Original Article

Human Papillomavirus-11 as a Risk Factor for Ocular Surface Squamous Neoplasia

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ABSTRACT

Purpose: To evaluate the association between human papillomavirus type 11 (HPV-11) infection and ocular surface squamous neoplasia (OSSN).

Study Design: Analytical observational study with a case-control design.

Place and Duration of Study: Ngoerah Hospital, Bali, Indonesia, from March 2020 to March 2024.

Methods: In this study, the case group comprised 25 Histopathologically confirmed OSSN samples, while the control group consisted of 25 conjunctival autograft tissues obtained from pterygium surgeries. HPV-11 DNA detection was performed using real-time polymerase chain reaction. Descriptive statistics were used to summarize demographic and clinical characteristics. The association between HPV-11 infection and OSSN was assessed using bivariate analysis to calculate odds ratios with 95% confidence intervals. Multivariate logistic regression analysis was performed to adjust for potential confounding factors. Statistical significance was set at $p < 0.05$.

Results: The mean age of patients was 52.28 years in the OSSN group and 51.0 years in the control group, with males comprising 60% of the OSSN cases. HPV-11 DNA was detected in 14 OSSN samples (56%) compared with one control sample (4%). Bivariate analysis showed a strong association between HPV-11 infection and OSSN (OR = 27.00; 95% CI: 24.84–29.15). Multivariate analysis identified HPV-11 infection (adjusted OR = 17.79; 95% CI: 1.88–167.68) and outdoor occupation (adjusted OR = 7.36; 95% CI: 1.46–37.00) as significant risk factors.

Conclusion: HPV-11 infection is significantly associated with OSSN and may contribute to its pathogenesis, particularly in individuals with increased ultraviolet exposure.

Keywords: Ocular surface squamous neoplasia, Human papillomavirus, HPV-11, Polymerase chain reaction, Pterygium, Risk factors.

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INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted infection globally and is associated with significant morbidity.[1] Cervical cancer is the leading HPV-related malignancy in women, ranking third in incidence worldwide. The prevalence of HPV infection is higher in developing countries (42.2%) than in developed countries (22.6%). In 2018, HPV-related cervical cancer caused 311,365 deaths, more than 85% of which occurred in low- and middle-income countries.[1]

HPV has also been implicated in ocular disease, ranging from benign conjunctival papilloma to malignant ocular surface squamous neoplasia (OSSN). Reported HPV detection rates in OSSN vary widely

from 0% to 100%, with a mean prevalence of approximately 33.8%.[2–4] Low-risk HPV types, including subtypes 6 and 11, are typically associated with benign and low-grade lesions, while high-risk types, such as HPV-16 and HPV-18, have established oncogenic potential.[5–6] An African study detected HPV in 66.7% of OSSN specimens, with HPV-11 as the most common subtype (61.9%), followed by HPV-16 (52.4%) and HPV-18 (33.3%).[7] Despite its classification as a low-risk genotype, HPV-11 was found more frequently than other subtypes in OSSN samples.

OSSN can cause significant visual morbidity through direct scleral invasion, spread along the anterior ciliary pathway, or intraocular seeding during surgery.[8] The role of HPV, particularly HPV-11, in OSSN pathogenesis remains uncertain, with studies showing conflicting results and no data available from the Indonesian population. Given the vision-threatening nature of OSSN and the unclear etiological contribution of HPV-11, this study aimed to evaluate the association between HPV-11 infection and OSSN. Clarifying this relationship could provide valuable insights into disease prevention, improve diagnostic accuracy, and inform targeted screening strategies in populations at risk.

METHODS

This study was conducted from March 2020 to March 2024 at the Ngoerah Hospital, Bali, Indonesia. An analytical observational study with a case–control design was employed. HPV-11 DNA status served as the independent variable, and ocular surface squamous neoplasia (OSSN) was the dependent variable. A matched-pair design was used, with the case group comprising OSSN samples from paraffin-embedded tissue blocks and the control group comprising paraffin-embedded conjunctival autograft tissue from pterygium surgeries. All tissues were obtained retrospectively from the Department of Anatomical Pathology. There were 25 cases and 25 matched controls included in the study.

