Epidemiological aspect of retinoblastoma in the world: a review of recent advance studies

Leili Koochakzadeh¹, Abbasali Yekta², Hassan Hashemi³, Reza Pakzad⁴, Samira Heydarian⁵, Mehdi Khabazkhoob⁶

¹Department of Pediatrics, Children’s Medical Center Hospital, Tehran University of Medical Sciences, Tehran 1968653111, Iran
²Refractive Errors Research Center, Mashhad University of Medical Sciences, Mashhad 3453545, Iran
³Noor Research Center for Ophthalmic Epidemiology, Noor Eye Hospital, Tehran 1983963113, Iran
⁴Department of Epidemiology, Faculty of Health, Ilam University of Medical Sciences, Ilam 693185147, Iran
⁵Department of Rehabilitation Science, School of Allied Medical Sciences, Mazandaran University of Medical Sciences, Sari 4818893813, Iran
⁶Department of Basic Sciences, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran 1968653111, Iran

Correspondence to: Hassan Hashemi. Noor Research Center for Ophthalmic Epidemiology, Noor Eye Hospital, Tehran 1983963113, Iran. hhashemi@noorvision.com

Received: 2022-10-10        Accepted: 2023-04-04

Abstract
● AIM: To collect and present updated evidence about epidemiological aspects of retinoblastoma (Rb) in the world.
● METHODS: A comprehensive search without the time and language restrictions was conducted in international databases, including MEDLINE, Scopus, Web of Science, and PubMed. The search keywords were “retinoblastoma” OR “retinal Neuroblastoma” OR “retinal glioma” OR “retinoblastoma eye cancer” OR “retinal glioblastoma”.
● RESULTS: The worldwide incidence of Rb is 1 in 16 000-28 000 live births, but was higher in developing compared to developed countries. Several attempts for improving early detection and treatment had increased the Rb survival rate from 5% to 90% in developed countries over the past decade, but its survival was lower in developing countries (about 40% in low-income countries) and the majority of mortalities occurred in developing countries. The etiology of Rb could be viewed as genetics in the heritable form and environmental and lifestyle factors in the sporadic form. Some environmental risk factors such as in vitro fertilization; insect sprays; father’s occupational exposure to oil mists in metal working, and poor living conditions might play a role in the occurrence of the disease. Although ethnicity might affect Rb incidence, sex has no documented effect and the best treatment approaches were now ophthalmic artery chemo surgery and intravitreal chemotherapy.
● CONCLUSION: Determining the role of genetics and environmental factors helps to accurately predict the prognosis and identify the mechanism of the disease, which can reduce the risk of tumor development.
● KEYWORDS: epidemiology; retinoblastoma; leukocoria; children; RB1 gene

DOI:10.18240/ijo.2023.06.20

INTRODUCTION

Retinoblastoma (Rb) is a rare disease with a low incidence; however, it is responsible for about 6% of all cancers in children below 5y of age. It is one of the most common childhood ocular malignancies in the first 3-5y of life[1,2]. The Rb has two forms: hereditary and non-hereditary. The hereditary Rb is usually bilateral and accounts for 6% of all cases. The non-hereditary type is usually unilateral and comprises 94% of the cases. Therefore, most cases of Rb are unilateral[1]. In the USA, 69.6% of the Rb cases are unilateral[1]. Incidence of Rb and the Role of Sex and Ethnicity in its Occurrence There is limited information about the incidence of Rb and most available studies could not provide a generalizable estimate of its incidence due to their population-based design. Since most Rb cases occur from birth to 4y of age, it is better to confine incidence estimates to this age range. The incidence of Rb varies up to 50 times among different populations[1]. A recent report showed that the highest incidence was related to Africa and Asia, particularly Southeast Asia[4]. Among Asian countries, the highest incidence was reported in India followed by China[5]. Table 1[1,4-16] presents a summary of some epidemiological aspects of Rb.
The incidence of Rb not only varies between different countries but there are also different reports in the same country. For example, an incidence of 12.9 in 1 000 000 children aged 0-4y was reported in the USA that has not changed in many years[17], but the incidence is higher in non-Hispanic black and Hispanic white populations[4,18]. There is a similar pattern in European countries so that the highest incidence was seen in Western Europe like Belgium and the lowest was reported in Austria[18]. However, the greatest variation relates to Asia with an incidence difference of up to 16 times among different countries[4,18]. In Asia, the highest incidence was observed in Jordan (16.9 in one million) and Saudi Arabia (16.6 in one million), and the lowest incidence was reported in Qatar (0.9 in one million)[4,18]. Africa has a similar pattern to Asia and the incidence of Rb was reported to be higher in Sub-Saharan Africa compared to Northern Africa. However, the incidence varies greatly within Sub-Saharan Africa; for example, it was higher in Eastern Africa and lower in Central and Southern Africa[4,18].

