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Human papilloma virus vaccination and incidence of ocular surface squamous neoplasia

Joy N. Carroll, M.D.[#a], **Zachary I. Willis, M.D., M.P.H.**[#b], **Annabelle de St Maurice, M.D., M.P.H.**[b], and **Sahar Kohanim, M.D., M.P.H.**[a]

[a]Vanderbilt Eye Institute, Vanderbilt University Medical Center, Nashville, TN.

[b]Department of Pediatrics, Division of Infectious Diseases, Vanderbilt University Medical Center, Nashville, TN.

[#] These authors contributed equally to this work.

I: Ocular Surface Squamous Neoplasia

Ocular surface squamous neoplasia (OSSN) includes a range of disease from mild dysplasia to carcinoma in situ and invasive squamous cell carcinoma. Affected sites include the conjunctiva, limbus, and cornea. Terminology varies and designations of invasive, pre-invasive and benign OSSN have been proposed.[1] Clinically, OSSN may present as an elevated mass or irritation with blood vessel tufts.[1] The appearance may be gelatinous, papillomatous or leukoplakic.[1,2] Location is most frequently the interpalpebral nasal limbus.[3,4]

Epidemiology

The incidence of OSSN varies by geographic region. A 2013 meta-analysis determined the incidence of squamous cell carcinoma of the conjunctiva and cornea using data from the International Agency for Research on Cancer. Despite limitations to the surveillance data, the authors estimated the global age-standardized incidence of ocular squamous cell carcinoma of 0.18 cases per year per 100,000 males, and 0.08 cases per year per 100,000 females. However, in Africa, the annual incidence was far greater, estimated to be 1.38 cases per 100,000 males and 1.18 cases/100,000 females. After Africa, incidence was greatest in Central and South America, followed by Oceania, North America, Asia, and lowest in Europe, with 0.05 and 0.01 cases per year per 100,000 males and females respectively.[5] In a retrospective study of veterans in Florida, the prevalence of OSSN was 0.1%.[6] Ethnicity may play a role as well, as a study in the United States identified Hispanic race as a risk factor but did not control for secondary factors such as geographic location or occupational sun exposure.[7]

Risk factors for OSSN include ultraviolet (UV) radiation exposure; immunocompromising conditions, in particular human immunodeficiency virus (HIV) infection; and HPV infection. The role of HPV will be discussed later. Presence of pterygium has also been

Corresponding Author Sahar Kohanim, M.D., M.P.H., Vanderbilt Eye Institute, 2311 Pierce Avenue, Nashville, TN 37232, sahar.kohanim@vanderbilt.edu, Tel: 615-936-2020, Fax: 615-936-1540.

associated with OSSN.[6] Some studies have shown associations of OSSN with sun exposure.[8] In a case-control study of 318 cases of ocular surface carcinoma in situ and squamous cell carcinoma in Uganda, direct sun exposure of two hours or greater per day was a statistically significant risk factor.[9] An Australian case control study found a strong association between skin cancer diagnosed before age 50 and development of OSSN.[10] Other statistically significant risk factors included a history of solar keratoses, significant sun exposure as a young child (measured as spending >50% of time outdoors prior to age 6), and proximity to the equator (measured as cumulative time spent within 30 degrees of the equator).[10,11]

Because HIV infection and acquired immunodeficiency syndrome (AIDS) have been associated with increased incidence of both AIDS-defining cancers and other malignancies,[12,13] HIV has been extensively studied as a risk factor for the development of OSSN. HIV infection has been associated with increased incidence of OSSN in multiple studies.[12,14-1718-22] HIV-infected individuals develop OSSN at a younger age and present at a more advanced stage compared to those without HIV.[23-25] The incidence of OSSN in HIV positive individuals correlates inversely with CD4+ T cell count, leading some investigators to hypothesize that antiretroviral therapy may decrease the risk of OSSN.[26] The role of immunologic dysfunction in the development of OSSN in supported by the observation that immunosuppression due to organ transplantation also increases the risk of OSSN.[27]

