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Ocular surface squamous neoplasia: Population demographics, pathogenesis and risk factors

Authors:
Roland Hollhumer[1,2]
Susan Williams[1]
Pamela Michelow[3]

Affiliations:
[1]Department of Neurosciences, Division of Ophthalmology, University of the Witwatersrand, Johannesburg, South Africa

[2]The Cornea Foundation, Johannesburg, South Africa

[3]Cytology Unit, National Health Laboratory Service and Department of Anatomical Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Corresponding author:
Roland Hollhumer,
hollhumer@gmail.com

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Background: Ocular surface squamous neoplasia (OSSN) is a unifying term used to describe conjunctival intra-epithelial neoplasia, squamous cell carcinoma *in situ* and invasive squamous cell carcinoma.

Aim: The aim of this article was to describe the demographics, clinical features, pathogenesis and risk factors of OSSN.

Method: A literature search was conducted using the search criteria 'ocular surface squamous neoplasia', 'diagnosis', 'epidemiology', 'pathogenesis' and 'risk factors'.

Results: Ocular surface squamous neoplasia is the most common ocular tumour, with incidence rates ranging from 0.01 to 3.4 per 100 000 persons/year. There are two main patterns of disease presentation: older white males in temperate climates where human immunodeficiency virus (HIV) and human papilloma virus (HPV) are not associated; and a younger patient population in tropical climates where HIV and HPV are more prevalent. The pathogenesis primarily revolves around ultraviolet B exposure and HPV infection that cause genetic mutations and uncontrolled cellular proliferation, whilst HIV infection and vitamin A impair tumour surveillance mechanisms. Ocular surface squamous neoplasia is first suspected clinically before formal confirmation of the diagnosis. Morphologically, it can be divided into three groups: placoid, nodular and diffuse. Placoid lesions can further be sub-divided into gelatinous, leukoplakic and papilliform lesions. Nodular lesions have the poorest prognosis, with the highest risk of metastasis and recurrence.

Conclusion: Ocular surface squamous neoplasia is a common ocular tumour associated with ultraviolet radiation, HPV and HIV infection. The pathogenesis revolves around acquired genetic mutations, unregulated cellular proliferation and impaired tumour surveillance mechanisms.

Keywords: conjunctival neoplasm; squamous cell cancer; human immunodeficiency virus; human papillomavirus; ultraviolet radiation.

Introduction

Squamous cell carcinoma of conjunctiva was first described by Von Graefe in 1860. Owing to inconsistency in terminology used in the literature, Lee and Hirst coined the term 'ocular surface squamous neoplasia' (OSSN) in 1995 to describe all conjunctival squamous tumours.[1] These include conjunctival intra-epithelial neoplasia (CIN), squamous cell carcinoma *in situ* and invasive squamous cell carcinoma. Conjunctival intra-epithelial neoplasia lesions are characterised by dysplastic cells that progressively occupy the conjunctival epithelium from the basal layer. When the entire epithelium consists of dysplastic cells with an intact basement membrane, the lesion is called squamous cell carcinoma *in situ*. Once the basement membrane is breached and the substantia propria of the conjunctiva is involved, a diagnosis is made of invasive squamous cell carcinoma.[1]

Ocular surface squamous neoplasia is the most common ocular tumour with an incidence of 0.03–1.9 per 100 000 persons/year in the United States and Australia. In sub-Saharan Africa (SSA), the incidence is 1.6–3.4 per 100 000 persons/year. [1,2,3] The large difference between these two population groups is largely attributed to the human immunodeficiency virus (HIV) pandemic in SSA. The prevalence of disease in Africa is higher in females, which is likely associated with the higher prevalence of human papilloma virus (HPV) and HIV in this cohort. Two main patterns of disease presentation have been identified: older white males in temperate climates, where HIV and HPV are not associated; and a younger patient population in tropical climates, where HIV and HPV are more prevalent.[3] Sub-Saharan Africa falls into the latter category with an estimated HIV infection rate of 13% in South Africa in 2018.[4]

Pathogenesis

The corneal limbus is a transition zone between the conjunctiva and cornea. Stem cells reside in niches in the limbus that are responsible for continuous regeneration of the corneal epithelium and act as a barrier to prevent conjunctivalisation of the cornea. These niches are maximal in the nasal limbus, corresponding to the most common location for the development of OSSN. Ocular surface squamous neoplasia develops from the basal layer of the epithelium to involve full thickness before breaking through the basement membrane to become invasive squamous cell carcinoma. The following three main events characterise the development of OSSN: DNA damage, failed DNA repair and decreased immunity.[5]