There is no agreement on the role of sex in the incidence of disease. Overall, it seems that there is no sex-related difference in this regard[1]. However, some studies conducted in Turkey, Jordan, China, Australia, India, Ecuador, Zimbabwe, Columbia, and Portugal found a higher incidence in men while other studies conducted in Sweden, Switzerland, Costa Rica, Brazil, and Algeria reported a higher incidence in women[6-7].

There are controversial reports regarding the role of ethnicity. Some studies rejected the role of ethnicity in the incidence of Rb[7] while a body of evidence indicates that ethnicity is a determinant of the Rb incidence, and the incidence is higher in Asian and African compared to American and European ethnicities[9]. Table 1 provides a summary of some epidemiologic aspects of Rb.

### Table 1 Summary of epidemiological aspects of retinoblastoma

<table>
<thead>
<tr>
<th>Aspects</th>
<th>Epidemiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>1 in 17000 live births[1]</td>
</tr>
<tr>
<td>Etiology</td>
<td>Genetics in the heritable form and environmental and lifestyle factors</td>
</tr>
<tr>
<td>Genetic risk factor</td>
<td>Mutations in the RB1 gene[5,6]</td>
</tr>
<tr>
<td>RB1 gene composition</td>
<td>27 exons and 26 introns[7]</td>
</tr>
<tr>
<td>Environmental risk factor</td>
<td>In vitro fertilization; insect sprays; poor living conditions[7,10]</td>
</tr>
<tr>
<td>Survival rate</td>
<td>90% in developed countries[11-12]</td>
</tr>
<tr>
<td>Sex difference</td>
<td>No[1]</td>
</tr>
<tr>
<td>Racial difference</td>
<td>Possible; because the risk varies in different places[2]</td>
</tr>
<tr>
<td>Place</td>
<td>The incidence is high in poor living conditions, especially sporadic Rb[3]</td>
</tr>
<tr>
<td>Genetic locus</td>
<td>q14 band of chromosome 13[8]</td>
</tr>
<tr>
<td>Age of onset</td>
<td>&lt;1y in the hereditary form and 3-5y in the non-hereditary form[13]</td>
</tr>
<tr>
<td>Most common sign</td>
<td>Leukocoria or white pupillary reflex[14]</td>
</tr>
<tr>
<td>Treatment options</td>
<td>Cryotherapy; radioactive plaques; external beam radiation therapy; enucleation; ophthalmic artery chemosurgery; intravitreal chemotherapy; combined intra-arterial chemotherapy and intravitreal melphalan[15-16]</td>
</tr>
<tr>
<td>Best treatment</td>
<td>Ophthalmic artery chemosurgery, intravitreal chemotherapy[14]</td>
</tr>
</tbody>
</table>

**Etiology of Rb and Hereditary Factors** The Rb is often caused by a mutation in the RB1 gene[20]. However, it is categorized into three groups; familial Rb (the mutated gene is inherited from one of the parents), sporadic heritable Rb (mutation occurs in the germ line, usually during conception), and non-heritable Rb (mutation occurs after conception in retinal cells). Depending on the type, genetic or environmental factors may be involved in Rb development. Although the role of genetics in the development of Rb is explained by the “two-hit” model[20], attention should also be paid to environmental factors as well as maternal and paternal exposures. Several studies found that gene abnormality may occur due to a random mistake in the copy process during cell division or due to stress on the cells during cell division (for example as a result of exposure to some carcinogens)[9]. Table 2[21-32] presents the results of several studies investigating the etiology and environmental factors associated with Rb. Consanguinity is an influential factor in the occurrence of Rb. Consanguinity seems to increase the risk of Rb in developing countries; however, the incidence of Rb has decreased despite the constant rate of consanguinity according to some studies. It should be noted that consanguinity does not affect the incidence of Rb because the RB1 gene is inherited in an autosomal dominant manner.