Classification

OSSN is classified as benign, pre-invasive and invasive. The benign category includes papillomas, benign hereditary intraepithelial dyskeratosis and pseudoepitheliomatous hyperplasia. Neoplastic lesions that remain intraepithelial are defined as pre-invasive. There are three grades of pre-invasive OSSN. Grades I, II and III dysplasia correspond to dysplastic cells located in the outer, outer and middle, and entire epithelial layer, respectively. Grade III pre-invasive OSSN is synonymous with carcinoma in situ. Invasive OSSN is characterized by dysplastic cells extending beyond the epithelium past Bowman's layer and into the stroma.[1]

Pathogenesis

The pathogenesis of OSSN is an area of active inquiry, as a better understanding of the mechanism of disease may lead to improved methods of prevention and treatment. Proposed theories of carcinogenesis include dysregulation of limbal stem cells and alterations in transcription factor activation due to phosphorylation of receptor sites for cytokines and growth factors.[28] Ultraviolet light, specifically UVB radiation (290-320 nm wavelength), may damage DNA by forming dimers through crosslinking, resulting in disruption of DNA polymerase function.[29] Furthermore, ultraviolet radiation exposure may contribute to reactivation of HPV infection.[4]

Mutation of p53, with resultant dysregulation of tumor suppression, has been identified in a portion of OSSN cases.[30] HPV may contribute to OSSN pathogenesis is through the formation of a protein complex between the HPV E6 protein and the host p53 protein product, which results in inhibition of the p53 tumor suppressor action.[31]

UV radiation induces mutagenesis through base dimer formation,[29] and may induce transcription of HPV proteins E6 and E7. In cells that harbor latent HPV infection these proteins may lead to formation of potentially premalignant papillomas.[32]

Treatment

Surgery has historically been the mainstay of treatment. In a case series of 397 cases of corneal or conjunctival squamous cell carcinoma (SCC) or conjunctival intraepithelial neoplasia (CIN) in Uganda, a standardized surgical excision with 3mm margins or excision to the limbus of conjunctival lesions and shallow keratectomy or epithelial sharp dissection for lesions involving the cornea resulted in a recurrence rate of 3.2% over a median 32-month follow-up period.[3] Other reported rates of recurrence have been significantly higher, with 5% recurrence with margins clear of tumor and 53% recurrence with dysplastic or tumor cells present at the surgical margin.[2] Cryotherapy has been employed simultaneously with surgery.[33]

In addition, topical chemotherapy has also been used, both for debulking prior to surgical excision[34] and as an adjuvant to surgery. In a case series of thirteen immunocompromised patients with ocular squamous cell carcinoma, interferon alpha-2b and mitomycin C were used in combination with surgery. The patients in this study who received interferon alpha-2b and surgical excision did well with no recurrence of tumor.[24] However, only five patients received this treatment and follow-up was limited to a mean of ten months.

Nonsurgical therapy of OSSN with interferon alpha-2b has shown promise with a recent study demonstrating no statistical difference in recurrence rates between patients treated with interferon therapy and surgical excision.[33] The rate of tumor resolution through treatment of carcinoma in situ with interferon alpha-2b has been as high as 92%.[35] Interferon alpha-2b is a chemotherapeutic agent with uses in other cancer treatment regimens such as renal cell carcinoma.[33] Interferon alpha-2b has been applied via topical eye drops, subconjunctival injection, or both.[33] Potential benefits of topical therapy include avoidance of surgery and a theoretical decrease in the risk of symblepharon formation. However, no symblepharon formation occurred in either surgical or medical intervention groups in a 2014 case review comparing surgical and medical therapy.[33] Side effects of discomfort, conjunctivitis and irritation, and corneal epithelial defects have been reported.[33] The presence of HPV did not affect the rate of treatment failure of interferon alpha-2b in OSSN.[36]

No high-quality clinical trials of OSSN treatment in HIV-infected patients have been performed, therefore more research is needed to determine efficacy.[37]