DNA damage is the central factor responsible for OSSN and could be divided into genetic and epigenetic damage. Genetic damage primarily involves oncogenes and tumour suppressor genes, whereas epigenetic factors affect cell function and may cause DNA mutations. The two main factors responsible for DNA damage are ultraviolet (UV) radiation and HPV infection. In the UV spectrum, ultraviolet-A (UVA) and ultraviolet-B (UVB) can cause damage. Ultraviolet-A causes damage by inducing production of reactive oxygen species that cause DNA strand breaks. These can be repaired, and no study has found evidence of UVA-induced damage in OSSN. Ultraviolet-B causes damage by cross-linking adjacent bases which results in the formation of cyclobutene pyrimidine dimers (CPD). The most common dimer transition is the CC →TT transition in the *p53* tumour suppressor gene, which results in the loss of its cellular repair mechanism.[5]

Human papilloma virus is a double stranded DNA virus with its global prevalence ranging from 1% to 26%.[6] It is predominantly classified as mucosal and cutaneous types, with the mucosal type further classified into high- and low-risk types according to their association with cervical cancer. It is an epitheliotropic virus with an affinity for transitional mucosal surfaces such as the corneal limbus. To cause infection, the virus requires a break in the epithelial surface, after which it invades the basement membrane, infects the epithelial cells and internalises itself in the cell nucleus. Ultraviolet-B exposure is known to cause reactivation of the virus. Human papilloma virus infection has its primary oncogenic effect by blocking the retinoblastoma and *p53* gene. Functionally, it is divided into the following three regions: the early, late and long-control regions. The early region codes for proteins E1–E7, with E6 and E7 playing an important role in the pathogenesis of OSSN.[7] Under normal conditions, basal epithelial cells leave the cell cycle to migrate across the cornea, E7 causes the cells to remain active in the cell cycle by inactivating the retinoblastoma gene (*pRB*), keeping the cells in a proliferative state. E6 binds to the *p53* gene, suppressing its cellular repair function. Lastly, in high risk HPV types, E6 and E7 cause DNA instability.[5]

DNA repair is maintained by cell cycle checkpoints and the *p53* tumour suppressor gene. The *p53* gene is responsible for arresting cells with DNA damage in the cell cycle. The DNA is then repaired before re-entering the cell cycle, failure to repair damage results in apoptosis. Mutations of the *p53* gene therefore results in DNA instability and failure of the cellular repair mechanism.[5]