Paternal age is another risk factor for sporadic heritable Rb. The stem cells that evolve into sperm are divided continuously and the need for division increases with age; for example, 197, 427, and 772 cell divisions are required to transform stem cells into sperm in individuals aged 20, 30, and 45y, respectively[33]. Therefore, the stem cells would be more likely to undergo mutation during DNA replication in an older man[34]. Some studies have suggested the role of maternal exposure to insect sprays and some others have proposed the role of paternal occupational exposures[32].
Epidemiological aspect of retinoblastoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Place</th>
<th>Study goal</th>
<th>Study details</th>
<th>Summary of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heck et al</td>
<td>2012</td>
<td>USA</td>
<td>To examine the association between perinatal factors and Rb risk</td>
<td>609 Rb cases and 209051 controls</td>
<td>For bilateral Rb: older paternal age (OR=1.73; 1.20 to 2.47); twin births (OR=1.93; 0.99 to 3.79) and maternal infection during pregnancy with any STD (OR=3.59; 1.58 to 8.15). For unilateral Rb: Hispanic mothers (OR=1.34; 1.01 to 1.77) and mothers with lower than 9y of education (OR=0.70; 0.49 to 1.00). Living place of parents (OR=3.81; 2.13 to 6.85); mother feeding pets before pregnancy (OR=2.30; 1.13 to 4.13); and father's exposure to harmful chemicals before pregnancy (OR=6.06; 2.80 to 13.15) were the independent risk factors of Rb.</td>
</tr>
<tr>
<td>Yang et al</td>
<td>2016</td>
<td>China</td>
<td>To investigate the risk factors of Rb as controls</td>
<td>133 Rb patients as cases, and 133 healthy children as controls</td>
<td>Children born after fertility treatment were at an increased risk for Rb (RR=1.62; 1.12 to 2.35). The risk of having a child with unilateral Rb was associated with maternal homozygosity for the DMR1B/dpdel genotype (OR: 3.78; 1.89 to 7.55).</td>
</tr>
<tr>
<td>Hargrave et al</td>
<td>2013</td>
<td></td>
<td>To examine the association between fertility treatment and the risk for cancers such as Rb in children</td>
<td>25 cohort and case-control studies pooled using Meta-analysis</td>
<td>For non-heritable Rb: father’s definite occupational exposure to oil mists in metal working increased the risk of Rb (OR=1.85; 1.05 to 3.36). No association was observed for paternal contraceptive use.</td>
</tr>
<tr>
<td>Orjuela et al</td>
<td>2012</td>
<td>Mexico</td>
<td>To examine maternal intake of folate from vegetables during pregnancy and its association with the risk of Rb in offspring</td>
<td>Case-control study design (case group: 103 mothers of children with unilateral Rb; control group: 97 mothers with healthy children)</td>
<td>The risk of having a child with unilateral Rb was associated with maternal homozygosity for the DMR1B/dpdel genotype (OR: 3.78; 1.89 to 7.55).</td>
</tr>
<tr>
<td>Ghosh et al</td>
<td>2013</td>
<td>USA</td>
<td>To evaluate prenatal exposures to traffic exhaust and their association with cancer risk in very young children</td>
<td>Case-control study</td>
<td>Exposure to some traffic-related air pollutants, specifically nitric oxide, in the third trimester of pregnancy increased the risk of Rb (OR=1.15; 1.01 to 1.33).</td>
</tr>
<tr>
<td>MacCarthy et al</td>
<td>2009</td>
<td>UK</td>
<td>To examine the association between paternal occupational exposures and Rb</td>
<td>Case-control study (1318 cases of Rb born and diagnosed in Great Britain between 1962 and 1999, and 3118 controls matched for sex, date of birth, and birth registration sub-district)</td>
<td>For non-heritable Rb: father’s definite occupational exposure to oil mists in metal working increased the risk of Rb (OR=1.85; 1.05 to 3.36). No association was observed for paternal contraceptive use.</td>
</tr>
<tr>
<td>Anand et al</td>
<td>2011</td>
<td>India</td>
<td>To estimate the prevalence of high-risk human papillomavirus genotypes in Rb patients</td>
<td>64 formalin-fixed paraffin-embedded tissue blocks and 19 fresh-frozen specimens were subjected to multiplex PCR using PGMY09/11 primers, HPV genotyping, non-isotopic in situ hybridization and immunohistochemistry for p16 and p16/40A</td>
<td>24% of Rbs contained HPV DNA; 90% of HPV genotypes were of a high-risk type and 10% were of intermediate-risk type; No low-risk genotypes were identified.</td>
</tr>
<tr>
<td>Bhuvaneswari et al</td>
<td>2012</td>
<td>India</td>
<td>To examine the possible route of HPV infection transmission to the child from the mother in cases of Rb</td>
<td>A total of 21 sporadic Rb cases and 15/21 corresponding mothers’ cervical brushings were collected and tested by multiplex PCR followed by genotyping using line blot assay to detect HPV</td>
<td>Both high- (83%) and intermediate-risk (17%) HPV types were found in 12/21 (57%) Rb samples and only high-risk (100%) types were found in 6/15 (40%) cervical brushing samples.</td>
</tr>
<tr>
<td>Heck et al</td>
<td>2015</td>
<td>Canada</td>
<td>To evaluate the association of Rb with maternal health conditions and reproductive factors</td>
<td>A multicenter case-control study (case: parents of 280 non-familial Rb children; control: parents of 146 normal children)</td>
<td>A positive association was found between bilateral Rb and maternal underweight before pregnancy (OR: 4.5; 1.01 to 20.1). A negative association was observed between unilateral Rb and the use of condoms in the year before pregnancy (OR: 0.4; 0.2 to 0.9).</td>
</tr>
<tr>
<td>Bunin et al</td>
<td>2013</td>
<td>USA</td>
<td>To investigate the role of parents’ nutrient intake before a child’s conception in the child’s risk of sporadic bilateral Rb resulting from a new germine RB1 mutation</td>
<td>A case-control study (parents of 206 children with Rb comprised the cases and 269 fathers and relatives comprised controls)</td>
<td>The father’s intake of dairy-associated nutrients and his use of calcium supplements decreased the risk of Rb, while his intake of copper, manganese, and vitamin E increased the risk. Mother’s use of multivitamins close to conception decreased the risk of Rb. Father’s calcium intake (adjusted OR: 0.46–0.63) and calcium supplement use (OR: 0.35–0.41) and the mother’s multivitamin use (OR: 0.28–0.48) were protective factors.</td>
</tr>
<tr>
<td>Omidkhah et al</td>
<td>2017</td>
<td>USA</td>
<td>To examine parental pesticide exposure and development of sporadic Rb</td>
<td>A multicenter case-control study (cases: parents of 99 unilateral and 56 bilateral Rb children; controls: parents of normal children)</td>
<td>Unilateral Rb was associated with parental nicotine use (OR: 2.8; 1.1 to 6.7) and the use of professional lawn or landscape services (OR: 2.8; 1.0 to 8.2). There were positive associations between maternal smoking before and during pregnancy with unilateral Rb (OR: 2.4; 1.3–4.7). No association was found for maternal or paternal alcohol consumption.</td>
</tr>
<tr>
<td>Azary et al</td>
<td>2016</td>
<td>Canada</td>
<td>To examine parental tobacco smoking or alcohol consumption (pre- or post-conception) and the development of bilateral or unilateral sporadic Rb</td>
<td>Two large multicenter case-control studies (cases: parents of 488 Rb children; controls: parents of 424 normal children)</td>
<td>Rb: Retinoblastoma; OR: Odds ratio; STD: Sexually transmitted disease; RR: Risk ratio; PCR: Polymerase chain reaction; HPV: Human papilloma virus.</td>
</tr>
</tbody>
</table>