Outcomes of OSSN

With therapy, the prognosis for OSSN is good. The rate of metastasis is <2%, with a 5% local recurrence rate.[38] Untreated OSSN can result in extension into the globe, orbit, or distant metastasis.[25] Management of larger tumors includes enucleation, for tumors extending into the eye, and exenteration, for those invading the orbit.[25] In a case-control study of 200 patients, the tumor was more likely to present as Stage IV (defined as invasion of the orbit) or to recur in patients with HIV than in immunocompetent patients.[25] In

immunocompromised patients, death has been reported as a result of aggressive recurrence with squamous cell carcinoma invasion of the brain.[38] For patients with HIV, antiretroviral therapy is likely to be beneficial, as evidenced by a case report of a patient with biopsy-proven squamous cell carcinoma of the conjunctiva with orbital invasion in whom total regression and resolution of the tumor occurred following antiretroviral therapy alone.[39]

II. Human Papillomaviruses

As noted above, HPV has been implicated in the pathogenesis of OSSN. Papillomaviruses cause infection in a wide range of vertebrate species, but they are species-specific. Papillomaviruses are nonenveloped, with an icosahedral capsid enclosing a double-stranded DNA genome.[40] HPVs are typed based on genotypic homology of the genome segment encoding the major capsid protein. There are at least 184 known HPV types.[41]

Common benign manifestations of HPVs include common warts, anogenital warts, recurrent respiratory papillomatosis, and oral squamous cell papillomas. HPV types can be grouped by propensity to cause infection at either cutaneous (e.g., common warts) or mucosal sites (e.g., anogenital warts). Mucosal types can be further divided into those associated with high or low risk of malignant transformation. The prototypical HPV-associated malignancy is cervical carcinoma;[42] HPV types 16 and 18 account for 71% of invasive cervical cancer lesions worldwide.[43] Additional high-risk HPV types include 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 67, 68, 73, and 82.[41]

The causal link between HPV and cervical carcinoma was established via several lines of evidence. Cervical carcinoma was observed to be less common in Catholic nuns;[44] conversely, a positive association has been noted between number of lifetime sexual partners and risk of cervical cancer.[45] These and similar observations suggested a sexually transmitted risk factor for cervical cancer. In one meta-analysis, infection with high-risk HPV types was associated with a relative risk for cervical squamous cell carcinoma of 189 (95% confidence interval: 133-267).[45] The magnitude of this risk far exceeds other putative risk factors. Prospective studies have found that persistent infection with high-risk HPV types is the primary risk factor for the development of cervical intraepithelial neoplasia.[46] Finally, receipt of HPV vaccination has been associated with a decreased risk of cervical cellular atypia and cervical intraepithelial neoplasia.[47]

In addition to epidemiologic studies, the biology of high-risk HPV types supports their oncogenic potential. The viral proteins E6 and E7 act cooperatively by numerous mechanisms to promote integration of foreign DNA into the cellular genome and immortalize human cells, and these proteins are consistently expressed in lesions.[48] Furthermore, xenografts of human foreskin infected with HPV type 16 develop intraepithelial neoplasia in severe combined immunodeficiency mice.[49]

Taken together, these data strongly suggest a causal role of high-risk HPV types in cervical cancer. In addition, oncogenic HPV types have been convincingly implicated in oropharyngeal,[50] anal,[51,52] vulvar,[52] vaginal,[52] and penile cancers.[53] Relationships between HPV and esophageal squamous cell carcinoma,[54] sinonasal carcinoma,[55] lung cancer,[56] and

breast cancer,[57,58] have been posited, but the role of HPV remains controversial. The putative role of HPV in the pathogenesis of ocular squamous surface neoplasia is discussed below.

III: Role of HPV in OSSN

The mechanism by which HPV infection may lead to the development of dysplasia and carcinoma is under investigation. HPV is present in some cases of OSSN, but not all, and is likewise present in a portion of normal tissue biopsies in many studies. HPV is not necessary or sufficient to cause OSSN, but may contribute to tumorigenesis.