Inclusion criteria were paraffin-embedded tissue blocks with histopathological diagnoses of OSSN or conjunctival autograft from pterygium surgery, meeting histological reading standards and available in sufficient quantity. Exclusion criteria comprised of incomplete medical records and tumour excision specimens weighing <0.25 mg or unsuitable for real-time polymerase chain reaction (PCR) analysis of HPV-11 DNA. The study protocol was approved by the Institutional Review Board of Ngoerah Hospital, Bali, Indonesia (**Reference Number:1735/UN14.2.2. V1I.14/LT/2024).**

Samples were obtained through consecutive sampling from anatomical pathology records. Eligible samples had identifiable patient data and met all inclusion and exclusion criteria. OSSN cases were confirmed via histopathology and classified as conjunctival intraepithelial neoplasia (CIN), carcinoma in situ (CIS), or squamous cell carcinoma (SCC). Tumour tissues were fixed in 10% formalin and embedded in paraffin. Control samples were derived from paraffin-embedded conjunctival autograft tissue obtained during pterygium surgery.

Matching was performed by pairing OSSN cases with controls of the same sex and within ±5 years of age. Twenty-five matched pairs were established. Data recorded included patient age, sex, and tumour type. All case and control samples were analysed for HPV-11 DNA using real-time PCR with the Zymo Cat D 3067 DNA isolation kit, and results were reported as positive or negative.

Descriptive statistics were used to summarize subject characteristics. Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on data normality assessed by the Shapiro–Wilk or Kolmogorov–Smirnov test. Bivariate analysis of the association between HPV-11 infection and OSSN was performed using a 2×2 contingency table to calculate the odds ratio (OR = b/c) with a 95% confidence interval (CI). Multivariate analysis with multiple logistic regression was applied to control for potential confounders and to determine the adjusted OR. All statistical analyses were conducted using SPSS version 25.0 for Windows, with a significance threshold of $p < 0.05$.

RESULTS

The Shapiro–Wilk test was used to assess the normality of age distribution. The mean age in the control group was 51.0 years, while the case group had a mean age of 52.28 years. Details are depicted in Table 1.

In the OSSN group, conjunctival intraepithelial neoplasia (CIN) was the most common diagnosis (n = 17, 68%), followed by squamous cell carcinoma

(SCC) (n = 6, 24%) and carcinoma in situ (CIS) (n = 2, 8%). Among HPV-11–positive OSSN cases, CIN accounted for 12 cases and SCC for two cases (Table 2).

Detection of HPV-11 DNA was performed on 50 paraffin-embedded tissue specimens (25 OSSN cases and 25 controls) using real-time polymerase chain reaction (PCR). Fourteen OSSN samples (56%) assessed positive for HPV-11 DNA, compared with one sample (4%) in the control group (Table 3).

Table 1: *Characteristics of Research Samples.*

Variable	Case	Control
Age range (years)	26-82	28-77
Mean	52.28 ± 15.29	51 ± 14.21
Gender (n=50)		
Male	15 (60%)	15 (60%)
Female	10 (40%)	10 (40%)
Occupation		
Outdoor	16 (64%)	3 (12%)
Indoor	9 (36%)	22 (88%)

Table 2: *OSSN Diagnosis.*

Diagnosis	Total (n=25)	HPV Infection		Percentage (%)
		+	-	
Conjunctival intra-epithelial neoplasia (CIN)	17	12	5	68
Conjunctival squamous carcinoma in situ (CIS)	2	0	2	8
Squamous cell carcinoma (SCC)	6	2	4	24

Bivariate analysis showed a significantly higher proportion of HPV-11 infection in the OSSN group compared with controls, with an odds ratio (OR) of 27.00 (95% confidence interval [CI]: 24.84–29.15). This finding indicates a strong association between HPV-11 infection and the risk of OSSN (Table 3).

Table 3: *Risk Factors between HPV-11 Infection and OSSN.*

		Control		OR	CI 95%	P-value
		+	-			
Case	+	1	13	27.00	24.84-29.15	<0.01
	-	0	11			

*Statistically significant

Table 4: *Results of Logistic Regression Test of the Relationship between HPV-11 Infection and OSSN Incidence after Controlling for Job Variables in Analysis.*

Variable	*Adjusted OR* (aOR)	CI 95%	p-value
HPV-11 Infection (+)	17.79	1.88 – 167.68	0.012*
Outdoor Occupation	7.36	1.46 – 37.00	0.015*

*Statistically significant

Multivariate logistic regression identified HPV-11 infection and outdoor occupational exposure as significant risk factors for OSSN. HPV-11 infection had an adjusted OR (aOR) of 17.79 (95% CI: 1.88–167.68), indicating that infected individuals had a 17.79-fold higher risk of OSSN compared with those without infection. Outdoor occupation was associated with an aOR of 7.36 (95% CI: 1.46–37.00), suggesting an increased risk of OSSN in individuals with higher environmental ultraviolet exposure (Table 4).