Some studies found a higher risk of Rb in children born after in vitro fertilization (IVF) or other assistive reproductive therapies (ARTs)\(^{(10)}\). One study conducted in Sweden showed that the risk of Rb increased with longer durations of breastfeeding but the dose-response effect was unclear possibly due to the maternal intake of drugs, heavy metals, and volatile organic compounds during pregnancy. According to another study, reduced intake of fruits and vegetables during pregnancy with the resulting decrease in the absorption of nutrients necessary for DNA methylation and retinal synthesis/function like folate and lutein/zeaxanthin, increases the risk of sporadic Rb\(^{(24)}\). It has also been suggested that gestational exposure to X-rays, morning sickness medication, and lower maternal educational level increase the risk of non-heritable Rb. Moreover, exposure to air pollution in the second and third trimesters, especially nitric oxide (NO), increases the risk of bilateral Rb\(^{(25)}\). A case-control study was conducted by McCarthey et al\(^{(26)}\) to investigate the relationship between paternal occupational exposures and Rb. The results of that study showed that non-heritable Rb was significantly positively associated with the father’s occupational exposure to oil mists in metal working (OR=1.85, 95%CI: 1.05 to 3.36); however, this correlation was not found in heritable cases. Moreover, no significant relationship was observed for other exposures like tobacco,
agriculture, animals, electromagnetic field, hydrocarbons, and paints. The authors concluded that due to the low study power and other methodological flaws like recall bias, the study findings could not support the hypothesis that paternal occupational exposure is an important etiologic factor for Rb. Another cohort study by MacCarthy et al.[35] showed that the cumulative risk for the occurrence of any tumor 50y after Rb diagnosis was 48.3% for heritable cases and 4.9% for non-heritable ones. This finding indicated a higher risk of non-ocular tumors in survivors of heritable Rb. Although some studies reported that Rb incidence was similar among different geographical regions and the role of environmental factors was unclear[19], discrepancies in Rb incidence between different regions[19] indicate the effect of the environment on the disease. The fact that sporadic Rb has not been equally distributed across the world and its incidence is higher in less developed countries and among low-income people suggests a correlation between Rb and poor living conditions. This diverse distribution can be secondary to exposure differences to infectious and other environmental factors[1]. Moreover, some studies proposed that parents’ sexual behaviors correlate with the Rb occurrence since herpes papillomavirus (HPV) infection increases the risk of Rb and the use of protections like condoms decreases the risk[16]. Nevertheless, some studies claimed no causal relationship between HPV and Rb[33-34].