A 2013 meta-analysis demonstrated that the relative risk of OSSN is increased with the presence of HIV and cutaneous HPV subtypes. Of sixteen studies identified that address mucosal HPV and OSSN, only five studies addressed both cutaneous and mucosal HPV subtypes in association with OSSN. In those five studies, there was no significant risk associated with mucosal HPV subtype infection and OSSN.[16]

A meta-analysis of the prevalence of HPV in pterygia and OSSN estimated prevalence of 18.6% in pterygia and 33.8% in OSSN. [59] This review was limited by the variation in methodology across the studies, the lack of controls in some studies, and the inconsistent definition of the study population. Among these reports, HPV prevalence ranged from 0 to 100% for both pterygia and OSSN, suggesting a high risk of bias within the source literature.[59] A table summarizing the original literature, which consists of case-control studies and case series, is shown in Table I.

Of the thirty-four studies reviewed, HPV was detected in at least one case of OSSN in 27 studies (79%). Comparison across studies is limited due to differences in viral detection methods, which likely results in highly variable sensitivity. Methods of detection of HPV included polymerase chain reaction (PCR) with various primers specific for broad reading frames present in all strains of HPV, or with primers specific to fewer HPV strains, or immunohistochemistry with enzyme-linked immunosorbent assay (ELISA). The tissue tested was frequently paraffin embedded or frozen, although one study employed conjunctival swabs of living tissue. Positive and negative controls were variably employed in these studies.

IV. Vaccination for Human Papillomaviruses

In 1992, Kirnbauer et al. discovered that the major capsid protein of HPV, L1, assembled itself into a particle closely resembling the intact virion and that this virus-like particle (VLP) induced neutralizing antibody responses in rabbits.[90] After these findings were confirmed in other mammals, a human study found that HPV-11 VLP induced high specific antibody titers in women, and the sera of women with high-titer responses neutralized HPV-11.[91] A Phase II trial of HPV-16 VLP confirmed immunogenicity and safety with and without an adjuvant.[92] This was followed by a randomized controlled trial demonstrating 100 percent efficacy by vaccination with HPV-16 VLP in preventing persistent HPV-16 infection.[93]

Subsequent clinical trials demonstrated the efficacy of a bivalent vaccine containing HPV types 16 and 18[94] and a quadrivalent vaccine containing HPV types 6, 11, 16, and 18.[95] The quadrivalent vaccine, developed by Merck and marketed as Gardasil, was approved by the Food and Drug Administration (FDA) in 2006 for use in females between 9 and 26 years of age.[96] The bivalent vaccine, developed by GlaxoSmithKline and marketed as Cervarix, was approved by the FDA in 2009 for use in females aged 10 through 25 years of age.[97] Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP) Both vaccines are administered on a three-dose schedule, with the second dose given 1-2 months after the first and the third dose given 6 months after the first. The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommended vaccination of girls aged 11 or 12 years with catch-up vaccination recommended up to age 26; no preference was expressed for either product.[97]

A randomized trial of boys and men between 16 and 26 years of age demonstrated efficacy of quadrivalent vaccine in the prevention of genital infection with HPV types 6, 11, 16, and 18.[98] In 2009, quadrivalent HPV vaccine was licensed by the FDA for use in males. The ACIP subsequently recommended routine vaccination of males aged 11 or 12 years with catch-up vaccination recommended between ages 13 and 21 and an option between ages 22 and 26.[99]

A 9-valent HPV vaccine, adding types 31, 33, 45, 52, and 58 to the quadrivalent vaccine, was demonstrated to have efficacy of 96.7% in protecting against the newly added types and generated antibody responses equivalent to those generated by quadrivalent vaccine against types 6, 11, 16, and 18.[100] The 9-valent vaccine, developed by Merck and marketed as Gardasil 9, was approved by the FDA in 2014.[101] The ACIP recommended routine vaccination of both males and females at age 11 or 12 years and catch-up vaccination of females through age 26 years and males through age 21 years. Females can be vaccinated with either of the three available vaccines, while it is recommended that males receive either quadrivalent or 9-valent vaccine. In addition, it is recommended that immunocompromised persons and men who have sex with men receive either quadrivalent or 9-valent vaccine up through age 26 years.[101]

All three approved HPV vaccines are generally safe. Injection-site pain, redness, and swelling are common for all three vaccines, as are low-grade fever and headache.[96,97,101] Syncope following vaccination has been described for the bivalent and quadrivalent vaccines.[97,102] No other adverse events have been reported to occur at rates above the expected baseline.[102,103]

Follow-up studies of bivalent HPV vaccine and of quadrivalent HPV vaccine have demonstrated persistent seropositivity and vaccine effectiveness after 9 years[104] and 8 years, [105] respectively. Further inquiries into the duration of protection are ongoing.

