HPV infections in retinoblastoma: a systematic review

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Abstract

Background: Retinoblastoma is the most common primary intraocular malignancy in children less than 4 years. Retinoblastoma (RB) contains about 3%–5% of all childhood cancers. Recent studies demonstrated that interacting between RB tumor suppressor and oncoproteins of DNA tumor viruses such as human papillomavirus (HPV). The objective of the current systematic review study was to present conducted studies in the field of HPV infection and its possible role in retinoblastoma.

Methods: For this systematic review, all relevant original research studies were assessed by searching in electronic databases include PubMed, Embase, Scopus, Google Scholar, and Web of Science by using relevant keywords. The study was designed based on the PRISMA criteria. All publications with English literature and original researches are considered for screening.

Results: Conducted search results lead to 4070 studies. The title and abstract screening lead to 11 studies. Data extraction was performed on 8 included studies. The prevalence of the HPV was ranged from 0 to 69%, and HPV genotype 16 and 18 were the most detected types. The most used method for the detection of the viruses was PCR, and the most assessed sample was formalin-fixed, paraffin-embedded tissue blocks.

Conclusion: The association between HPV and retinoblastoma is still inconsistent. The prevalence of the HPV in RB was ranged from 0 to 69%, which indicates a wide range and highlights the importance of further investigation for more accurate statistical of HPV prevalence in RB. Thus, further worldwide studies of larger sample sizes of cohorts should be investigated to clarify this uncertainty.

Keywords
human papillomavirus, human papillomavirus 16, human papillomavirus 18, retinoblastoma
1 | INTRODUCTION

Retinoblastoma (RB) is the most common primary intraocular malignancy in children less than 4 years old and is associated with a lack of function of the retinal cell retinoblastoma gene (RB1). Leukocoria, eye pain, irritation, and blindness are the common symptoms of retinoblastoma. Retinoblastoma contains about 3%-5% of all childhood cancers. It occurs with an incidence of one in 16,000–18,000 live births. Meanwhile, there are few cases of retinoblastoma in older children and adults. Retinoblastoma occurs in sporadic or nonheritable and heritable or germlinal forms. According to the previous studies, 60–70% of RBs are unilateral and the others are bilateral. Heritable RB is found in 40% of cases including all the bilateral and unilateral multifocal diseases. Retinoblastoma cells lack functional retinoblastoma protein (pRB). The pRB binds and inactivates transcription factors, such as E2F members, thereby regulating cell cycle progression.

Recent studies demonstrated that interacting between RB1 tumor suppressor and oncoproteins of DNA tumor viruses such as adenovirus E1A, SV40 large T Antigen, and human papillomavirus E7 can lead to cancerous cells. Studies indicated that lifestyle, nutrition, hygiene, and other environmental factors can affect the incidence of some cancers like cervical cancer, which is caused by HPV. This virus can be transmitted to newborns through the vaginal canal during delivery. It has been indicated that pRB could be inactivated by HPV-16 and HPV-18, which suggested this virus as a factor in the development of retinoblastomas. Also, the human adenovirus type 12 and JCV can induce retinal tumors in the eyes of newborn rodents or baboons. Furthermore, some researches showed that human adenovirus type 12 cannot be an etiologic factor of retinoblastoma disease. Published data in the field of the HPV and retinoblastoma tumorigenesis and cell proliferation are controversial. The current systematic review study aimed to present conducted studies in the field of HPV infection and its role in retinoblastoma.

2 | MATERIAL AND METHODS

2.1 | Search strategy

For this systematic review, all relevant original research studies were assessed by searching in electronic databases including PubMed, Embase, Scopus, Google Scholar, and Web of Science by using Retinoblastoma, Viruses, HPV, Human papillomavirus, and Eye Neoplasms as keywords and all search results limited from 2009 to 2019.

2.2 | Inclusion and exclusion criteria

The study was designed based on the PRISMA criteria. The inclusion criteria for the current study assumed as publication in 2009–2019, the publication with English literature and original researches. The exclusion criteria were including low eligibility, review articles, meta-analysis studies, and congress abstracts.

2.3 | Bias assessment

There are few studies in the field of retinoblastoma and viral infections. Furthermore, the risk bias for the nonrandomized controlled trials (RCT) was assessed by using the 13 items in the Research Triangle Institute (RTI), Evidence-based Practice Center. Also, the risk bias for the randomized controlled trials (RCT) studies was assessed by the Cochrane Collaboration’s tool for assessing risk bias.

