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A case-control study of ocular surface squamous neoplasia (OSSN) in Uganda

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HIV increases the risk of OSSN. Here we investigate other factors in a case-control study from Uganda with 318 cases (48 CIN I, 66 CIN II, 81 CIN III and 123 with invasive disease) and 762 controls. Initial analyses were stratified by HIV serostatus (204 cases and 202 controls were HIV seropositive), but since findings were similar in infected and uninfected people, the combined results are presented here. The risk of OSSN increased with increasing time spent in direct sunlight (p_{trend} = 0.003, adjusted for age, sex, residential district and HIV serostatus): compared to those who reported spending up to 1 hr a day in direct sunlight, the risk was 1.7 (95% Confidence Interval [CI] 1.2–2.4) in those reporting 2–4-hr exposure and 1.8 (95% CI 1.1–3.1) in those reporting 5+ hr. The risk was also increased among people reporting a previous injury to the affected eye (OR 2.4, 95% CI 1.2–4.5). Pinguecula in the nasal quadrant of the unaffected eye were evident on clinical examination for 98% of cases (293/300) and for 91% of the same quadrant in the right eye (246/271) of controls (OR = 6.4, 95% CI 2.5–16.1). We confirm associations with exposure to solar ultraviolet radiation and with the presence of pinguecula and report a role for previous ocular trauma in the aetiology of OSSN. We did not identify any additional factors that point to an underlying infectious cause, although this is an area of on-going research.

In the years before the HIV epidemic, corneo-conjunctival intraepithelial neoplasia (CIN) and carcinoma (together called ocular surface squamous neoplasia (OSSN)) were reported to be more frequent in African countries, such as Uganda, than in Europe and the USA.[1] Since the 1980s there has been a marked increase in cases of conjunctival neoplasia, mostly in sub-Saharan Africa and a link with HIV infection has been confirmed (reviewed in Ref. 2). The clear excess risk of ocular surface epithelial dysplasias among HIV infected people (and among immunosuppressed renal transplant recipients) suggests a possible role for an underlying infection in the aetiology.[2,3] Various HPV types (including cutaneous types) have been identified in some, but not in all, tumor specimens from several small case series but results from case-control studies have, to date, been inconclusive.[2] Here, we describe a case-control study of OSSN conducted in Uganda, with a view to identifying risk factors, other than infection with HIV. In particular, we examined socioeconomic and demographic factors that might be relevant to the transmission of, or exposure to, infectious disease and specific factors that might cause irritation to the eye. A primary aim was to accrue biological material to aid in the hunt for an underlying infectious cause. However, although an active search for oncogenic infections is ongoing, no new candidate virus (if one exists) has yet been identified.[4]

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Material and Methods

Between November 2001 and February 2005, in country-wide ophthalmology clinics across Uganda, anyone with a suspected ocular surface squamous neoplasia was offered surgical treatment and histology, together with enrolment into a case-control study. Serological testing for HIV was also offered, after pre-test counseling from appropriately qualified research staff, in the local language. Information about the disease, its treatment and HIV testing and the research project was provided in private in vernacular by counselors and consent was confirmed by signature or thumbprint. Following fully informed consent, each patient completed a brief questionnaire asking about various social and demographic variables, exposure to solar ultraviolet radiation and factors that may be related to the transmission of, or exposure to, infectious disease. In addition, factors that might cause irritation to the eye were examined, such as exposure to smoke from cooking fires. A sample of venous blood was obtained for onsite HIV testing, with confirmation at the Uganda Virus Research Institute (2 enzyme immunoassay tests in parallel, with Western blot if required)—the remaining material was stored for future use. Ocular lesions were photographed and details of eye and general health were recorded,

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including various ophthalmological clinical parameters for the majority. Data were computerized and checked by 1 of the investigators (KW), using EPI INFO (Version 6). Lesions judged removable leaving a normal eye, were dealt with as described in Ref. 5. If this was impossible, enucleation was advised. If too advanced for this, incision biopsy was performed to confirm diagnosis and referral offered for further management. Surgery was carried out by 1 of the investigators (KW). Larger lesions were stored in a RNA fixative and then put into liquid nitrogen for future use. A sample of all lesions was stored in formalin and sent to St Thomas' Hospital, London, in the United Kingdom for histological review by 1 of the investigators (SL), in 1 of many frequent shipments. Final histology was fed back to local investigators in a timely fashion to inform clinical decisions. CIN was classified into 3 stages according to one, two or three thirds thickness being dysplastic; invasive tumors were diagnosed when the basement membrane was breached. In addition, the nasal quadrant of the unaffected eye was examined for clinical evidence of allergy, hyperaemia, pigmentation, pinguecula and pterygia.