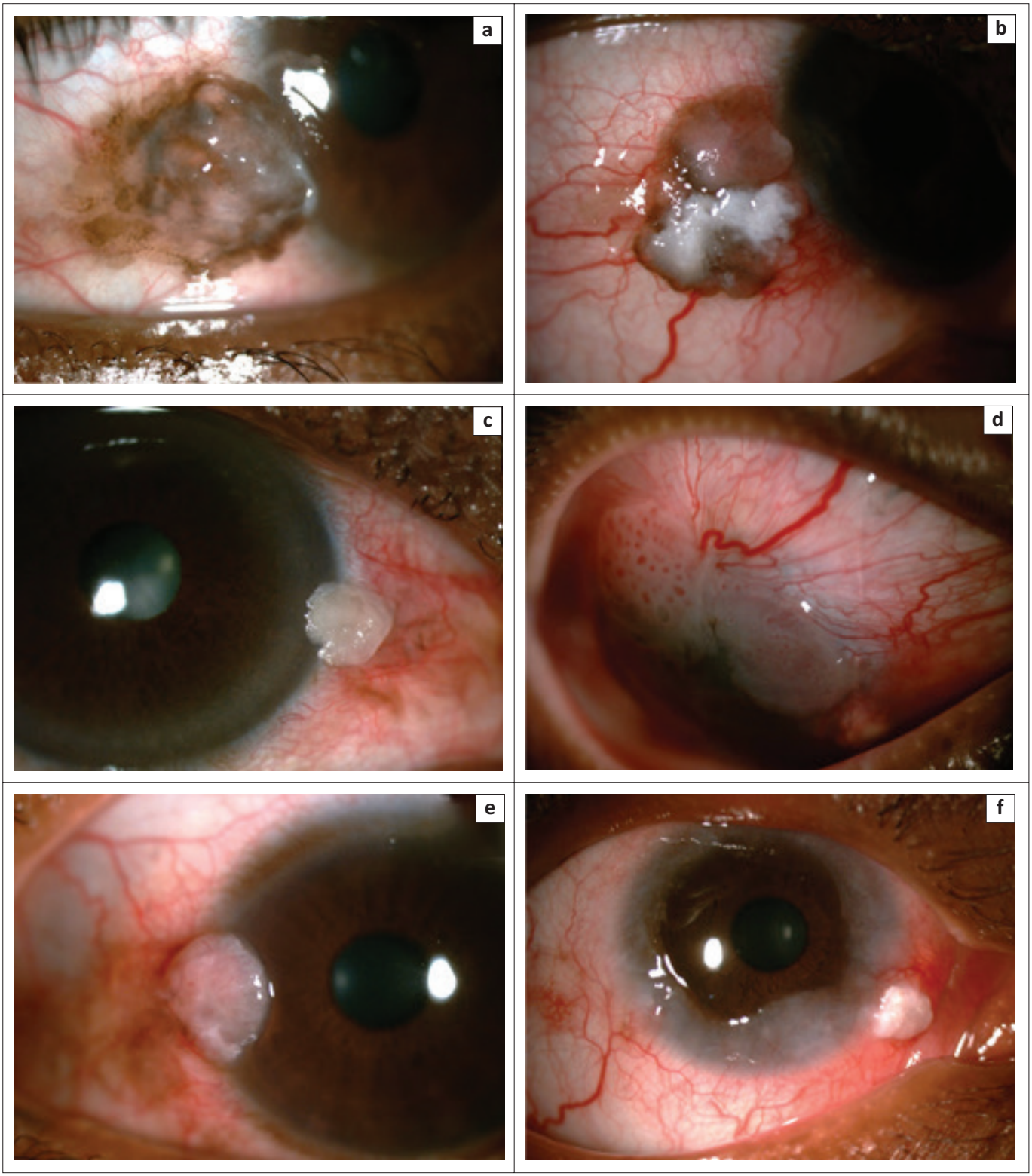
Lastly, the *immune system* is responsible for identifying tumour cells and destroying them. Ultraviolet radiation suppresses cellular immunity and HIV infection reduces immunosurveillance. Human immunodeficiency virus infection also has been associated with increased infection with oncogenic viruses such as HPV and causes a chronic state of inflammation, both of which have oncogenic effects. Vitamin A plays an important role in maintaining the integrity of ocular surface, immune-homeostasis and maintaining normal stem cell differentiation. It is therefore hypothesised that vitamin A deficiency compromises epithelial integrity which allows for HPV invasion and the associated sequelae, impairs cell-mediated immunity and stem cell differentiation.[5] Human immunodeficiency virus infection has been associated with both vitamin A deficiency and HPV infection.[8]

Altogether, the oncogenic process is initiated by UVB radiation that induces genetic and epigenetic damage and activates latent HPV. The oncoproteins from HPV infection prevent the arrest of mutated cells and result in uncontrolled proliferation, whilst HIV infection, UVB and vitamin A deficiency weaken the tumour surveillance mechanism.

Clinical presentation

Ocular surface squamous neoplasia may present with non-specific symptoms such as foreign body sensation, redness, irritation and a variable degree of visual impairment.[1,9] The average duration of symptoms is 3 months and most patients present within 6 months.[1] A growth is noticed by the patient on the eye surface, or only identified on clinical examination. The macroscopic appearance of the lesion is typically raised, well demarcated from the surrounding conjunctiva, and has a variable degree of pigmentation and feeder vessels.[1] In African patients, the lesions can have a greater degree of pigmentation.[3] They are most commonly located at the nasal limbus of the eye, extending onto the adjacent cornea and conjunctiva.[1] Morphologically, OSSN is divided into the following three groups: placoid, nodular and diffused.[2,10] Placoid lesions are further sub-divided into gelatinous, leukoplakic and papilliform lesions. Gelatinous lesions (Figures 1a and 1b) are the most common type with a velvety, tufted vascular appearance. Leukoplakic lesions (Figures 1b, 1c and 1f) have a characteristic white appearance because of large amounts of keratin on the surface. Papilliform lesions (Figure 1d) resemble benign papillomas with a typical frond like appearance. Nodular lesions (Figure 1e) are circumscribed rapidly by growing nodules that invade the adjacent conjunctiva. They are less common, with a higher risk of metastasis and recurrence. Diffused lesions (Figure 1f) are the rarest form of OSSN; they are flatter and fimbricated, covering a larger surface area of the cornea and conjunctiva. These may initially be misdiagnosed as chronic conjunctivitis,

