# Risk Factors Associated with Dysplastic or Malignant Transformation in HPV-Related Recurrent Respiratory Papillomatosis: A Systematic Review and Meta-Analysis

Kenny Do, M.D.,[1] Nabih Ghani, B.S.,[1] Caroline Liu, M.D.,[1] William Montagne, M.D.,[1] Benjamin Tam, M.D.,[1] Kurtis Young, M.D.,[1] Emily S. Sagalow, M.D.[1], Suparna Shah, M.D.,[1] Sisi Tian, M.D.,[1] Robert C. Wang, M.D.,[1]

KIRK KERKORIAN SCHOOL OF MEDICINE | UNLV

DEPARTMENT OF OTOLARYNGOLOGY HEAD & NECK SURGERY

[1] Department of Otolaryngology – Head & Neck Surgery, Kirk Kerkorian School of Medicine at UNLV

## Introduction

- Recurrent respiratory papillomatosis (RRP) is a benign neoplastic disease caused primarily by human papillomavirus (HPV) types 6 and 11, characterized by recurrent growth of squamous papillomas throughout the aerodigestive tract.
- RRP occurs in both juvenile-onset (JoRRP) and adult-onset (AoRRP) forms and can cause substantial morbidity due to frequent recurrence, repeated surgical interventions, and potential extension into the lower airway.
- Although histologically benign, RRP can undergo dysplastic or malignant transformation. Dysplasia has been reported in approximately 10–50% of patients, while 1–7% may progress to carcinoma.
- Current management relies primarily on surgical debulking, with adjuvant therapies including bevacizumab, cidofovir, and HPV vaccination used to reduce disease burden and recurrence.
- Prior studies have identified several potential risk factors for dysplastic or malignant transformation, including older age, smoking, immunosuppression, HPV subtype, and certain adjuvant therapies; however, findings remain inconsistent.
- **Objective:** To systematically evaluate and quantify factors associated with dysplastic and malignant transformation in HPV-associated RRP through a systematic review and meta-analysis.

## Methods

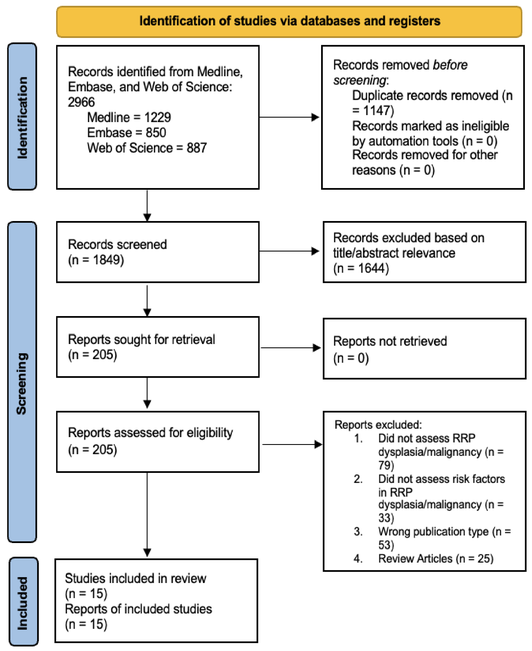


Figure 1: PRISMA Flowchart

## Results

| Characteristic | Finding |
|---|---|
| Studies included | **15** |
| Total patients | **1,196** |
| Study design | 13 retrospective; 2 prospective |
| Population | Adult- and juvenile-onset RRP; predominantly male |
| Juvenile-onset RRP (JoRRP) | **≥289 patients** |
| JoRRP age at presentation | 6 months–18 years; mean 5–8 years |
| AoRRP age at presentation | 18–83 years; mean 45–55 years |
| Initially benign RRP | **1,033 patients** |
| Developed dysplasia | **117 (11.3%)** |
| Malignant transformation | **62 (6.0%)** |
| Reported dysplasia grades | 63.7% mild; 16.2% moderate; 15.9% severe/CIS |