Several ecological studies of the public-health effect of HPV vaccination programs have been conducted. National studies have demonstrated declines in detection of targeted HPV vaccine strains from cervical samples[106,107] and in diagnosis of HPV-related benign genital

lesions.[108-110] An ecological study in Australia found that, during the three years following introduction of quadrivalent HPV vaccination, the incidence of high-grade cervical abnormalities declined in females less than 18 years of age but not in older females.[111]

In addition to these ecological studies, receipt of HPV vaccination has also been linked to decreased risk of cervical dysplasia.[47,112113] A systematic evidence review concluded that the incidence of infections due to vaccine-strain HPV, incidence of anogenital warts, and incidence of cervical dysplasia were declining and that the decline was likely due to HPV vaccination programs.[114] No evidence is yet available about the effect of HPV vaccination on the incidence of cervical cancer or other HPV-related cancers.

V: Potential Role of HPV vaccine in OSSN

The commercially available HPV vaccines discussed above provide protection against many of the HPV strains associated with OSSN. Although not all associated strains are targeted by the vaccines, a degree of cross-protection against HPV strains not specifically targeted by the available vaccines has been demonstrated with the bivalent vaccine for subtypes 31, 33, 45, and 51.[115-117] The quadrivalent vaccine has also shown cross-protection for HPV subtypes 31, 33, and 45,[116,117] however, the bivalent vaccine has shown higher cross-protective efficacy for HPV-31 and HPV-45.[117]

Of the strains of HPV covered by the 9-valent vaccine, eight of the nine strains have been associated with OSSN. HPV-58 is the only vaccine strain not associated with OSSN. Additional strains of HPV identified in association with OSSN, but not targeted by the HPV vaccine include HPV-1, 5, 8, 12, 14, 17, 19, 23, 24, 35, 36, 37, 38, 44, 51, 66, 80, 100, RTRX7, DL-473, PPHLIFRC, and CJ198. Not all of these strains have been shown to be oncogenic, as such their presence may or may not contribute to the pathogenesis of OSSN. Additionally, the degree of cross-protection from immunization against these strains, if present, is unknown.

Efficacy of HPV vaccines is highest when immunization occurs prior to viral exposure, thus prior to sexual debut.[115] The U.S. Food and Drug Administration (FDA) approved HPV vaccinations for prevention of cancers of non-ocular organs discussed previously, what affect vaccination against the virus has on OSSN is unknown at this time. The association between HPV infection and OSSN has been repeatedly demonstrated, particularly with HPV 16, and many HPV strains identified in OSSN are targeted by the HPV 9-valent vaccine. Since the population that develops OSSN is considerably older than the currently vaccinated population and because the vaccine is relatively new, our knowledge of the potential effect of HPV on OSSN is limited. As the population of vaccinated persons continues to grow and age, the epidemiology of ocular surface disease may or may not respond.

VI: Conclusions

The role of HPV in the pathogenesis of OSSN has been debated for decades. The available literature, summarized above and in Table 1, suggests that HPV likely plays a role in a subset of OSSN cases. While there is a clear association between HPV and OSSN, with several suggested mechanisms by which the virus can initiate the cascade of tumorigenesis,

infection does not appear to be required for the development of OSSN. As carcinogenesis could conceivably result in the reactivation of latent virus, causation must be determined. The proportion of OSSN cases in which HPV plays a role is ill-defined. Even less is known about the natural history of ocular HPV infection. Studies of cervical HPV infection clearly established prolonged infection with an oncogenic genotype as the primary risk factor for cervical cancer. Analogous studies of HPV infection of the ocular surface have not been performed. It is clear that, to prevent cervical cancer due to a particular HPV genotype, vaccination against that type must occur prior to acquisition via sexual transmission. The timing and mechanism of ocular acquisition of HPV is not known. It does, however, seem unlikely that acquisition of most oncogenic genotypes, which are largely tropic to the genitourinary tract, would occur prior to the onset of sexual activity.