pannus or limbal stem cell failure.[1,11] Corneal extension of OSSN is seen clinically as a progressive superficial grey epithelial opacity.[10,12] The masses are usually mobile, with a fixed lesion suspicious of invasive squamous cell carcinoma where direct invasion is the primary form of spread.[9] At presentation, scleral invasion has been found in 30% – 37%, intra-ocular invasion in 11% and orbital extension 11% – 15%.[13,14] Ocular surface squamous neoplasia is staged by the American Joint Committee on Cancer according to the tumour, node, metastasis (TNM) classification (Table 1).[15] Important nuances of this classification include: all CIN lesions fall into the tumour *in situ* (Tis) stage; only



Source: Photos courtesy of Dr Roland Höllhumer

FIGURE 1: Anterior segment images of ocular surface squamous neoplasia morphology. (a) Gelatinous, (b) gelatinous with an area of leukoplakia, (c) leukoplakic, (d) papilliform, (e) nodular, (f) diffused with an area of leukoplakia.

invasive squamous cell carcinoma is staged from T1–T4; corneal extension of a lesion does not imply invasion; invasion of the cornea only occurs if there is a breach in Bowman's membrane (seen on ultra-sound biomicroscopy or at surgery).[16] The differential diagnosis for OSSN and their differentiating features are highlighted in Table 2.

Risk factors

The leading risk factors for the development of OSSN are UVB radiation exposure and infection with HPV.[2] Other predisposing factors include cigarette smoke exposure, vitamin A deficiency, ocular surface injury, chronic ocular inflammation (e.g. allergic conjunctivitis), exposure to petroleum chemicals, chronic viral infections (hepatitis B and C, HIV) and immunodeficiency.[2,20,21] With a poorly understood pathophysiology, the aetiology is most likely multifactorial.

Ultraviolet-B

Ultraviolet-B is the main risk factor for OSSN by causing DNA mutations, activating latent HPV and impairing cancer immunosurveillance.[5] It has been found that spending more than 50% of time outdoors in the first 6 years of life, living within 30° of the equator, having fair skin and pale irides are risk factors for UVB-induced OSSN.[1] Newton et al. found a clear association between UVB exposure and OSSN, with 49% decrease in the incidence of disease for every 10° increase in latitude.[22] These lesions occur most commonly at the nasal limbus because of the focussing effect of the cornea on temporal incident light, which increases light intensity by a factor of 20.[23] A Kenyan cohort of predominantly HIV positive participants showed that greater time spent in the sun (6.9 h/day vs. 4.6 h/day, $p < 0.001$) was found to be associated with OSSN, and the use of hats or caps had a protective effect (odds ratio (OR): 0.22, 95% confidence interval (CI): 0.07–0.67). Sunglasses were not shown to offer any protection, which is most likely attributed to the lack of protection from temporal incident light.[20] A United States study of predominantly immune competent adults similarly found an association with patients in latitudes of less than 35° and a higher erythemal exposure rate of > 170, indicating an association between OSSN and UV exposure.[24] Clear et al.[25] found an increased incidence of OSSN in patients within 30° of the equator in Malawi. This association was made in African patients before the onset of HIV pandemic, highlighting the importance of UVB and the compounded effect of the two associated factors.[25,26]

TABLE 1: American Joint Committee on Cancer staging for ocular surface squamous neoplasia.

T category	T criteria
TX	Primary tumour cannot be assessed.
T0	No evidence of primary tumour.
Tis	Carcinoma *in situ*.
T1	Tumour (≤ 5 mm in greatest dimension) invades through the conjunctival basement membrane without invasion of adjacent structures.
T2	Tumour (> 5 mm in greatest dimension) invades through the conjunctival basement membrane without invasion of adjacent structures.
T3	Tumour invades adjacent structures (excluding the orbit).
T4	Tumour invades the orbit with or without further extension.
T4a	Tumour invades orbital soft tissues without bone invasion.
T4b	Tumour invades bone.
T4c	Tumour invades adjacent paranasal sinuses.
T4d	Tumour invades brain.

