Chapter

Epidemiological and Genetic Considerations in Retinoblastoma

Ido Didi Fabian, Faisal Al Qahtani and Covadonga Bascaran

Abstract

Retinoblastoma (Rb) is the most common primary intraocular malignancy of childhood. The incidence of Rb is stable worldwide at one case per 16,000–18,000 live births. It is estimated that 7800–8800 Rb cases were newly diagnosed globally in 2017. Over 80% of these are in low- and middle-income countries (LMICs) in Asia and Africa. So far, there is no validated evidence that retinoblastoma incidence is associated with gender, ethnicity or geographical factors. A link between human papillomavirus (HPV) and Rb is being investigated to establish its role in the pathophysiology of the sporadic form of the disease. Survival rates for Rb vary greatly between countries: while almost all Rb cases from high-income countries survive, cases in LMICs have a mortality rate of up to 70%.

Keywords: retinoblastoma, incidence, *RB1*, hereditary

1. Introduction

Retinoblastoma (Rb) is the most common intraocular malignancy of childhood, but a relatively rare disease, occurring in approximately 1: 16,000–18,000 live births [1]. Its incidence is uniform across populations, with no known gender, racial or ethnic predilection. Rb develops in early childhood, with the vast majority of cases that present before the age of 5 years. The disease can involve one or both eyes and can be inherited from an affected parent or developed *de novo* in a child with no family history of Rb. This chapter discusses the epidemiological aspects of Rb, including basic concepts in Rb development, incidence and prevalence, age, sex and racial considerations, associated environmental factors, trilateral Rb and secondary non-Rb malignancies.

2. Genetic considerations

Rb can be inherited by an affected parent or developed *de novo* in a child with no known family history of Rb (i.e., sporadic). The neoplasm can involve one or both eyes and may present in an asymmetrical manner, with different grades in each eye at presentation or even initially appearing as unilateral and becoming bilateral in the course of the disease. The disorder, which is believed to originate from an immature cone photoreceptor cell early in childhood, is initiated in most cases by a mutation in the *RB1* gene. *RB1* loss initially produces a retinoma, the benign precursor of Rb, and causes genomic instability that subsequently leads to the cancerous tumor, Rb.

In hereditary Rb cases, a single *RB1* allele is mutated in most or every cell of a child's body. An additional "hit" in the second allele in the retina will result in clinical Rb. These cases usually present with bilateral and multifocal disease at a median age of 15 months, but can present also in unilateral disease, albeit less frequently. Between 30 and 37% of Rb cases are bilateral [2], and all bilateral cases are hereditary. However, it is estimated that up to 18% of unilateral cases are also hereditary [3]. This emphasizes the importance of genetic testing in addition to clinical examination, as it has direct impact on the recommended screening frequency of the fellow eye and occasionally on management decisions.

Non-hereditary cases (i.e., somatic) usually present at a later age (median: 24 months) with unilateral unifocal disease. In order for the disease to develop in this scenario, two consecutive "hits" occur in a retinal cell, resulting in both *RB1* alleles mutated and the development of clinical Rb.

All familial cases are hereditary, but not necessarily vice versa. A mutation can occur at or after conception in an individual with no family history of Rb, and depending on the stage at which it occurs, some of the fetus' cells will have a mutated *RB1* allele, resulting in mosaicism. Children with mosaicism are at increased risk of developing Rb. The disease in this scenario is not inherited, hence siblings of the proband are not at risk, but offspring potentially are, and therefore should be screened soon after birth.

Hereditary Rb has been associated with an increased risk of developing secondary non-Rb malignancies [4, 5], including sarcomas, carcinomas, malignant melanoma, and neuroectodermal cancers. Secondary tumors were reported to occur in up to 20% of cases in 10 years and the incidence was reported to directly correlate with the time lag from initial diagnosis. It is also well established that treatment by radiotherapy increases the risk of developing secondary tumors, both in and outside the field of radiation [6]. Draper et al. showed in a series of nearly 400 hereditary cases that close to 10% developed secondary malignancies, mainly osteosarcomas, most of which were in the field of radiation [6].

Trilateral Rb is a syndrome consisting of unilateral or bilateral hereditary Rb associated with an intracranial neuroblastic tumor that develops most often in the pineal gland (i.e., Pinealblastoma). On a meta-analysis by Kivelä [7], 2% of trilateral Rb cases had a brain tumor but no intraocular Rb, 12% had unilateral Rb and the remaining had bilateral disease.

3. Magnitude and distribution of Rb

3.1 Global incidence and prevalence

The reported incidence of Rb is constant worldwide at one case per 16,000–18,000 live births [8, 9]. In 2009 the estimated global annual incidence of Rb ranged from 7200 to 8100 children. The global birth rate has dropped since then, from 20.3 to 18.6 births per 1000 population, but the world's population has grown from 6593 to 7550 million [10], resulting in an estimated 7800–8800 newly diagnosed Rb cases globally in 2017. The highest disease prevalence is recorded in areas with high birth rates, which is the case of many low- and middle-income countries (LMICs).