Rb Signs and Diagnosis The clinical signs of Rb vary depending on the stage of the disease at diagnosis. The most common and noticeable sign is leukocoria (or white pupillary reflex) also known as cat’s eye reflex, which can be detected when the tumor is large. Strabismus may be seen in small tumors. Other non-specific signs and symptoms include decreased visual acuity, red-eye, exophthalmos, and glaucoma[33-38]. In bilateral Rb, the eyes are asymmetrically involved and the signs and symptoms are more severe in one eye. Many children are diagnosed before the age of 5y but the age of onset depends on the Rb type (heritable vs non-heritable). For example, in the UK, bilateral cases are usually diagnosed in the first year of life while unilateral cases are usually diagnosed between 24-30mo of age[39]. In general, Rb cases with a positive family history are usually detected in earlier stages because of the more regular fundus examinations in these patients[21]. Nonetheless, unilateral Rb is usually diagnosed when the tumor has grown substantially[21]. Some studies found an association between mental retardation and Rb[40]. Any change in chromosome 13q14 could result in mental retardation and Rb. It should be noted that some children with Rb having 13q cytogenetic abnormalities may exhibit some levels of mental retardation despite normal development[41].

Rb Prognosis and Screening The prognosis of Rb is affected by several factors. Many researchers believe that insufficient healthcare providers’ information about Rb results in delayed diagnosis, delayed treatment, metastasis, and death. Moreover, poor access to healthcare services deteriorates the situation[42]. The survival rate of Rb patients has substantially increased during the past decades; a survival of 5% was reported in 1867[43] while it is now more than 90%. Rb is curable cancer and 9 of 10 children with Rb live through adulthood in developed countries; however, its overall worldwide survival rate is about 50% with the majority of mortalities occurring in developing countries[1,42]. This difference can be attributed to timely diagnosis tools in developed countries. Nonetheless, even in developed countries, a significant percentage of survivors develop moderate to severe visual impairment. It should be noted that the survival rate is different between hereditary and non-hereditary types. In hereditary Rb, there is an increased risk of second primary malignancies and about 50% odds of transferring the RBL1 gene mutation to the offspring[44].

Canturk et al[45] conducted a systematic review to investigate the survival of Rb patients in less-developed countries (LDCs). The mentioned study evaluated 164 publications, including 14 800 patients from 48 LDCs. According to the results, the estimated survival rate was 40% in lower-income countries, 77% in lower-middle-income countries, and 79% in upper-middle-income countries. Moreover, it was found that physician density and human development index were significantly directly correlated with survival. A major limitation of this study was the lack of reports from some African countries that are considered low-income[45]. Marees et al[46] evaluated 998 Rb survivors from 1862 to 2005 to investigate long-term cause-specific mortality and found that the mortality risk was higher in hereditary Rb survivors, indicating the importance of lifelong follow-up in hereditary Rb survivors.

