming to hospital. Incidence studies in Africa put the incidence estimates at 20 cases per million in Malawi[24] and 9.3 per million in Guinea Conakry.[25] These are much higher than rates in USA. This has been attributed to some unknown environmental influences and the higher birth rates in Africa.

In Nigeria, retinoblastoma is the commonest childhood intraocular malignancy with a mean age at presentation of 29 months. For bilateral retinoblastoma which accounted for 13% of cases, the mean age at presentation was younger at 15 months.[26]

3. Sex distribution

Most studies from different parts of the world suggest no sex discrepancy in the incidence of retinoblastoma. In the USA, studies by different workers[12,13] have found an age adjusted incidence of 11.3 for males and 12.4 for females suggesting a mild female predominance. This difference however was not significant.

In Mexico,[27] a study carried out in sixteen centers over a 5-year period showed a non significant mild male predominance of 1.1: 1.0 for all the cases seen. These studies do not show any breakdown of the sex distribution between the age groups and between the unilateral, bilateral and other types of retinoblastoma.

In Great Britain, the study by MacCarthy et al[14] showed that overall, males and females had no difference in the distribution of retinoblastoma for all ages. However, for the 0-1year age group in bilateral retinoblastoma category, there is a 1.1: 1.0 male predominance. For the 1-2 year age group, the male: female predominance for the bilateral tumours is 1.3: 1.0 while for

the 2-3year age group, it is 2.2: 1.0. All other age groups showed no significant M:F difference in the incidence of bilateral retinoblastoma. For bilateral tumours for all ages, the M:F ratio 1.3: 1.0.

In Pakistan, Arif Mohamed et al[16] found an equal sex distribution for retinoblastomas in childhood. There was also no gender difference between the unilateral and the bilateral cases.

In China,[17] between the years 1977 to 1996, there was a marked male predominance of 3: 2 and an insignificant overall male predominance of 2.6: 2.0. As in many other studies, the sex distribution between the unilateral and bilateral tumours is not stated.

In Southern Africa studies,[18] there is a marked male predominance over females (3:1) in the bilateral cases. However, for the unilateral cases, the ratio of males to females is 1.2: 1.0. For the1-2year age group, the M: F ratio is about 2: 1. Overall however the M: F ratio is 4:3.

Studies from Congo[19] show a M: F predominance for all cases of retinoblastoma seen over a 6year period to be 2:1. Some other African studies show a male: female ratio of 1.1[20,21]

In Ilorin, Nigeria,[26] there was a mild female predominance of 1.2: 1 overall. The mean age for females and males was also not significant at 31 months and 27 months respectively. However, Akang et al[20] from Ibadan, Nigeria reported a female predominance of 3:2.

4. Geographical/racial distribution

Retinoblastoma has a worldwide distribution. It has been reported from different parts of the world. Because the pathogenesis of retinoblastoma is linked with genetic alterations in the tumour suppressor Rb gene on chromosome 13q14, one would expect a racial variation.

A study by Krishna et al[28] covering a 7year period between 1993 and 1997 and using data from International agency for Research on Cancer, a comparison of the racial and geographic incidence patterns of retinoblastoma in North America, South America, Oceania and Eroupe was carried out. This, to our knowledge, is the most comprehensive that attempts to find a racial and geographic pattern in the incidence of retinoblastomas. This work found a higher incidence of retinoblastoma in Hispanics in the USA than in white children in 3 areas- Los Angeles, San Francisco and New Mexico. However, when adjustments were made and comparison with White population was made, there was no significant difference. This was interpreted to mean that retinoblastoma was similar in White and Hispanic populations in the United States. However, Pendergrass and Davis[12] and Howe et al[29] had found higher rates in Hispanic population over the White population. The consensus, however, is that the perceived difference can be attributed to confounding factors such as cancer registration practices or number of cases. In this study, the rate of retinoblastoma in whites in Europe was found to be the same as in Whites in USA. There was also no significant difference in the incidence in White populations in Oceania and USA. It was only the rates in Portugal and Sweden that were significantly higher than rates in the US Whites. This was attributed to cancer reporting practices[30]. The rates in Canada were similar to that in USA. The Broaddus et al study[12] in USA also showed no significant difference between Whites and Blacks in the USA.

Comparing the incidence of retinoblastoma in Africans with that of other advanced countries is difficult because calculating rates in Africans countries is fraught with problems. However, rates of up to 20 per million children under five[24] 9.3 per million age standardized in Guinea Conakry[25] have been noted. These would suggest that the rates are much higher in Africa than the rest of the world. This has been attributed to ignorance, poor health facilities and high birth rates. What, however, is certain is that African retinoblastomas are diagnosed at a significantly later age than in the advanced world.

5. Summary

Retinoblastoma is a childhood cancer with 90% diagnosed before the age five years. Only 24 cases have been reported in adults between 20-74 years worldwide. Unilateral cases are commoner than bilateral cases in a ratio of 2.7: 1. With increasing age at diagnosis, unilateral cases increased significantly while the bilateral cases decreased significantly. However, the overall incidence of retinoblastoma decreases with advancing age. The peak age of presentation is before the age of one year in advanced countries but between the ages of two and three years in Africa due to late presentation. Although many studies show a mild female predominance, this is not significant. However, some European studies note a significant male predominance for bilateral tumours and retinoblastoma diagnosed in the two to three year age group.

The incidence rate varies worldwide with higher levels in Africa and much lower levels in Europe. However, in multiracial countries like the USA, no significant difference between races was found

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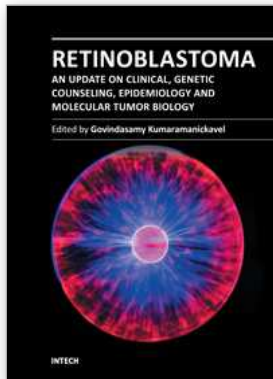
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