Table 1. Characteristics of Included RRP Studies and Patient Population

| Factor | Studies | Key Findings |
|---|---|---|
| **Older Age — AoRRP** | Meeker; Karatayli-Ozgursoy; Gluvajic; Hall; Chandrasekar; Gerein; Rahmoun | Pooled analysis: transformation group was **6.78 years older** (95% CI 0.68–12.88; **p = 0.03**; $I^2$ = 72%). Individual cohorts reported **55.3 vs 43.9 years (p = 0.009)** and **56 vs 45 years (p = 0.0005).** |
| **Earlier Onset — JoRRP** | Karatayli-Ozgursoy; Sajan; Rahmoun | Malignant vs nonmalignant cases presented at **15.5 vs 48 months** in one study and **2 ± 1 vs 6 ± 4 years (p = 0.009)** in another. Pediatric data were insufficient for pooled analysis. |
| **Smoking** | Blumin; Meeker; Karatayli-Ozgursoy; Freeman; Gluvajic; Hall; Chandrasekar; Gerein; Rahmoun; Lee; Reidy | Pooled **OR 1.74** (95% CI 0.88–3.47; **p = 0.11**). One study found malignancy in **16.3% of smokers vs 3.6% of nonsmokers.** Another reported smoking in **71% vs 43%** of dysplastic vs nondysplastic patients **(p = 0.044).** |
| **Cidofovir** | Blumin; Meeker; Gupta; Karatayli-Ozgursoy; Gluvajić; Sajan; Chandrasekar | No evidence of increased transformation risk. Dysplasia occurred in **11% treated vs 29% untreated (p < 0.09)** in one study. Cidofovir exposure was **8% vs 6%** in transformed vs nontransformed patients **(p = 0.582).** |
| **HPV-11** | Gerein; Rahmoun; Reidy | Associated with aggressive disease. One study reported **13% malignancy** among HPV-11+ patients; all pulmonary spread **(6/6)** and malignant cases **(5/5)** were HPV-11+ **(p = 0.012** and **p = 0.004)**. Another series identified HPV-11 in **9/9 SCC cases.** |
| **HPV E6/E7 Expression** | Khreefa | Malignancy occurred in **4/187 (2%)**. High E6/E7 expression and low E2 expression were associated with malignant transformation. |
| **Diabetes Mellitus** | Meeker; Lee | One study found dysplasia in **16/68 (23.5%)** specimens, with **0 cases** among patients with DM **(p = 0.49)**. Another reported DM in **21% vs 24%** with vs without dysplasia **(p = 0.84)** and **0% vs 26%** with vs without malignancy **(p = 0.32)**. |
| **Laryngopharyngeal Reflux** | Meeker | LPR occurred in **67.8% vs 76%** of dysplastic vs nondysplastic patients **(p = 0.55)** and **86% vs 69%** of malignant vs nonmalignant patients **(p = 0.37)**. |
| **Immunosuppression** | Meeker | Immunosuppression occurred in **14.2% vs 5%** with vs without dysplasia **(p = 0.28)** and **14% vs 10%** with vs without malignancy **(p = 0.70)**. |
| **HPV Vaccination** | Meeker; Chandrasekar | Vaccination occurred in **32% vs 29%** with vs without dysplasia **(p = 0.79)**. In one cohort, **0/7 malignant cases** were vaccinated **(p = 0.08)**. |