DISCUSSION

In this study, OSSN occurred more frequently in men than in women, consistent with previous research that has shown a male predominance in OSSN cases.[9,10] The mean age of patients with OSSN in this study was similar to that reported in earlier studies, suggesting that the age distribution in our population aligns with global patterns.

The higher prevalence in men is likely attributable to greater cumulative ultraviolet (UV) exposure, often related to outdoor occupational activities.[11] UV radiation is recognized as the most significant environmental risk factor for OSSN, as it causes DNA damage and impairs DNA repair mechanisms.[12] In our cohort, a greater proportion of OSSN patients had outdoor occupations compared with controls, where indoor work was more common. Farming was a frequent occupation among OSSN patients, indicating prolonged sun exposure during peak daylight hours.

Ultraviolet B radiation has also been implicated in HPV reactivation, potentially increasing susceptibility to OSSN. Previous studies have demonstrated significant associations between OSSN, high-risk HPV infection, and a history of intense sun exposure.[11,12] Other research has also linked occupational type and age with more aggressive histopathological subtypes of OSSN.[13] Our findings support this, as outdoor

occupation remained a significant independent risk factor for OSSN after adjusting for other variables.

The HPV-11 was the most common subtype identified in certain OSSN cohorts, with high detection rates also reported for HPV-16 and HPV-18.[7,12,13] In the present study, HPV-11 was detected more often in OSSN cases than in controls. Detection of HPV-11 in normal conjunctiva has been rarely reported, with most studies showing negative results in normal specimens.[7,14,15] Occasional positive findings in histologically normal tissues in other anatomical sites have been interpreted as possible early infection before visible morphological changes occur.[16]

The association between HPV and OSSN remains debated,[17] as some studies have shown no correlation while others report strong links, particularly when multiple HPV genotypes are present.[5,7,17] Our findings indicate a clear association between HPV-11 and OSSN, even though HPV-11 is typically classified as a low-risk subtype. Outdoor occupational exposure and HPV-11 infection both emerged as significant factors associated with OSSN in our analysis similar to earlier studies.[12,13,18]

From a public health perspective, preventive strategies are crucial. OSSN can lead to significant vision loss by affecting the visual axis, inducing corneal astigmatism, or invading deeper ocular and orbital structures, with potential for metastasis.[7,19] HPV vaccination has proven effective in reducing the burden of HPV-related diseases, and incorporating protection against HPV-11 could be considered as part of broader cancer prevention efforts.[19]

This study was conducted in a tropical region with high UV exposure, which may limit the applicability of findings to populations in other climates. Reliance on retrospective data restricted the assessment of certain risk factors, such as HIV status, recreational sun exposure, and sun protection habits. The sampling method may have introduced selection bias, and histopathological confirmation of control tissues prior to molecular analysis was not performed, which could affect accuracy.

Prospective studies should collect primary data, including structured assessments of UV exposure and HIV status, while ensuring histopathological confirmation of control tissues. Matching for occupational variables would improve comparability between groups. Further investigation into the potential role of HPV vaccination in preventing OSSN, especially among individuals with high UV exposure, is warranted.

CONCLUSION

HPV-11 infection and outdoor occupational exposure are both independently associated with an increased risk of OSSN. Although HPV-11 is typically considered a low-risk genotype, its presence in OSSN cases suggests a potential role in disease pathogenesis. Preventive strategies, including public health measures to reduce UV exposure and consideration of HPV vaccination, may help lower the incidence of OSSN, particularly in high-risk populations. Further prospective studies are warranted to clarify causal relationships and to evaluate targeted prevention approaches.

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Patient's Consent: Researchers followed the guidelines set forth in the Declaration of Helsinki.

Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval: The study was approved by the Institutional review board/Ethical review board **(1735/UN14.2.2 VII.14/LT/2024).**

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Authors Designation and Contribution

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