Over the same time period, controls were recruited from 2 sources. The first group comprised patients attending the ophthalmology clinics with concerns or conditions other than OSSN. This group also included those individuals who were originally recruited as cases, but where histology subsequently revealed another diagnosis. Of the 295 individuals recruited from this source, 170 turned out to have a normal eye, 39 had Kaposi's sarcoma, 18 had retinitis, 18 had uveitis, 17 had infection with herpes simplex virus, 15 had cataract and the remainder had a variety of other conditions. Many of these people were recruited at the Ruharo Eye Hospital in Mbarara. These individual had details of their ocular examination recorded, including an examination of the nasal quadrant of the right eye, where possible, for clinical evidence of allergy, hyperaemia, pigmentation, pinguecula and pterygia. The second group of controls comprised people who were recruited through the voluntary HIV counseling and testing service—this source was used in an effort to recruit more people who may have had a diagnosis of HIV and these individuals did not undergo an ocular examination (and so are excluded from analyses that used data obtained on clinical examination). Following informed consent (as described above), questionnaire data, ophthalmological examinations, and HIV tests were obtained (when possible) and recorded as for cases. Ethical approval for this study was obtained from the Science and Ethics Committee of the Uganda Virus Research Institute and from the Uganda National Council for Science and Technology.

Initial exploration of the relationship between OSSN and sex, age and residential district was done using Mantel-Haenszel χ^2 (FREQ procedure, the SAS System). Preliminary analyses were all stratified by HIV serostatus serostatus (204 cases and 202 controls were HIV seropositive), but revealed little difference in results between HIV seropositive and seronegative people and so all other factors were assessed using logistic regression models (GENMOD procedure, the SAS System), adjusting for age, sex, residential district and HIV serostatus. These results are presented in this article, with the exception of Table 5, which shows key findings stratified by HIV serostatus. Analyses of clinical variables included all cases and only those controls recruited from the ophthalmology clinic who had an ocular examination (Table 4). For each variable, a category of "missing values" was created and included in regression models, but the odds ratios for this group are not reported (and excluded altogether when testing for trend). An additional set of analyses was constructed that included self-reported daily hours in the sun as an adjustment, but it made little difference to the results (data not shown). Finally, analyses were conducted, restricting the control group to those individuals with other eye conditions and restricting the case group to those with invasive disease only, or excluding CIN I, but again, the results change little (data not shown).

Table 1. Distribution of cases with ocular surface squamous neoplasia and of controls, with respect to sex, age, HIV serostatus and residential district

	Cases (n = 318)	Controls (n = 762)
	Percentage/number	Percentage/number
Sex		
Male	43% (137)	42% (320)
Female	57% (181)	58% (442)
Age (years)		
15–29	24% (76)	36% (273)
30–44	59% (187)	51% (391)
45+	17% (55)	13% (98)
HIV serostatus		
Positive	64% (204)	27% (202)
Negative	36% (114)	73% (560)
Residential district		
Kampala	14% (43)	3% (26)
Masaka	15% (48)	4% (34)
Mbarara	14% (45)	49% (376)
Elsewhere	52% (166)	42% (321)
Missing	5% (16)	1% (5)

Results

Of the 395 people approached as possible cases, 318 with confirmed OSSN (48 CIN I, 66 CIN II, 81 CIN III and 123 with invasive disease), an HIV test result and a complete, or partially complete questionnaire, agreed to participate and are included in the analyses presented here. Similarly, 762 of 794 possible controls are included. Table 1 shows the distribution of cases and of controls by sex, age, HIV serostatus and residential district. In accord with previous studies, there

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Table 2. Distribution of cases with ocular surface squamous neoplasia and of controls, with respect to various socio-demographic and lifestyle factors