Table 2. Factors Associated With Dysplasia and Malignant Transformation in RRP

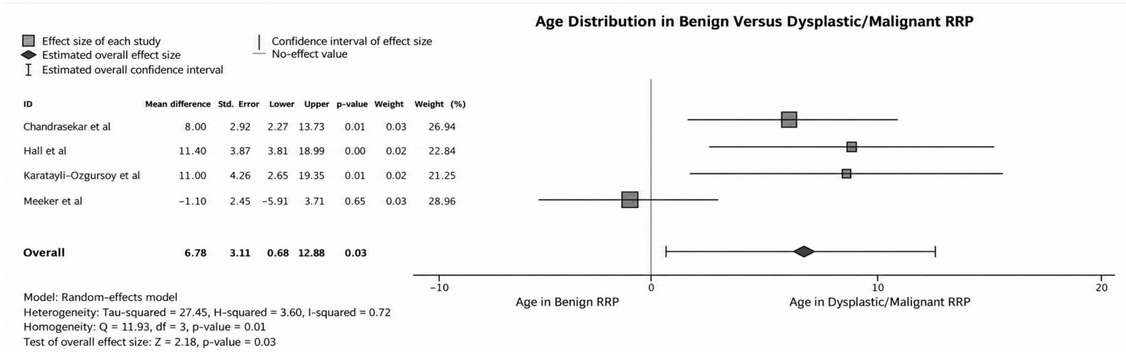


Figure 2: Forest Plot for Mean Age Difference Between Benign and Dysplastic/Malignant HPV-Related RRP Groups

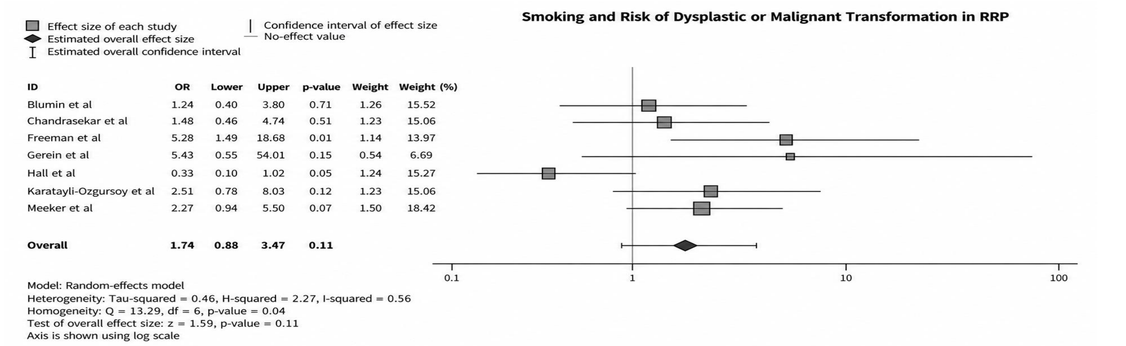


Figure 3: Forest Plot for Smoking in Benign and Dysplastic/Malignant HPV-Related RRP Groups

### Key Results

- 15 studies comprising 1,196 patients with HPV-related RRP were included. Among 1,033 patients with initially benign disease, 117 (11.3%) developed dysplasia and 62 (6.0%) progressed to malignancy.
- Older age was the strongest quantitative risk factor in AoRRP. Patients with dysplastic/malignant transformation were 6.78 years older than those with benign disease (95% CI 0.68–12.88; p=0.03).
- In JoRRP, individual studies suggested the opposite age relationship, with earlier disease onset associated with later malignant transformation (ex. 2 ± 1 vs 6 ± 4 years; p=0.009).
- Smoking showed increased pooled odds of transformation (OR 1.74; 95% CI 0.88–3.47), but the overall association was not statistically significant (p=0.11). Individual studies demonstrated stronger associations with smoking exposure and pack-years.
- HPV-11 was repeatedly associated with aggressive disease. One cohort found HPV-11 in all patients with pulmonary spread (6/6) and all malignant cases (5/5); another identified HPV-11 in 9/9 SCC cases.
- Cidofovir was not associated with increased dysplastic or malignant transformation across the included studies.
- Diabetes, laryngopharyngeal reflux, and immunosuppression showed no significant associations with transformation in the available studies. HPV vaccination also showed no statistically significant association, although available data were limited.