Source: Amin MB, Edge SB, Greene FL, et al., editors. AJCC cancer staging manual. Cham: Springer; 2017. https://doi.org/10.1007/978-3-319-40618-3

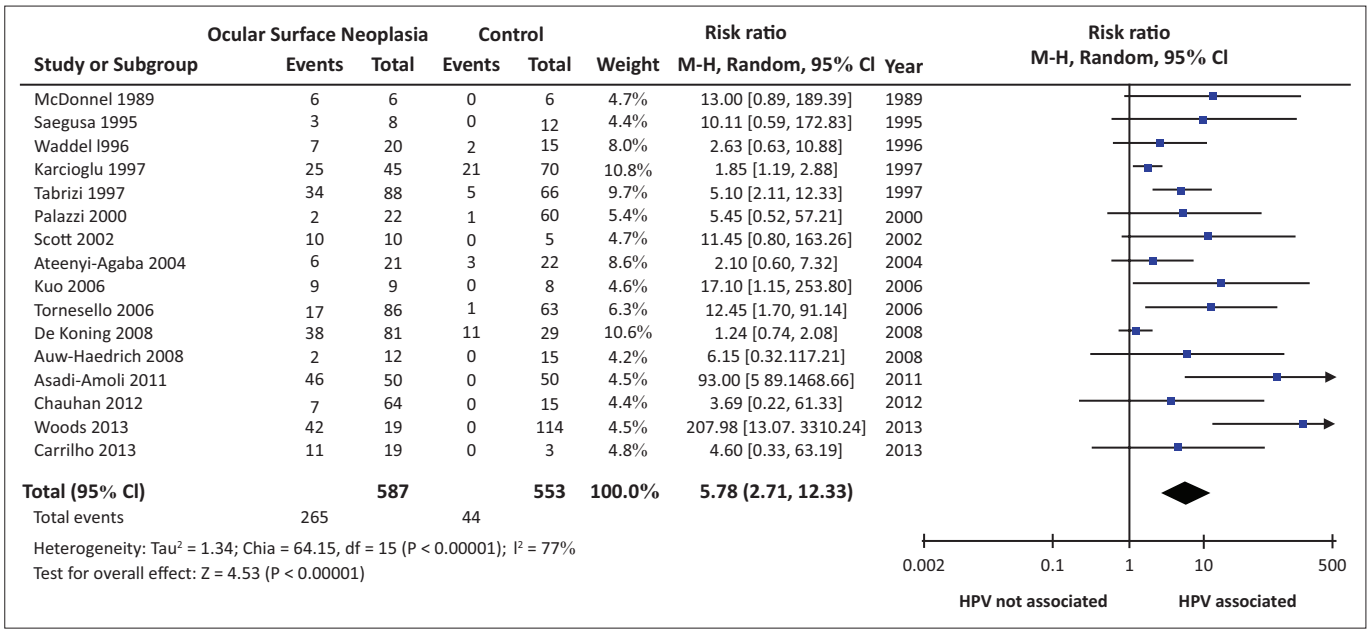
Human papilloma virus

Human papilloma virus has been described as a risk factor for the development of OSSN and can be detected with immunohistochemistry, *in situ* hybridisation and polymerised chain reaction (PCR) (in order of increasing sensitivity).[27] This association was first made by McDonnel et al.[28] in 1989, when HPV16 was found in 100% ($n = 6$) of OSSN lesions. This was followed by numerous studies that investigated association between mucosal HPV and OSSN. The results of these studies were inconsistent, with an association found in 0 to 100% of cases with an average prevalence of 34%.[7,28,29,30,31,32,33,34] Most studies have found an association with HPV 16 and HPV 18, although most studies only looked for the mucosal types based on the association between cervical cancer and HPV. Ateenyi-

TABLE 2: Differential diagnosis of ocular surface squamous neoplasia and its distinguishing features.