2.4 | Review section and data extraction

For the review of the search results, we used three distinct authors. All of the studies were listed in the EndNote software (EndNote X7, Thomson Reuters) and screened by two independent authors, and the third expert author strategy was used for conflicts. In review, we investigated the study design and its eligibility based on the inclusion criteria. All of the original research studies in every study setting refer to the investigation of HPV in RB patients regardless of the patient’s population or age range considered for screening and reviewing section. The first author’s name conducted study country, year of publication, sample size, mean age of patients, virus genotype, prevalence of HPV in the assumed population, HPV detection method, and the study design were extracted from all of the included primary studies. The prevalence of HPV in RB is considered a representable result.

3 | RESULTS

3.1 | Search result and bias assessment

Conducted search results lead to 4070 studies. By the title, abstract, and time limitation criteria screening, 11 studies remain and met the inclusion criteria. Final assessment performed on 8 included studies, and 3 were excluded due to irrelevance data. The search result and study flow chart were illustrated in Figure 1. Also, the bias assessments for the included studies were summarized in Tables 1 and 2.

3.2 | Retinoblastoma and viruses

The conducted study leads to 8 eligible studies (Table 3). All of the 8 included studies assessed the HPV. By the assessment of the cross-sectional studies, the prevalence of HPV was ranged from 0 to 69%. Based on the differences in the setting of the studies, we could not conclude a clear prevalence for the viral infection in retinoblastoma. The most used method for the detection of the viruses was PCR, and
the most assessed sample was formalin-fixed, paraffin-embedded tissue blocks. The highest rate of viral infection in retinoblastoma samples in conducted studies was 69%, and the lowest rate was 0%. Also, 8 of the included studies assessed HPV and the most reported genotypes were 16 and 18. Furthermore, the assessment of the geographical location indicates that 4 of the studies were conducted in India and others in Iran, Brazil, Thailand, and Korea.

4 | DISCUSSION

Retinoblastoma is a predominant primary ocular cancer mainly present among children. Retinoblastoma proteins are a major human tumor suppressor and a cell cycle regulator, which is encoded by RB1 gene located on the q14 band region of chromosome 13. Mutations or other factors that result in inactivation or absence of retinoblastoma protein (pRB) will lead to development of many types of cancers, including RB. For instance, various viral infections including HPV can disable the function of tumor suppressor proteins. HPVs are divided into the low-risk and high-risk HPV types due to their oncogenic potential. HPVs have various oncoproteins (e.g., E6 and E7) that can interfere with cell cycle regulators. E6 oncoproteins can bind to the cellular protein P53 and subsequently promote formation of tumors. E7 binds to pRB, eliminates unphosphorylated pRB, and suppresses its antitumor functions. Perhaps RB could be an infective agent-associated cancer and HPV
infection might be involved in it. In this systematic review, we discuss eight different studies that assessed the relationship between HPV and RB across different societies. Three of these studies concluded that there was no relationship between HPV and RB in their results. The remaining five studies indicated a possible correlation which might be involved in it. In this systematic review, we discuss eight different studies that assessed the relationship between HPV and RB across different societies. Three of these studies concluded that there was no relationship between HPV and RB in their results. The remaining five studies indicated a possible correlation

between these oncogenic viruses and this rare pediatric neoplasm. 28

In another study, Ryoo et al. examined the existence of HPV-DNA in FFPE tissues from 54 Korean patients diagnosed with retinoblastoma using in situ hybridization (ISH). In this study, HPV was not detected in any of the retinoblastoma samples. These scientists declared that the possibility of false-negative remained low, due to the fact that positive controls—cervical cancer specimen—consistently expressed HPV, which shows the analysis technique was reliable. Ryoo et al. demonstrated HPV infection may have no causal relationship with RB in the Korean patients. 30

Javanmard et al. assessed the prevalence of HPV-DNA among RB patients in a cross-sectional study. Overall, they tested 61 FFPE retinoblastoma tumor samples of Iranian patients by nested PCR, which increased the sensitivity of the test rather than using real-time PCR. Further, sequencing was performed to confirm positive cases. 88.5% of the cases were unilateral, and 90.2% had nonfamilial RB tumors. HPV-DNA was detected in 9.8% of the RB tumor samples, and HPV type16 was the most prevalent type. Furthermore, they found out that the HPV-positive RB cases all had unilateral and unfamiliar sporadic RB tumors. The scientists claimed that their finding may suggest a presumptive link between infection with HPV and incidence of sporadic RB. 31