## Discussion

### Discussion

- Age emerged as the most consistent factor associated with disease progression. Adults with dysplastic or malignant transformation were significantly older than those with benign RRP, suggesting that prolonged HPV persistence and cumulative viral exposure may contribute to carcinogenesis.
- HPV-11 was repeatedly associated with more aggressive disease, including high-grade dysplasia, pulmonary spread, and malignant transformation. Although traditionally considered a low-risk HPV subtype, HPV-11 may promote genomic instability through E6-mediated disruption of p53-dependent pathways, particularly in the setting of persistent infection.
- Severity of dysplasia appears to be an important marker of malignant potential. Gluvajić et al. reported progression to SCC in 17.1% of high-grade vs 0.8% of low-grade lesions, corresponding to a 21.8-fold relative risk. Meeker et al. similarly demonstrated greater carcinoma development among patients with high-grade dysplasia.
- Adult-onset RRP may represent a higher-risk phenotype than juvenile-onset disease. Several studies reported dysplastic and malignant transformation predominantly in adults. Malignant transformation in JoRRP was uncommon, but when present, was often associated with HPV-11 and pulmonary involvement.
- Smoking demonstrated inconsistent associations. Although individual studies identified relationships between tobacco exposure and dysplasia, the pooled analysis did not demonstrate a statistically significant association with overall transformation (OR 1.74; p=0.11).
- Despite historical concerns regarding carcinogenicity, cidofovir was not associated with increased dysplastic or malignant transformation in the larger clinical studies included in this review. Diabetes, immunosuppression, and LPR similarly showed no consistent associations.

### Clinical Implications

- Older patients, patients with HPV-11, and those demonstrating high-grade dysplasia may warrant particularly close surveillance for disease progression. The findings also provide reassurance that available clinical evidence does not demonstrate increased transformation risk with cidofovir therapy.