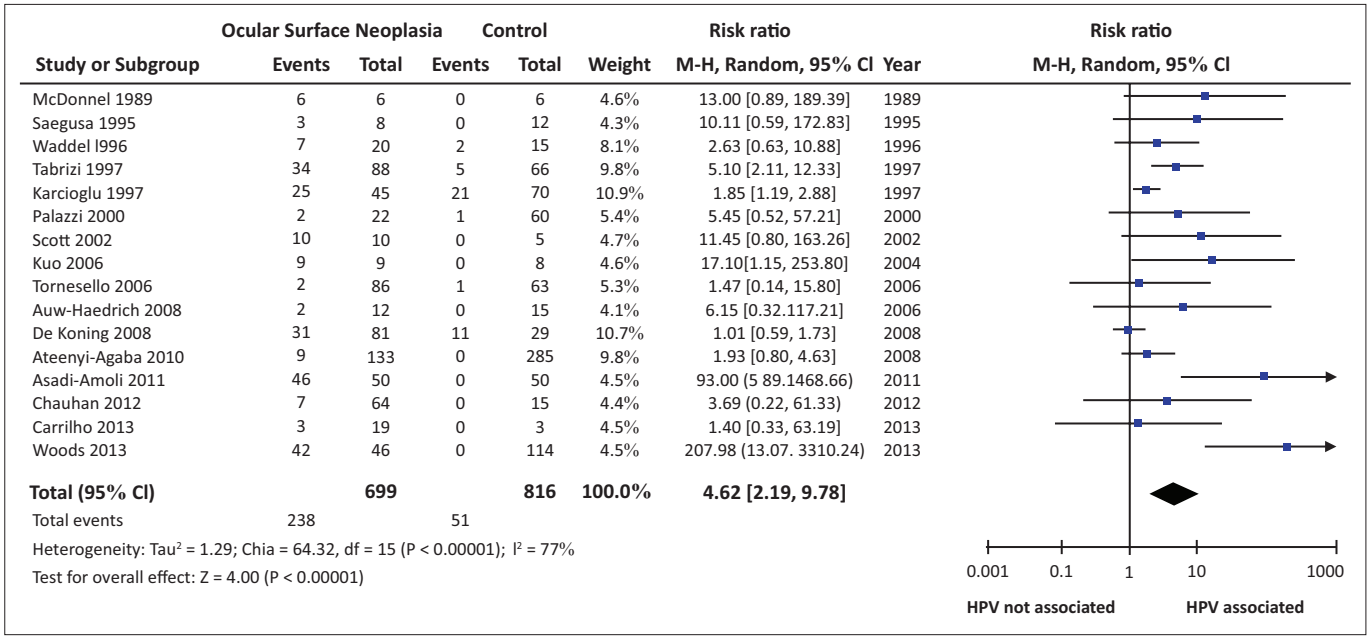
Condition	Distinguishing features
Pterygium	A benign fibrovascular wing-like growth of the conjunctiva that develops at the limbus in the palpebral fissure and extends onto the cornea.[17]
Pingueculum	A benign fibrovascular growth of the conjunctiva that develops at the limbus in the palpebral fissure without corneal extension.[17]
Papilloma	Occurs in younger patients as a fleshy pink mass with frond-like projections. May be present anywhere on the ocular surface, not only at the limbus. May need histology to distinguish from OSSN.[1,12]
Hereditary benign intraepithelial dyskeratosis	A heritable condition characterised by fleshy perilimbal plaques that can also be found in the buccal mucosa.[18]
Nevus	Mostly a pigmented lesion that occurs in younger patients. Located in the interpalpebral zone from the limbus to the caruncle. May have cysts and become inflamed or increase in size during puberty.[1,12]
Malignant melanoma	Mostly arises from pre-existing primary acquired melanosis. The lesion has a smooth surface and can be pigmented or amelanotic.[1,18]
Pyogenic granuloma	A fleshy, red, vascular mass that occurs after surgery or trauma. Responds well to topical steroids and beta-blockers.[12,19]
Dermoid	A congenital yellow-white mass that typically occurs at the infero temporal limbus. Often contains fine hair on slit lamp examination.[18]
Lympho-proliferative conditions	Typically presents as a painless pink mass, classically called a salmon patch.[12]
Pseudo-epitheliomatous hyperplasia	Rapidly growing leukoplakic lesion of the conjunctiva.[1] Usually associated with a pre-existing condition such as pterygium or pingueculum.[12]
Pannus	Fibrovascular tissue extending onto the cornea from the limbus. Not limited to the interpalpebral zone[17]
Limbal stem cell failure	Loss of limbal stem cells, resulting in a compromised corneal epithelium and loss of the limbal barrier function with peripheral corneal neovascularisation.[17]

OSSN, Ocular surface squamous neoplasia.



Source: Created with Review Manager (RevMan) [Computer program], version 5.3. The Nordic Cochrane Centre, Copenhagen, The Cochrane Collaboration, 2014
CI, confidence intervals; HPV, human papilloma virus.

FIGURE 2: Forest plot showing the risk ratio of mucosal and cutaneous human papilloma virus as an association with ocular surface squamous neoplasia. The overall risk ratio was 5.78 and 95% confidence interval: 2.71–12.33, with high heterogeneity of studies.