Also, Anand et al. assessed the prevalence of high-risk HPV genotypes in retinoblastoma. The study looked at a total of 83 RB tumor

| Author     | Year | Country | Selection bias | Performance bias | Detection bias | Attrition bias | Selective outcome | Confounding | Other bias | References |
|------------|------|---------|----------------|------------------|----------------|----------------|-------------------|-------------|------------|-------------|
| Andad      | 2011 | India   | L              | L                | L              | U              | U                 | L           |            | 32          |
| Shetty     | 2012 | India   | L              | L                | L              | U              | U                 | L           |            | 33          |
| Ryoo       | 2013 | Korea   | L              | L                | L              | U              | U                 | L           |            | 30          |
| Javanmard  | 2019 | Iran    | L              | L                | L              | U              | L                 | L           |            | 31          |

Abbreviations: L: Low risk of bias, H: High risk of bias, U: Unclear risk of bias.
samples, including 64 FFPE and 19 fresh cases of RB. They used multiplex PCR for the detection of HPV-DNA. Moreover, they also conducted nonspecific ISH on all HPV-positive cases that were positive for multiplex PCR. Furthermore, they carried out immunohistochemistry (IHC) for the detection of pRB and P16<sup>INK4a</sup>, 24% (20/83) of the RBs that contained HPV-DNA consisted of 11 of the 19 fresh cases and 9 of the 64 FFPE cases. According to IHC, 75% of HPV-positive RB (15/20) did not express pRB. All 20 HPV-positive tumors overexpressed P16<sup>INK4a</sup> as expected. They noticed that the higher frequency of HPV detection in fresh tissue (11/19) versus FFPE tissue (9/64), which it could reflect the DNA degradation over time. In conclusion, they found high-risk HPV types in RB tumors using more than one technique. The level of expression of the tumor suppressor pRB, which is the main target of the HPV-E7 oncogene, also revealed that the protein is not expressed in the majority of the HPV-positive cases. Finally, they observed a statistically significant association between HPV and pRB expression status.  

In a case-control study, Nuru et al. demonstrated the presence of HPV-16 in one-fourth of non-familial RB cases in North India. Their study cohort was made up of 39 fresh RB tumor tissues from 39 patients with a nonfamilial history and 42 normal retinal tissues to be used for the control group. Further, 28.2% of these patients were bilateral. HPV-DNA was detected in 25.6% of tumor tissues using PCR, and HPV-16 was the only subtype detected. They also assessed three cases with a family history of RB separately, but all three cases were negative for HPV. The strength of this prospective study is that all specimens were freshly obtained and no archival tissues were processed.  

Mohan et al. performed a study to examine the presence of the HPV genome in Indian unilateral RB by nested and semi-nested PCR. They also assessed the expression of RB protein in tumor tissue sections by IHC. The study was conducted on 44 fresh RB tumor samples. Moreover, these scientists also tested 30 nonfamilial donor retinas as a control group. Additionally, they carried out HPV-16 and 18 genotyping on HPV genome-positive samples. HPV-DNA was detected in 48% (21/44) of RB samples, but all 30 control tissues were negative for the HPV genome. Among the 21 positive cases for the HPV genome, the HPV-16 genome was detected in 57% (12/21) of tumors. None of the positive tumor tissue for HPV-DNA was HPV-18 positive. Additionally, they observed significantly more HPV-DNA in children aged <18 months compared with children aged >24 months. According to IHC analysis, RB protein was absent in 71% (16/21) of tumors that have HPV-DNA. Their study confirmed studies that showed an association between HPV-DNA and RB tumors.  

Shetty et al. tested 76 FFPE RB tissues samples from India for the presence of high-risk HPV (type16 and 18) DNA sequencing by PCR. They also carried out southern blotting to check the specificity of the PCR, and RT PCR to identify the transcription of E7 in RB. Moreover, they did an IHC analysis for the expression of cell cycle regulatory proteins (P105, P107, P30, P16, E2F-1, E2F-4, MiB-1). 69.7% of the RB cases were positive for HPV by PCR method. Cases with family history and negative for HPV were seen. They tested 6