## References

1. Rivera GA, Morell F. Laryngeal Papillomas. In: StatPearls. StatPearls Publishing; 2025. Accessed October 26, 2025. http://www.ncbi.nlm.nih.gov/books/NBK482327/
2. Benedict JJ, Derkay CS. Recurrent respiratory papillomatosis: A 2020 perspective. *Laryngoscope Investig Otolaryngol*. 2021;6(2):340-345. doi:10.1002/lio2.545
3. Pai SI, Wasserman I, Ji YD, et al. Pulmonary manifestations of chronic HPV infection in patients with recurrent respiratory papillomatosis. *Lancet Respir Med*. 2022;10(10):997-1008. doi:10.1016/S2213-2600(22)00208-X
4. Marrow MP, Gillespie E, Sylvester A, et al. DNA immunotherapy for recurrent respiratory papillomatosis (RRP): phase 1/2 study assessing efficacy, safety, and immunogenicity of INO-3107. *Nat Commun*. 2025;16(1):515. doi: 10.1038/s41467-025-56729-6
5. Seedat RY. The incidence and prevalence of juvenile-onset recurrent respiratory papillomatosis in the Free State province of South Africa and Lesotho. *Int J Pediatr Otorhinolaryngol*. 2014;78(12):2113-21 15. doi:10.1016/j.ijporl.2014.09.017
6. Omland T, Akre H, Vårdal M, Brondbo K. Epidemiological aspects of recurrent respiratory papillomatosis: a population-based study. *Laryngoscope*. 2012;122(7):1595-1599. doi:10.1002/lary.23327
7. Oh JK, Cho HY, Han M, Jung YS, Lee SJ, Ki M. Estimated incidence of juvenile-onset recurrent respiratory papillomatosis in Korea. *Epidemiol Health*. 2021;43:e2021019. doi:10.4178/epih.e2021019
8. Arana-Arri E, Portillo EJ, Rachet M, et al. Incidence and prevalence of recurrent respiratory papillomatosis among children in Alaska and Seattle, 2001–2010. *BMC Pediatr*. 2020;20(1):107. doi:10.1186/s12887-020-1819-4
9. Doyle DJ, Goodell GJ, Eadonde T, Miller RH. Recurrent respiratory papillomatosis: juvenile versus adult forms. *Laryngoscope*. 1994;104(3 Pt 1):323-327. doi:10.1002/lary.5541040303
10. Ahn SH, Chan EY, Work WP. Recurrent respiratory papillomatosis: review of prognosis after cidofovir for transformation after a decade. *Respir Med Case Rep*. 2023;45:101904. doi:10.1016/j.rmcr.2023.101904
11. Park I, Cardona S, Preciado D. Systematic review of the use of human papillomavirus vaccine as adjuvant therapy for juvenile-onset recurrent respiratory papillomatosis. *International Journal of Pediatric Otorhinolaryngology*. 2022;162:111314. doi:10.1016/j.ijporl.2022.111314
12. Blumin JH, Handler EB, Simpson CB, Cristpo V, Mersol AL. Dysplasia in adults with recurrent respiratory papillomatosis: incidence and risk factors. *Ann Otol Rhinol Laryngol*. 2009;118(7):481-485. doi:10.1177/000348940911800704
13. Meeker MD, Ivanov R, deSilva B, Mathis LA. Dysplasia and Carcinoma in Recurrent Respiratory Papillomatosis Patients Older Than 45 Years. *Laryngoscope*. 2023;133(5):1313-1319. doi:10.1002/lary.30220
14. Khan M, Naidu TK. Risk factors associated with severe recurrent respiratory papillomatosis. *S Afr J Infect Dis*. 2019;34(1):69. doi:10.4102/sajid.v34i1.69
15. Forbes HR, van Rooke PM, Escudero DL, et al. Recurrent respiratory papillomatosis: A state-of-the-art review. *Respir Med*. 2017;126:116-121. doi:10.1016/j.rmed.2017.03.030
16. Munoz S. Current treatment options for recurrent respiratory papillomatosis: A narrative review. *Auris Nasus Larynx*. 2025;52(4):307-313. doi:10.1016/j.anl.2025.04.014
17. Goon P, Sayed O, Schuemann M, et al. Recurrent Respiratory Papillomatosis (RRP)—Meta-analyses on the use of the HPV vaccine as adjuvant therapy. *ejc Vaccines*. 2023;8(1):49. doi:10.1155/2023/8940011703702
18. McMurray JS, Connor N, Ford CN. Cidofovir efficacy in recurrent respiratory papillomatosis: a randomized, double-blind, placebo-controlled study. *Ann Otol Rhinol Laryngol*. 2008;117(7):487-493. doi:10.1177/000348940811700702
