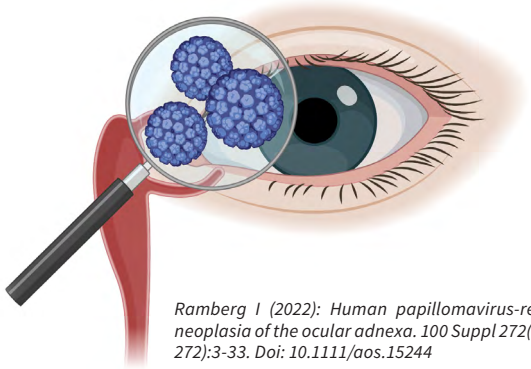
# Human Papillomavirus–

## A Contributor to Ocular Cancer Development



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*On August 26, 2022, Ingvild Margrethe Sellæg Ramberg defended her thesis "Human Papillomavirus-related Neoplasia of the Ocular Adnexa" at the University of Copenhagen. The PhD project was conducted at the Dept. of Pathology, Rigshospitalet, Copenhagen, and the Dept. of Ophthalmology, Rigshospitalet-Glostrup, Denmark. Her main supervisor was Prof. Steffen Heegaard, Dept. of Pathology, Rigshospitalet, Dept. of Ophthalmology, Rigshospitalet-Glostrup, Dept. of Clinical Medicine, Copenhagen University; with co-supervisors Peter Bjerre Toft, Dept. of Ophthalmology, Rigshospitalet-Glostrup, Dept. of Clinical Medicine, Copenhagen University, and Mikkel Funding, Dept. of Ophthalmology, Århus University Hospital.*

**Key points:**

- High-risk human papillomavirus (HPV) is associated with pre-malignant and malignant squamous cell neoplasia arising in the conjunctiva and lacrimal drainage system.
- The prophylactic 9-valent HPV vaccine covers most HPV genotypes implicated in ocular adnexal carcinomas.
- HPV-positive tumors of the conjunctiva and lacrimal drainage system differ from their HPV-negative counterparts in clinical, histopathological, and genomic parameters.

The human papillomavirus (HPV) globally contributes to around 5% of human cancers, imposing significant health and socioeconomic burdens. High-risk HPV genotypes primarily infect the stratified mucosal epithelium in the upper airways and urogenital region. However, all stratified mucosal epithelia, including the mucosal epithelium covering the conjunctiva and lacrimal drainage system, are susceptible to high-risk HPV infection and consequent HPV-driven carcinogenesis. The scientific literature presents divergent findings on the causative role of HPV in the ocular region, primarily due to limited reports and methodological challenges. Therefore, we aimed to evaluate the association between HPV and the development of carcinomas arising in the ocular adnexa and characterize the clinical, histopathological, and genomic features of these tumors.

We conducted a series of studies based on a Danish cohort spanning four decades. Patients with a conjunctival or lacrimal sac squamous cell carcinoma or a precursor lesion were identified in Danish nationwide registries and the corresponding clinical files, and formalin-fixed and paraffin-embedded tumor specimens were collected from a research biobank. Following the validation and staging of the tumor specimens, we performed HPV analyses using a combination of HPV DNA detection by polymerase chain reaction (PCR), HPV RNA detection (HPV E6 and E7 mRNA in situ hybridization), and the expression pattern of the tumor suppressor p16. The genomic profile of the tumors was investigated by next-generation DNA sequencing, targeting 523 genes commonly implicated in human cancers.

Our findings revealed that 67% of all lacrimal sac carcinomas and 21% of all conjunctival squamous cell carcinomas were HPV-positive. The high-risk HPV16 was the most implicated genotype. Almost all HPV DNA–positive cases exhibited full-thickness epithelial expression of the viral oncogenes E6 and E7. The HPV-positive carcinomas exhibited distinct histopathological and genomic features compared to their HPV-negative counterparts: patients with HPV-positive tumors were younger at diagnosis and had a higher risk of tumor recurrence. Further, the HPV-positive carcinomas displayed a non-keratinizing morphology, p16 overexpression, high transcriptional activity of the HPV oncogenes E6 and E7, and frequent somatic pathogenic variations involved in the PI3K-AKT signaling pathway. In contrast, the HPV-negative carcinomas were characterized by a keratinizing morphology, lacked p16 and HPV E6/E7 expression, and had frequent somatic pathogenic variations in the TP53, CDKN2A, and RB1 genes.

In summary, our study of the Danish cohort supports an etiological role of HPV in HPV-positive carcinomas arising in the lacrimal drainage system and conjunctiva. The HPV-positive tumors in these locations displayed distinct clinical, histopathological, and genomic features compared to their HPV-negative counterparts. Most genotypes detected in our cohort are covered by the commercially available HPV vaccines. Further, the HPV-positive carcinomas shared genomic and phenotypical features with HPV-positive carcinomas of other anatomic sites, making them eligible for inclusion in future basket trials and treatment regimens targeting HPV-driven diseases. Continued research efforts will contribute to a better understanding of the prognostic and predictive aspects of HPV in ocular adnexal carcinomas.

**Future directions:**

- The prognostic and predictive role of HPV in ocular adnexal carcinomas requires further investigation.
- Future research will explore the potential benefits of post-exposure HPV vaccination for patients with HPV-related ocular disease.

*References*

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