Therefore, it is possible that widespread vaccination against HPV may prevent future cases of OSSN. However, it is not known that HPV vaccination will precede ocular HPV acquisition, and the proportion of OSSN attributable to HPV is unknown. Given the rarity of the disease in immunocompetent individuals in the industrialized world, any potential benefit is perhaps most likely to be seen in the developing world and in immunocompromised patients. Before the effect of HPV vaccination campaigns on the incidence of OSSN can be estimated, the natural history of ocular HPV infection and the relationship between HPV and OSSN must be more clearly defined. Inversely, a decline in the incidence of OSSN in highly HPV-vaccinated populations, adjusted for changing epidemiology of immunocompromising conditions and availability of effective treatment for HIV, would strongly support the assertion that HPV has a causal role in OSSN, though such an effect is not likely to be seen for decades.

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Table 1

Ocular Surface Squamous Neoplasia and the Incidence of HPV Infection in the Literature.

Author	Country	Study type	Disease definition (n)	Comparison (n)	OSSN cases HPV (+) %	Comparison HPV (+) %	HPV strains
McDonnell 1987 [60]	U.S.A.	Case series	Dysplasia, CIN (28); Papilloma (28)	N/A	29	N/A	N/A
McDonnell 1989[61]	U.S.A.	Case control	Dysplasia, SCCC tissue; (6); Papilloma (2)	pterygium, nevus, melanoma, SK; (4)	75	0	16
Lauer 1990[62]	U.S.A.	Case series	CIN (5)	N/A	80	N/A	16, 18
Odrich 1991[63]	U.S.A.	Case series	SCCC, dysplasia, mucoepidermoid carcinoma vs. papillary inflammation; (3)	N/A	100	N/A	16
McDonnell 1992 [64]	U.S.A.	Case control	Dysplasia, dyskeratosis, CIN, SCCC tissue (38)	Pterygia, ligneous conjunctivitis, melanoma; normal conjunctiva (10)	88	0	16
Tuppurainen 1992 [65]	Finland	Case series	CIN, SCCC; (4)	N/A	0	N/A	N/A
Saegusa 1995 [66]	Japan	Case control	Dysplasia, SCCC, Papilloma; (24)	basal call epithelioma; (12)	63	0	16
Lewallen 1996 [67]	Malawi	Case series	SCCC (3)	N/A	0	N/A	N/A
Waddell 1996 [68]	Uganda	Case control	SCCC (20)	Pingueculae, conjuncitivits; (15)	35	33	16
Karcioglu 1997 [69]	Saudi Arabia	Case control	CIN (14), SCCC (31)	Climatic droplet keratopathy (20), corneal scar (31), normal conjunctiva (19)	56	30.0	16, 18
Nakamura 1997 [70]	Japan	Case control	Dysplasia (4), SCCC (4)	Histologically benign lesions (9)	50	44	16, 18
Tabrizi 1997 [71]	Australia	Case control	Dysplasia, carcinoma (total 88)	Pterygia, or normal (total 66)	39	7.5	1, 6, 11, 16, 18
Dushku 1999 [72]	U.S.A.	Case control	CIN (4), SCCC (4)	Pinguecula (1), pterygia (13), actinic keratosis (2), normal conjunctiva (6)	0	0	N/A
Palazzi 2000 [73]	Brazil	Case control	SCCC (10), CIN (9), BCC (1), dysplasia (3) papilloma (2), nevi (2), inflammation (3), pyogenic granuloma (1)	Normal conjunctiva (60)	13	1.6	11, 16
Toth 2000 [74]	Saudi Arabia and Hungary	Case series	SCCC (23)	N/A	22	N/A	16, 18
Eng 2002 [75]	Taiwan	Case series	CIN (6), SCCC (14), Papilloma of the conjunctiva (24)	N/A	0	32	6, 11
Scott 2002 [31]	U.S.A.	Case control	CIN (10)	Normal conjunctiva (5)	100	0	16, 18