19. Hoang MP, Kasperbauer JL, Rosenthal DW, Weinberger PM, Wetmore RF. Randomized trial of surgical treatment with and without cidofovir in recurrent respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg*. 2004;130(12):1377-1381. doi:10.1001/archotol.130.12.1377
20. Hoved RC, Thakchar AL, Hughan MD, Kupfer RA. Evaluation of Safety of Intralesional Cidofovir for Adjuvant Treatment of Recurrent Respiratory Papillomas. *JAMA Otolaryngol Head Neck Surg*. 2020;146(3):231-236. doi:10.1001/jamaoto.2019.4029
21. Gupta HT, Robinson RA, Murray RC, Kamell LH, Smith RJH, Hoffman HT. Degrees of dysplasia and the use of cidofovir in patients with recurrent respiratory papillomatosis. *Laryngoscope*. 2010;120(4):699-702. doi:10.1002/lary.20785
22. Karatayli-Ozgursoy S, Bishop JA, Hillel A, Akst L, Best SRA. Risk Factors for Dysplasia in Recurrent Respiratory Papillomatosis in an Adult and Pediatric Population. *Ann Otol Rhinol Laryngol*. 2016;125(3):225-241. doi:10.1177/0003489415608196
23. Freeman T, Erickson E, Koch B, et al. Smoking and Carcinoma Trends in Recurrent Respiratory Papillomatosis Patients. *Ann Otol Rhinol Laryngol*. 2023;132(11):1380-1385. doi:10.1177/00034894231158459
24. Khreefa Z, Isaac V, Prusik J, et al. Correlation Between EE and E7 Oncogenes and Malignant Transformation of Laryngeal Papillomatosis (LP) with Human Papillomavirus (HPV) in Pediatric Population. *Fetal Pediatr Pathol*. 2021;40(4):290-294. doi:10.1080/15513815.2019.1707921
25. Study Quality Assessment Tools | NHLBI, NIH. Accessed March 21, 2023. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
26. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. Routledge; 1988. doi:10.4324/9780203771587
27. Faraone SV. Interpreting Estimates of Treatment Effects. *P T*. 2008;33(12):700-711.
28. 6.5.2.3 Standard deviations from standard errors. Accessed July 25, 2024. https://handbook-5-1.cochrane.org/chapter_7/7_7_3_2_obtaining_standard_deviations_from_standard_errors_and.html
29. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135. doi:10.1186/1471-2288-14-135
30. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res*. 2018;27(6):1785-1805. doi:10.1177/0962280216669183
31. Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. *Int J Evid Based Healthc*. 2015;13(3):196-207. doi:10.1097/XEB.0000000000000065
32. McNeish D. Small Sample Methods for Multilevel Modeling: A Colloquial Elucidation of REML and the Kenward-Roger Correction. *Multivariate Behav Res*. 2017;52(5):661-670. doi:10.1080/00273171.2017.1344538
33. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I² index? *Psychol Methods*. 2006;11(2):193-206. doi:10.1037/1082-989X.11.2.193
34. Glovaci D, Hobjeik L, Biegel V, et al. Risk factors for the development of high-grade dysplasia and carcinoma in patients with laryngeal squamous cell papillomas: Large retrospective cohort study. *Head Neck*. Published online December 1, 2020. doi:10.1002/hed.26500
35. Sajan JA, Kershner JE, Mandel L, Taylor S, Bishop JA. Prevalence of dysplasia in juvenile-onset recurrent respiratory papillomatosis. *Laryngoscope Head Neck Surg*. 2010;120(1):71-74. doi:10.1001/archoto.2009.179
36. Hall JE, Chan K, Yoo MJ, Fletcher KC, Orsoff RH, Garrett CG. Natural progression of dysplasia in adult recurrent respiratory papillomatosis. *Otolaryngol Head Neck Surg*. 2011;144(2):253-256. doi:10.1177/0194599810391636
37. Derkay CS, Darrow DH, Bluher A, Myer CM, Smith RJH, Wiatrak BJ. Juvenile-onset recurrent respiratory papillomatosis. *Ann Otol Rhinol Laryngol Suppl*. 2008;198:5-11. doi:10.1177/00034899081170S202
