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REVIEW

A review of the aetiology of squamous cell carcinoma of the conjunctiva

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Summary Squamous cell carcinoma of the conjunctiva is a rare tumour with a multifactorial aetiology. There is strong epidemiological evidence that exposure to solar ultraviolet radiation is an important cause and that HIV infection predisposes to its development. The role of other factors, such as human papillomavirus infection, is unclear.

Keywords: squamous cell carcinoma; conjunctiva

Squamous cell carcinoma of the conjunctiva is an extreme form of a spectrum of conditions, collectively known as 'ocular surface epithelial dysplasias', which range in severity from mild dysplasia to carcinoma *in situ* and, ultimately, to invasive carcinoma. Although rare in Europe, Templeton (1973) noted that it was relatively common in parts of sub-Saharan Africa during the 1960s and suggested that exposure to solar ultraviolet radiation might be a cause. Lee *et al.* (1994) reported that the risk of ocular surface epithelial dysplasias is related to lifetime exposure to solar ultraviolet light. The strongest risk factor in this study was a past history of skin cancer (OR = 15, 95% CI 2-114), although other factors, such as having been outdoors for more than half of the first 6 years of life, fair skin, pale irides and propensity to burn on exposure to sunlight, were also important. In addition, Newton *et al.* (1996) found that the incidence of squamous cell carcinoma of the eye increases by 29% per unit increase in exposure to ambient solar ultraviolet radiation ($P < 0.0001$), equivalent to a 49% increase in incidence with each 10° decline in latitude. Ultraviolet B is known to damage DNA in human epithelial cells and thus is a plausible cause of the disease (IARC, 1992).

Two case reports of squamous cell carcinoma of the conjunctiva in HIV-seropositive males in the USA (Winward and Curtin, 1989; Kim *et al.*, 1990), coupled with a dramatic increase in the numbers of tumours being seen by ophthalmologists in at least two African centres (Kestelyn *et al.*, 1990; Ateenyi-Agaba, 1995), led to the suggestion of an association with HIV. Studies from Africa (Kestelyn *et al.*, 1990; Ateenyi-Agaba, 1995; Waddell *et al.*, 1996) and the USA (Goedert and Coté, 1995) have confirmed this association (Table I). Although each study is small, they show remarkably consistent results (summary OR = 13.0, 95% CI 7.2-23.1; derived from weighted averages of the log relative risks). Thus, with Kaposi's sarcoma and non-Hodgkin's lymphoma, squamous cell carcinoma of the conjunctiva is the third tumour to be clearly 'AIDS associated'. In other immunosuppressed groups, such as transplant recipients, there has been no suggestion of an increased risk, although a thorough literature review yielded one case report of a patient with malignant lymphoma on chemotherapy (Kushner and Mushen, 1975); this is perhaps not surprising, given the rarity of squamous cell carcinoma of the conjunctiva in Western populations (Newton *et al.*, 1996).

Several types of squamous carcinoma are associated with human papillomavirus (HPV) infection, most notably cancer of the uterine cervix, induced by HPV 16 and 18. Squamous carcinoma of the skin has also been associated with HPV 5 and 8 in immunosuppressed individuals (IARC, 1995). The evidence for an association between human papillomavirus and squamous cell carcinoma of the conjunctiva is conflicting. In 12 studies of ocular surface epithelial dysplasia, the proportion of lesions in which HPV (predominantly type 16, but also types 6, 11 and 18) was detected was variable (references listed in Table II). These results suggest that HPV alone is unlikely to cause conjunctival squamous cell carcinoma, although it may be a contributory factor.

Table I Studies of squamous cell carcinoma of the conjunctiva and HIV

Studies (location)	*Proportion HIV positive Cases*	*Controls*	*Relative risk (95% CI)*
Kestelyn *et al.* (1990) (Rwanda)	9/11	6/22	13.0 (2.2-76.9)
Ateenyi-Agaba (1995) (Uganda)	36/48	9/48	13.0 (4.5-39.4)
Waddell *et al.* (1996) (Uganda)	27/38	12/76	13.1 (4.7-37.6)
Goedert and Coté (1995) (USA)	4 observed	0.3 expected	13.0 (4.0-34.0)
Summary statistic			13.0 (7.2-23.1)

One other study from Rwanda, by Newton *et al.* (1995), considered the association of HIV with all ocular tumours, excluding retinoblastoma and melanoma. The proportion HIV positive was 2/8 cases and 8/200 controls (RR 8.0, 95% CI 0.8-96.9).

Little is known about other potential risk factors for the disease, although ocular trauma may also be important (Templeton, 1973; Margo and Groden, 1986). Of particular relevance is the existence of 'cancer eye' in cattle, which could be a useful animal model: it is a squamous cell carcinoma of the conjunctiva, which has been associated both with ultraviolet radiation and bovine papillomavirus infection (IARC, 1995).

In summary, there is strong epidemiological evidence that solar ultraviolet radiation is an important cause of squamous cell carcinoma of the conjunctiva. Another established risk factor is HIV infection, although it is not clear if it is acting directly or via immunosuppression, leading to the activation of potentially oncogenic viruses. The role of other factors, particularly conjunctival papillomavirus infection, has yet to be resolved.

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Table II Studies of the prevalence of human papillomavirus (HPV) infection in ocular surface epithelial dysplasias

Study[a]	*Proportion of HPV-positive tissues*	*HPV type found*
Lass *et al.* (1983)	1/2 papillomas	11
McDonnell *et al.* (1986)	23/47 papillomas 5/61 dysplastic lesions 0/6 control lesions	Unknown
McDonnell *et al.* (1987)	15/23 papillomas 0/28 dysplastic lesions	6
McDonnell *et al.* (1989)	5/5 dysplasias 1/1 squamous carcinomas 0/6 control lesions	16
Lauer *et al.* (1990)	4/5 dysplastic lesions	16 (+one 18)
Odrich *et al.* (1991)	2/2 bilateral squamous carcinomas	16
Tuppurainen *et al.* (1992)	0/4 squamous carcinomas	
McDonnell *et al.* (1992)	33/38 dysplastic lesions	16
Saegusa *et al.* (1995)	12/16 papillomas 2/4 dysplasias 1/4 squamous carcinomas	16
Adachi *et al.* (1995)	0/3 dysplasias 1/2 squamous carcinomas 0/9 control lesions	16
Serna *et al.* (1995)	1/9 squamous carcinomas	18
Waddell *et al.* (1996)	7/20 squamous carcinomas 2/21 control lesions	16

[a] Case reports have not been included.

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