Author	Country	Study type	Disease definition (n)	Comparison (n)	OSSN cases HPV (+) %	Comparison HPV (+) %	HPV strains
Tulvatana 2003 [76]	Thailand	Case control	SCCC (16), dysplasia (7), CIN (7)	Normal conjunctiva (30)	0	0	N/A
Ateenyi-Agaba 2004 [8]	Uganda	Case control	SCCC (21)	Pterygium (5), pingueculum (2), nevus (1), solar keratosis (2)	86	35	RTRX7-related, 8-related, 11, 12-related, 14, 24, 36-38
Moubayed 2004 [77]	Tanzania	Case series	Dysplasia (1), SCCC (13)	N/A	93	N/A	6/11, 16, 18
Kuo 2006 [78]	Taiwan	Case control	CIN (9)	SLK (2), pterygium (4), lymphoid proliferation (2), Cervical CIN (19)	100	0	6, 11, 16, 18, 33, 37, 58, 72
Tornesello 2006 [79]	Uganda	Case control	OSSN (86)	Pterygium, ocular trauma or other benign conditions (63)	20	1.6	6, 8, 14b, 20, 38, DL473, PPHL1FR, 100, CJ198
Sen 2007 [80]	India	Case control	OSSN (30), Papilloma (35)	Normal conjunctiva (30)	9	0	Not typed
Auw-Haedrich 2008 [81]	Germany	Case control	CIN (10), SCCC (2)	Normal conjunctiva (14), inflamed conjunctiva (1)	17	0	16
de Koning 2008 [82]	Uganda	Case control	CIN (57), SCCC (24)	Pinguecula (15), chronic inflammation (3), pyogenic granuloma (2), cavernous angioma (2), miscellaneous diagnosis (7)	47	38	5, 6, 8, 11, 14, 16-19, 23, 31, 33, 35-37, 44, 51, 52, 66, 80
Guthoff 2009 [30]	Germany	Case control	SCCC (7), CIN (24), Pterygia (11)	normal conjunctiva (5)	0	0	N/A
Manderwad 2009 [83]	India	Case series	CIN (21), SCCC (36)	N/A	0	N/A	N/A
Ateenyi-Agaba 2010 [15]	Uganda	Case control	SCCC (94), dysplasia (39)	Chalazia, cataract, ocular trauma, corneal laceration; total (285)	50	6	5, 8, 9, 12, 14, 15, 17, 19, 20-25, 36-38, 45, 49, 75, 76, 80, 83, 92, 93, 96
Simbiri 2010 [84]	Botswana	Case control	HIV+ with OSSN (28)	HIV+ with pterygium (8)	75	50	6, 11, 16, 18, 31, 33
Asadi-Amoli 2011 [85]	Iran	Case control	SCCC (50)	Normal conjunctiva (50)	92	0	
Peralta 2011 [86]	Mexico	Case series & review	SCCC (36)	N/A	22	N/A	16
Chauhan 2012 [87]	India	Case control	CIN (20), SCCC (64)	Conjunctiva with limbal stem cell deficiency (15)	11	0	16
Carrilho 2013 [88]	Mozambique	Case control	CIN (20), SCCC (13)	Conjunctivitis (1), pinguecula (3), melanosis (1)	58	0	16, 18
Woods 2013 [89]	Australia	Case control	Dysplasia (10), CIN (12), SCCC (24)	Pterygia (42), normal conjunctiva (69)	7	0	16

Abbreviations: Ctrl, Control; U.S.A., United States of America; SCCC, squamous cell carcinoma of the conjunctiva; CIN, carcinoma in situ; SK, seborrheic keratosis; MEC, mucoepidermoid carcinoma; BCC, basal cell carcinoma; SLK, superior limbic keratoconjunctivitis