3.2 Global distribution and survival

Over 80% of the newly diagnosed cases are in LMICs in Asia and Africa (**Table 1** and **Figure 1**) [3]. These regions also show the lowest survival rate, reporting up to 70% mortality from Rb. Only about 15% of children with Rb reside in high-income

	High incidence (1:16,000)	Low incidence (1:18,000)	Average incidence
	n	*n*	*n* (%)
Continent			
North America	273	242	258 (3.1)
Latin America and the Caribbean	669	595	632 (7.7)
Africa	2567	2282	2425 (29.5)
Asia	4656	4139	4398 (53.5)
Europe	504	448	476 (5.8)
Oceania	37	32	35 (0.4)
National income level			
Low	1413	1256	1335 (16.2)
Lower-middle	4221	3752	3987 (48.5)
Upper-middle	2272	2020	2146 (26.1)
High	800	711	756 (9.2)

Table 1.
Estimated number of newly diagnosed retinoblastoma patients in 2017.

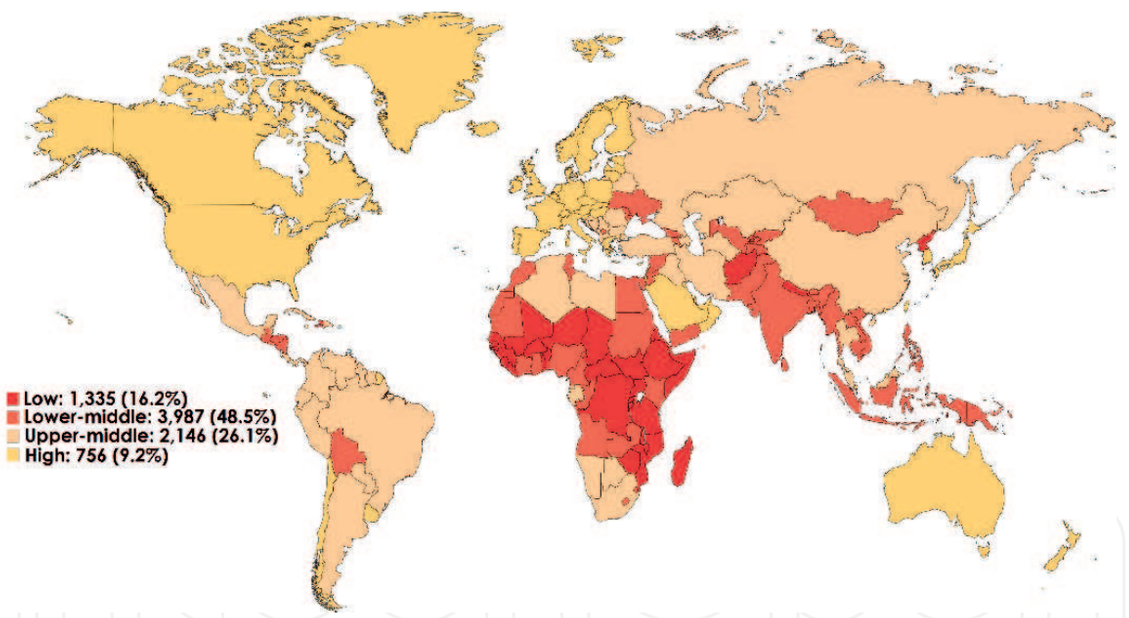

Figure 1.
Estimated average number of newly diagnosed Rb patients in 2017 by national income level. Income level data source: United Nations, Department of Economic and Social Affairs PD [10].

countries, and their prognosis is considered to be very good, with an estimated disease-free survival rate of nearly 100% [11].

4. Rb determinants

4.1 Age

According to the World Health Organization's compendium of data from cancer registries, the average Rb incidence rate in children aged 0–4 years is >10

per million compared to <1 per million in children aged 5–9 years, and significantly lower beyond that age [12].

It is difficult to accurately estimate the time at which Rb tumors first develop as information about the biological development of the disease is essentially lacking. There are three important time points associated with Rb development and the time of Rb diagnosis. These include (1) retinal tumor growth following two *RB1* mutative events, (2) parents/guardians noticing the first ocular sign, and (3) presentation to an Rb center, at which diagnosis is made and treatment given.

As discussed earlier, the median age of presentation for bilateral cases is 15 months, while for non-hereditary cases is 24 months. Most of the available knowledge originates from familial cases in high income countries, where Rb centers commonly perform screening tests for patients at risk (i.e., siblings of probands). Screening allows detection of small tumors very early in the course of disease, relatively soon after they develop. However, since sporadic cases are not screened, we rely only on age of presentation at two time points. First, the time at which the parents/guardians notice an ocular abnormality, it is usually a white pupillary reflex (i.e., leukocoria). Second, the time at which the final diagnosis is made, which is dependent on the time it takes the patient to reach the Rb center in the referral pathway.