Several studies investigated histopathological variables affecting Rb prognosis. Kashyap et al.[47] found that some clinical characteristics like older age, hyphema, pseudohypopyon, longer lag period, staphyloma, and orbital cellulitis could be used as predictors of high-risk histopathology in Rb patients. Some histopathological factors including massive choroidal invasion, retrolaminar invasion, involvement of resected end of the optic nerve, and scleral and extrascleral spread were reported as indicators of poor prognosis[48-51]. Although the hereditary Rb screening program is generally effective, these screening programs don’t have desired effectiveness in developing countries and the disease is usually diagnosed in advanced stages when it is accompanied by
other sophisticated intraocular diseases. Since early diagnosis is crucial for a patient’s survival and vision, professionally trained nurses have a prominent role in the early detection of Rb and increased patient survival\(^{[52]}\). Abramson et al\(^{[53]}\) studied the effectiveness of Rb screening and found that the disease was detected at a younger age (8mo of age) and in earlier stages in children with a family history of Rb screened for retinal tumors from birth. They concluded that to save the eyes and vision, Rb should be diagnosed before leukocoria develops, which is possible through routine dilated fundus examinations.

Considering the increased risk of second and third non-ocular cancers in patients with germline (hereditary) mutations\(^{[54]}\), some studies recommended evaluating RB1 gene mutations in the fetal stage, which would increase the chance of early detection of Rb and other non-ocular tumors and thus the possibility of successful treatment\(^{[54]}\). Richter et al\(^{[55]}\) identified 9 fetuses with germline RB1 gene mutations of whom 4 were born. One of them developed bilateral Rb and the remaining developed macular tumors. However, early focal treatment led to the preservation of 20/20 visual acuity in them. Another study in Hong Kong confirmed the accuracy of the screening method and reported that screening with prenatal genetic analysis is cost-effective and of great clinical importance\(^{[56]}\).

**Treatment** Treatment modalities for Rb have changed rapidly over the past decade\(^{[40]}\), and the survival of many Rb cases that used to die in the past has improved in recent years\(^{[37,59]}\).

In general, the available treatment options for Rb include surgery (including enucleation and pars plana vitrectomy); focal therapies (including c cryotherapy, laser photocoagulation, and transscleral photocoagulation); chemotherapy (including intravenous chemotherapy, intra-arterial chemotherapy, and intravitreal chemotherapy), and radiotherapy (including plaques and external beam techniques)\(^{[40]}\). Enucleation (surgical removal of the affected eye) is still one of the treatment methods. Although enucleation is associated with grave outcomes like blindness, it is a useful method when there is advanced intraocular disease and the risk of metastasis to other tissues.

External beam radiation therapy is also used for Rb treatment; however, it may damage other ocular structures\(^{[40]}\). Several efforts have been made to determine the therapeutic dose in external beam radiation therapy to prevent damage to other ocular components including the crystalline lens, lacrimal glands, and optic nerve\(^{[56]}\). There is now a decreasing trend in the use of enucleation and external beam radiotherapy and alternative methods like ophthalmic artery chemosurgery and intravitreal chemotherapy are preferred since these methods\(^{[16]}\), are more effective in mild to moderate Rb, are associated with a higher success rate and fewer complications and do not result in globe loss\(^{[16]}\). Moreover, several studies found that ophthalmic artery chemosurgery improved the survival rate of patients more than other methods. In some studies, the effect of plant-derived natural products on the treatment of various tumors, including Rb, has been shown\(^{[61,62]}\).

In conclusion, Rb is the most common ocular malignancy in children under 5y of age with no significant sex-related difference in its incidence. According to some studies, Rb incidence varies among different ethnicities, which may be due to genetic or environmental factors, lifestyle, and health infrastructures affecting diagnosis. Mutation in the RB1 gene, which is a tumor suppressor, is considered the most important cause of hereditary Rb and the genetic defect in this context is explained by the “two-hit” model. Patient survival has increased markedly over the past decade from 5% to 90% in developed countries. However, the survival rate is lower in developing countries. Several studies investigated the role of personal and environmental factors in Rb and found that some variables like older maternal age at pregnancy, maternal exposure to insect sprays, father’s exposure to some chemicals, ARTs, low intake of fruits and vegetables during pregnancy, exposure to traffic pollutants like nitric oxide, and some infections during pregnancy like HPV increased the risk of the disease.

Although enucleation was the best treatment method for years, ophthalmic artery chemosurgery and intravitreal chemotherapy have been recently introduced as better and more effective treatment options. Determining the role of genetics and environmental factors helps to predict the prognosis accurately and identify the mechanism of the disease, which can reduce the risk of tumor development.

**ACKNOWLEDGEMENTS**

**Conflicts of Interest:** Koochakzadeh L, None; Yekta A, None; Hashemi H, None; Pakzad R, None; Heydarian S, None; Khabazkhoob M, None.

**REFERENCES**


Epidemiological aspect of retinoblastoma