### Table 3

| No. | First author | Country | Year | Sample size | Gender | Mean age (month) | Virus | Genotype | Method | Study design | Ref. | Case | Control | Case | Control | Sample size | Gender | Women (%) | Prevalence (%) |
|-----|--------------|---------|------|-------------|--------|-----------------|-------|-----------|--------|-------------|------|-------|----------|-------|----------|-------------|--------|-----------|----------------|
| 1   | Mohan        | India   | 2009 | 44          | 30     | 11±6            | HPV   | 16        | PCR    | CC          | 12  | 48    | 0        | 0     | HPV      | 38.63       |        |           |                 |
| 2   | Antonelli    | Brazil  | 2011 | 153         | 44     | 44              | HPV   | 16, 33, 45, 18, 39, 40, 42, 46, 9.1 | PCR    | CC          | 26  | 4.6   | 9.1      | 48.7 | HPV      | 22.4        |        |           |                 |
| 3   | Andad        | India   | 2011 | 83          | ~32.4  | HPV             | 45, 59, 68, 52, 82, 73, 18 | multiplex PCR/ISH | CS          | 32  | 24    | 67.7     | 0     | HPV      | 32           |        |           |                 |
| 4   | Shetty       | India   | 2012 | 76          | 69.7   | -               | HPV   | 18, 16    | PCR    | ISH/Liquid CS | 33  | 0     | 25.6     | 0     | HPV      | 9.8         |        |           |                 |
| 5   | Ryoo         | Korea   | 2013 | 54          | 51.8   | -               | HPV   | 16        | PCR    | -           | 30  | 0     | 0        | 0     | HPV      | -           |        |           |                 |
| 6   | Nuru         | India   | 2016 | 39          | 42     | 41.8±26.2       | HPV   | -         | ISH    | -           | 29  | 12    | 49.5     | 47.5 | HPV      | -           |        |           |                 |
| 7   | Santanasane  | Thailand| 2018 | 80          | 12     | 28.6±17.3       | HPV   | 16, 18, 6, 11 | PCR    | Real-time PCR | 31  | 0     | 98       | 98    | HPV      | -           |        |           |                 |
| 8   | Jawambad     | Iran    | 2019 | 61          | 61     | 49.5            | HPV   | 16, 18, 6, 11 | Nested-PCR | CS          | 31  | 0     | 98       | 98    | HPV      | -           |        |           |                 |

Abbreviations: CS, cross-sectional study; CC, case-control; ISH, in situ hybridization; HPV, human papilloma virus.

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non-neoplastic eyeballs as a negative control group, and the HPV-DNA was not detected. The majority of the patients in this study had unilateral disease. Overall, Shetty’s study supported the hypothesis that the infection of HPV-16/18 may play an important role in the development of the nonfamilial form of RB in children in India.33

As we mentioned earlier, there are two forms of retinoblastoma: Heritable and Sporadic. Heritable retinoblastoma may be caused by inheritance of mutant RB1 gene, but cause of sporadic RB remains unclear. The majority of retinoblastoma cases are sporadic. Due to the fact that most of the sporadic RB cases have been reported from less industrialized and not affluent countries with poor sanitation facilities (eg, India, South America, and Africa),7,34,35 we believe that sporadic RB may be traced back to environmental and behavioral factors. Following this logic, RB may be attributed to the exposure infections, such as HPV. Anand et al. mentioned in their study that the higher frequency of HPV detection in fresh tissue versus FFPE tissue reflects the DNA degradation over time that could have taken place in disparately buffered formalin-fixed tissue. The three studies that indicated a negative correlation between HPV and retinoblastoma, all used FFPE tissues, and their negative results might be due to DNA degradation. Furthermore, as mentioned in Chauhan et al.36 letter, there are limited data in this particular field of study. Some limitations in primary studies are reflected in the current study; for instance, most conducted studies originated from Eastern countries and extrapolation of these results to Western populations is questionable; significant heterogeneity was encountered, which could be due to the study population or different study setting and geographical location, limitation in primary studies and possibility of potential bias. A major limitation in our current study was limited primary studies in this field, which led us to perform a not greatly optimized search strategy. Furthermore, the absence of methodological confirmed registration code for systematic reviews on the PRISMA and Cochran is a major limitation in current study. Another limitation of the study is the investigated period of time (2009–2019). There might be more primary studies in recent years (2019–2021), which could be missed in the current study.

5 | CONCLUSION

In conclusion, the association between HPV and RB is still inconsistent. The prevalence of the HPV in RB was ranged from 0 to 69%, which indicates a wide range and highlights the importance of further investigation for more accurate statistical of HPV prevalence in RB. Thus, further worldwide studies of larger sample sizes of cohorts should be investigated to clarify this uncertainty.

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CONFLICT OF INTERESTS

The authors report no conflicts of interest in this work.

AUTHORS CONTRIBUTIONS

S.S, AF, and M.E designed the study. S.S, S.AR, A.R, M.E, and A.F were primarily responsible for data collection. A.T, P.Y, M.Z, and A.Z contributed to material preparation and analysis. S.S, AF, A.T, P.Y, M.Z, and M.E contributed to the first draft of the manuscript. All authors reviewed and approved the manuscript.

DATA AVAILABILITY STATEMENT

All data associated with this manuscript are inclusive in this paper.

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