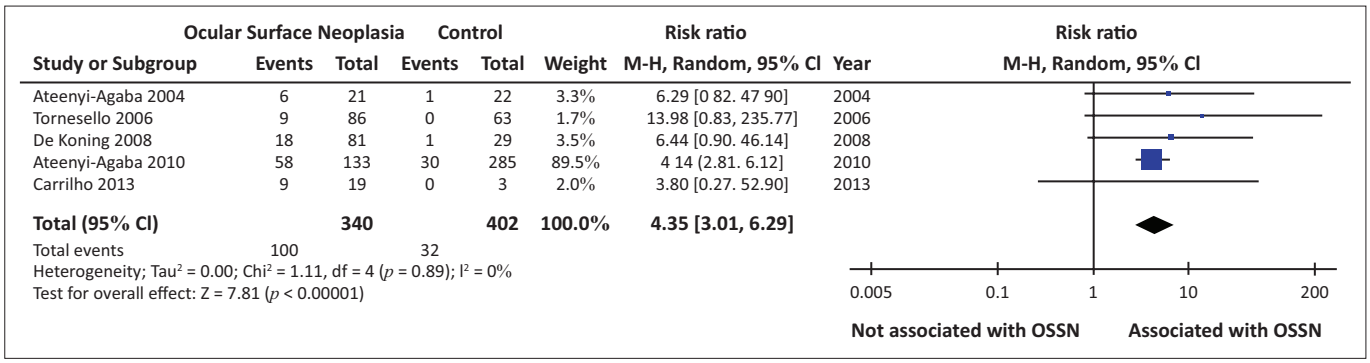


Source: Created with Review Manager (RevMan) [Computer program], version 5.3. The Nordic Cochrane Centre, Copenhagen. The Cochrane Collaboration, 2014
CI, confidence intervals; HPV, human papilloma virus.

FIGURE 3: Forest plot showing the risk ratio for mucosal human papilloma virus as an association with ocular surface squamous neoplasia. The overall risk ratio was 4.62 and 95% confidence interval: 2.19–9.78, with a high heterogeneity of studies.

Agaba et al.[35] was the first to investigate and find an association between cutaneous HPV and OSSN. They used PCR to identify the presence of mucosal and cutaneous subtypes in 21 OSSN lesions and 22 controls, finding no association between mucosal HPV and OSSN (vs. 9% of controls) but found cutaneous HPV in 86% of OSSN cases (vs. 36% of controls). This finding was repeated in subsequent studies and the subtypes 5 and 8 were found to have the highest association.[36,37] Studies following this have investigated both mucosal and cutaneous HPV types but without consistent results.[27,28,29,33,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53]

Figures 2–4 show an association between HPV and OSSN, with results from studies investigating mucosal HPV showing a high degree of heterogeneity, whilst the results from studies of cutaneous HPV group have low heterogeneity. This may suggest a more consistent association between cutaneous HPV and OSSN, although the study numbers are smaller. The inconsistent association may be attributed to several factors, including patient selection, HPV prevalence pattern, sample handling, testing methodology and the assays used.[20] Commercial testing kits are freely available for mucosal



Source: Created with Review Manager (RevMan) [Computer program], version 5.3. The Nordic Cochrane Centre, Copenhagen. The Cochrane Collaboration, 2014

CI, confidence interval; OSSN, ocular surface squamous neoplasia.

FIGURE 4: Forest plot showing the risk ratio for cutaneous human papilloma virus as an association with ocular surface squamous neoplasia. The overall risk ratio was 4.35 and 95% CI: 3.01–6.29, with a low heterogeneity of studies.

subtypes of HPV but limited for cutaneous HPV types. Many studies therefore only tested for limited types but earlier studies favoured the mucosal types. Altogether, this has resulted in inconsistent reports and uncertainty on the role of different types of HPV in the pathogenesis of OSSN.[3] The different HPV types are relevant when considering public health immunisation programmes and their impact on cancer prevention. Current HPV vaccines only cover mucosal types and would therefore not offer any protection if cutaneous HPV is the leading associated type.