38. Gerein V, Rasinger-Egeli L, Gerein J, Graf W, Schiren J. Incidence, age at onset, and potential means of malignant transformation in recurrent respiratory papillomatosis patients: 20 years experience. *Otolaryngol Head Neck Surg*. 2005;132(3):392-394. doi:10.1016/j.otohns.2004.09.035
39. Rahmoun M, Aussel A, Bouzid S, et al. Genomic diversity of HPV6 and HPV11 in recurrent respiratory papillomatosis: Association with malignant transformation in the lungs and clinical outcome. *Tumour Virus Res*. 2024;18:200294. doi:10.1016/j.tvr.2024.200294
40. Lee LA, Cheng AJ, Fang TJ, et al. High incidence of malignant transformation of laryngeal papilloma in Taiwan. *Laryngoscope*. 2008;118(1):50-55. doi:10.1097/MLG.0b013e3181f35e28b
41. Reidy PM, Dedo HH, Rabin R, et al. Integration of human papillomavirus type 11 in recurrent respiratory papilloma-associated cancer. *Laryngoscope*. 2004;114(11):1906-1909. doi:10.1097/01.mlg.0000147918.81733.49
42. Lee CJ, Allen CT, Merati AL. Prevalence of diabetes mellitus and its impact on disease severity in adult recurrent respiratory papillomatosis. *Otolaryngol Head Neck Surg*. 2013;149(4):603-607. doi:10.1177/0194599813496899
43. Bodeker C, Unkenmeir ME, Machaela MJ, Vinokurova S, Wentzensen N. Genomic characterization of viral integration sites in HPV-related cancers. *Int J Cancer*. 2016;139(5):2001-2011. doi:10.1002/ijc.30243
44. Zhou YX, Ma XH, Wang TT, Qu XL, Zhang XQ. Analysis of age-specified and genotype distribution of HPV multiple infections in the Chinese population. *Sci Rep*. 2024;14(1):2578. doi:10.1038/s41598-024-53271-1
45. Association of age and viral factors with high-risk HPV persistence: A retrospective follow-up study - PubMed. Accessed October 29, 2025. https://pubmed.ncbi.nlm.nih.gov/31240996/
46. Ma Y, Zhang Y, Cui J, et al. Risk factors for HPV persistence: A meta-analysis. *Medicine*. 2020;99(51):e23587. doi:10.1097/MD.0000000000023587
47. Thomas JT, Oh ST, Terhorst RR, Lemme LA, Cellular changes induced by low-risk human papillomavirus type 11 in keratinocytes that stably maintain viral episomes. *J Virol*. 2001;75(16):7564-7571. doi:10.1128/JVI.75.16.7564-7571.2001
48. Reidy PL, Schnadig VJ, Weiss RL, Hughes TK, Tyring SK. Malignant Transformation of Recurrent Respiratory Papillomavirus Type 11 DNA and Mutation of p53. *The Laryngoscope*. 1998;108(5):735-740. doi:10.1097/00005537-199805000-00021
49. Havre PA, Yuan J, Hedrick L, Cho KR, Glazer PM. p53 inactivation by HPV16 E6 results in increased mutagenesis in human cells. *Cancer Res*. 1995;55(19):4420-4424
50. Horton G, Phillips J, Lin RJ. Malignant Transformation of Dysplastic Vocal Fold Lesions. *JAMA Otolaryngol Head Neck Surg*. 2024;150(7):556-563. doi:10.1001/jamaoto.2024.1008
51. Waller M-L, Narkool P-L, McConley C, Nelson H m. The risk and interval of malignancy of patients with laryngeal dysplasia: a systematic review of case series and meta-analysis. *Clinical Otolaryngology*. 2010;35(5):364-372. doi:10.1111/j.1749-4486.2010.02181.x
52. Cidofovir. In: *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Accessed November 1, 2025. http://www.ncbi.nlm.nih.gov/books/NBK548417/
53. Ramsey MJ, Derkay CS, Seery AM, Omari AA, Akroyd G, Sataloff RT. Intravenous Cidofovir: A Systematic Review of Administration Routes and Juvenile Recurrent Respiratory Papillomatosis. *Journal of Voice*. Published online August 22, 2023. doi:10.1016/j.jvoice.2023.07.017
54. Donne AJ, Hampson L, He XT, et al. Potential risk factors associated with the use of cidofovir to treat benign human papillomavirus-related disease. *Antivir Ther*. 2009;14(7):939-952. doi:10.3851/IMP1421
55. Lott DG, Kravcisz PR. Squamous cell carcinoma associated with intralesional injection of cidofovir for recurrent respiratory papillomatosis. *Laryngoscope*. 2009;119(3):567-570. doi:10.1002/lary.20082