The body of knowledge on Rb is based on retrospective studies, hence, the most accurate data in this context reports the age of the child's first presentation at an Rb center. Nevertheless, several studies have investigated the lag time from the first ocular sign as noticed by parents, to the presenting sign at the Rb center. In this respect, a huge gap exists between high-income countries and LMICs. In the UK, the referral time from sign onset to visiting primary care was found to be 28 days, primary care to ophthalmologist 3 days, and the time from local ophthalmologist to an Rb Unit was 6 days. In low-income countries, these time lags are considerably longer, and can take 6 months or more [13].

Rarely, Rb can develop in adults older than 20 years of age, with fewer than 50 case reports found in the literature. Adult-onset Rb is quite different in its presentation compared to its pediatric form, and due to its rarity, it is usually not considered in the differential diagnosis, often leading to delay in diagnosis.

In trilateral Rb [7], rates of familial Rb, the age at diagnosis and laterality were found to be similar to ordinary hereditary Rb. Cases of suprasellar trilateral Rb, however, were diagnosed at an earlier age as compared to Pinealblastoma. The median age of Rb diagnosis was 5 months, and cases of familial Rb were diagnosed at an earlier age than non-familial cases.

4.2 Gender

There is no known gender predilection in Rb, and although this notion is widely quoted in many scientific reports in the field, it has not actually been thoroughly investigated. Based on data available from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, Tamboli et al. calculated the incidence of Rb in the United States from 1974 to 1985 and found no gender differences [14]. Gurney et al. used the same data source for similar years (1974–1989), but concluded that rates of Rb were higher in females [15], and Wong et al., in contrast, found an excess of Rb cases in males using the SEER database for the years 2000–2009 [8]. *RB1* gene is located on chromosome 13 and there is no known relation to any of the sex chromosomes. There is also no evidence of an association between sex hormones and Rb. Cases of trilateral Rb do not show any gender predilection either [7].

4.3 Race

Similar to sex, there is no known association between race and Rb, although some exceptions have been reported. Gurney et al. found higher rates of Rb in blacks as compared to whites in the United States [15]. Broaddus et al., in contrast, found that the overall mean age-adjusted incidence of Rb was 11.3 for Caucasians and 13.0 for blacks, with no significant difference between the two populations [8]. Krishna et al. examined the incidence of Rb using data from the International Agency for Research on Cancer [16], and found no significant difference between white populations in the United States and Europe/Australia, Hispanic populations in Spain and the United States, and Hispanic populations in Uruguay and the United States. They concluded that Rb incidence is similar among varied populations.

4.4 Environmental factors

Several studies have shown a link between human papillomavirus (HPV) and the development of sporadic Rb [17, 18]. Shetty et al. analyzed enucleated eyes with Rb and found that 70% were positive for HPV [17], suggesting that the virus may play a role in the development of sporadic RB. Anand et al. tested the presence of HPV in Rb tissue (formalin-fixed paraffin-embedded tissue and fresh-frozen specimens) and found that nearly a quarter of the specimens were positive for HPV [19]. However, the implications of the presence of HPV in Rb tissue and its role in carcinogenesis warrant further study. Jemal et al. investigated the relation between Rb incidence and ultraviolet (UV-B) radiation levels in the SEER program and found no statistically significant correlations [20]. To the best of our knowledge, there are no other reports focused on any additional environmental factors in association with Rb development.

5. Conclusions

Rb is the most common primary intraocular malignancy of childhood. The disease can involve one or both eyes and can be inherited or sporadic. The incidence of Rb is stable worldwide at one case per 16,000–18,000 live births. The average Rb incidence rate in children aged 0–4 years is >10 per million compared to <1 per million in children aged 5–9 years, and significantly lower beyond that age. In 2017, globally, an estimated 7800–8800 Rb cases were newly diagnosed. Over 80% of these are in LMICs in Asia and Africa.

So far, there is no validated evidence that retinoblastoma incidence is associated with gender, ethnicity or geographical factors. Studies have shown the presence of HPV in sporadic Rb tissue. Its role in carcinogenesis and the development of sporadic Rb warrants further investigation.

We lack accurate information about the biological development of Rb which creates difficulties in estimating the time at which Rb tumors first develop. In familial cases from high-income countries, genetic screening is routinely conducted. However, in low-income countries this is not the case, and in all settings sporadic cases are not screened. In these cases, we rely on time of presentation, which is strongly influenced by the referral pathways in different settings.

Survival rates are related to the time taken for the child to present at an Rb center and vary greatly between countries: while almost all Rb cases from high-income countries survive, cases in LMICs have a mortality rate of 70%.

Conflict of interest

No conflicts of interest to disclose.

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