Human immunodeficiency virus

Ocular surface squamous neoplasia is recognised as an acquired immune deficiency syndrome (AIDS)-related cancer with 60% – 77% of patients with OSSN in Africa infected with HIV. In endemic countries, it has been found to be the presenting feature of HIV infection in 50% – 86% of patients.[3,9,54,55] There has been a steady increase in the incidence of OSSN with the onset of the HIV pandemic. This has been reported in the United States, Tanzania, Zimbabwe and Uganda, where the incidence of OSSN increased sixfold between 1970 and 1988.[3,56] Human immunodeficiency virus increases the risk of OSSN by 8–19-fold, with the highest risk in the first 2 years of AIDS.[3,9,32] The association is assumed to be related to decreased immunosurveillance and increased oncogenic viral infections (HPV); however, this risk has been found to be independent of HIV category, CD4 count and duration of infection.[3,9,49] A study conducted by Gichuhi et al.[20] found a strong association with HIV positive patients not on highly active antiretroviral therapy (HAART) (OR: 48.42, 95% CI: 7.73–303.31), compared to patients on HAART, who were at a lower risk (OR: 19.16, 95% CI: 6.60–55.57). Although incidence of OSSN does not have a linear relationship with CD4 count, it was also found that a CD4 count of less than 500/mm^3 was associated with an increased risk of OSSN, and a CD4 count of more than 500/mm^3 inferring no additional risk. Human immunodeficiency virus is probably not an isolated risk factor, as 30% of OSSN in SSA is not associated with HIV.[20] Age of onset is incongruent between studies, with some studies showing an earlier age of onset in HIV positive individuals, whilst others show no difference.[57] Human immunodeficiency virus patients are shown to have an increased severity of OSSN, greater likelihood of bilaterality, worse prognosis and a higher chance of recurrence.[20,54,57,58]

Other associated factors

Vitamin A is required for the normal health of mucosal membranes, and a deficiency thereof has been associated with the development of OSSN.[10] Gichuhi et al.[20] found lower median retinol levels in OSSN patients when compared with controls (44.9 ug/dL vs. 51.0 ug/dL, p = 0.03). Vitamin A is stored in the liver and released to maintain constant serum levels.[17] Although vitamin A deficiency is caused by decreased dietary intake, it has been also associated with HIV infection.[8] Artificially low vitamin A levels have been found during HIV seroconversion, which do not respond to vitamin A supplementation. It is therefore useful to review C-reactive protein levels when interpreting serum vitamin A levels.[8,59]

Smoking is commonly cited as a risk factor for OSSN. This is based on a small case control study comprising 38 participants, which found an association between cigarette smoking and OSSN.[21] Gichuhi et al.[20] found no association in a case control study conducted in Kenya. Similarly, no association was found in a study conducted in India.[57]

Chronic ocular inflammation is a risk factor for OSSN. A strong association between allergic conjunctivitis and OSSN (OR: 30.78, 95% CI: 4.05–234) was described in a case control study conducted in Kenya. Vernal keratoconjunctivitis (VKC) is common in Africa, with prevalence rates of up to 40% found in school-going children. Vernal keratoconjunctivitis in Africa also tends to be of limbal type. It is thought that this chronic inflammation and/or the use of topical steroids could predispose to mutations in the limbal cells and cause local immunosuppression that predisposes to OSSN.[20]

Exposure to petroleum products is a risk factor for developing OSSN, as described by a small case control study comprising 38 participants. The retrospective study sent out questionnaires to patients with proven OSSN, which showed a relative risk of 2.46 in participants that had exposure to oil, gasoline or grease.[21]

Immunosuppression in post-organ transplant patients has been reported to increase the risk of HPV-induced malignancies. This has been reported in a case report of OSSN in a renal transplant patient.[60] Ocular surface squamous neoplasia has also been associated with leukaemia and lymphoma.[1]

Xeroderma pigmentosum is a condition characterised by an increased susceptibility to UV-induced DNA damage (by the formation of pyrimidine dimers) with impaired DNA repair mechanism. Patients with this condition are at an increased risk of cutaneous and conjunctival malignancies.[1] A case series in India of 14 patients with xeroderma pigmentosum and OSSN was presented with a median age of 12 years. At presentation, 43% of the patients had invasive squamous cell carcinoma and the overall recurrence rate for the series was 64% with a combination of medical and surgical therapy.[61]

Conclusion

Ocular surface squamous neoplasia is the most common ocular tumour, with the highest incidence found in SSA. Ultraviolet-B exposure is the primary risk factor, with HPV, HIV and vitamin A deficiency playing contributory roles. The role of HPV remains poorly defined because of heterogeneity between studies. The HIV pandemic has resulted in an increased incidence as well as severity and higher risk of recurrence of this disease.

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Competing interests

The authors have declared that no competing interests exist.

Authors' contributions

R.H. is the primary author of this work. S.W. and P.M. contributed to the development, academic content and review of this work.

Ethical considerations

This article followed all necessary ethical standards.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Disclaimer

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