	Number of cases/ controls	Odds ratio (95% confidence intervals
Education		
None or some primary school	102/228	1.0
At least complete primary school	178/351	0.8 (0.6–1.2)
Paid work		
No	77/132	1.0
Yes	212/588	0.8 (0.6–1.2)
Of those who have paid work		
Full-time	77/146	1.0
Part-time	129/441	0.9 (0.6–1.3)
Monthly income (Ug. shilling)		
20th+	125/290	1.0
Up to 20th	95/327	1.1 (0.8–1.6)
Accommodation		
Owned by participant	196/546	1.0
Rented	66/93	1.1 (0.7–1.7)
Other	28/113	0.6 (0.4–1.0)
Main household cook		
No	125/273	1.0
Yes	173/482	1.0 (0.6–1.6)
If yes, cook indoors/outdoors		
Outdoors	24/111	1.0
Indoors	124/320	1.3 (0.7–2.4)
Tobacco use		
Nonsmoker	257/642	1.0
Ex-smoker	19/75	0.8 (0.4–1.4)
Current smoker	23/37	1.3 (0.7–2.5)
Number self-reported lifetime sexual partners		
0–3	162/409	1.0
4+	130/302	0.9 (0.7–1.3)
Number of hand washes/day		
0–4	120/383	1.0
5+	164/341	1.1 (0.8–1.5)
Previously seen eye doctor for any condition		
No	280/714	1.0
Yes	17/38	0.7 (0.3–1.3)
Previous injury to affected eye (cases), or any eye in controls		
No	270/720	1.0
Yes	25/27	2.4 (1.2–4.3)

Note: numbers do not always add to the total because of missing values. Odds ratios adjusted for age, sex, HIV serostatus and district of residence.

Table 3. Distribution of cases with ocular surface squamous neoplasia and of controls, with respect to factors that might relate to exposure to solar ultraviolet radiation

	Number of cases/ controls	Odds ratio (95% confidence intervals
Place of work		
Indoors	81/176	1.0
Indoor and outdoor	82/326	0.8 (0.5–1.3)
Outdoor	118/198	1.7 (1.1–2.6)
Hours spent in direct sunlight/day		
1 hr	136/402	1.0
2–4 hrs	129/289	1.7 (1.2–2.4)
5+ hrs	33/63	1.8 (1.1–3.1)
		χ^2(trend) = 8.7, $p = 0.003$
Hours spent cultivating/week		
None	81/137	1.0
1–9	174/478	1.0 (0.7–1.5)
10+	43/138	1.2 (0.7–2.1)
		χ^2(trend) = 0.1, $p = 0.7$
Typically wear sun hat		
No	255/684	1.0
Yes	42/63	1.3 (0.8–2.2)
Typically wear sunglasses		
No	278/722	1.0
Yes	19/28	1.2 (0.6–2.3)

Note: numbers do not always add to the total because of missing values. Odds ratios adjusted for age, sex, HIV serostatus and district of residence.

were more women than men diagnosed with OSSN and nearly two thirds of cases were between the ages of 30 and 44 years old; as expected, the majority were HIV seropositive. Although the proportion of controls with evidence of infection with HIV was lower, the actual number of HIV seropositive controls was similar to cases (204 cases and 202 controls). Nearly half of controls were recruited from 1 centre (Ruharo Eye Hospital in Mbarara)—this compared to only 14% of cases.

Table 2 shows the association between various socio-demographic and lifestyle factors in relation to the risk of OSSN. Factors relating to education and income were not related to risk, and neither were exposure to tobacco or household smoke from cooking fires. The self-reported number of lifetime sexual partners was not related to risk, arguing against an underlying sexually transmitted cause. Although relevant for only a small number of cases (25), a self reported history of ocular trauma in the affected eye was associated with an excess risk of ocular surface squamous neoplasia (OR = 2.4, 95% CI 1.2–4.3). When results were stratified by HIV serostatus (Table 5), the

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findings appeared similar in both groups although among HIV seronegative people they were not statistically significant. T3 Table 3 shows the association between OSSN and factors that might relate to exposure to solar ultraviolet radiation. Compared to those with indoor occupations, outdoor workers were at an increased risk (OR = 1.7, 95% CI 1.1–2.6) and the risk increased significantly with increasing self-reported hours spent in direct sunlight each day ($p_{trend} = 0.003$); when these findings were stratified by HIV serostatus (Table 5), the results for HIV seropositive people were not statistically significant.

The relationship between OSSN and factors identified on clinical examination of the unaffected eye are shown in Table 4. The presence of allergic reactions, hyperaemia, pigmentation T4 and pterygium show no association with disease. In contrast, pinguecula in the unaffected eye were visible on clinical examination of the right nasal quadrant for 98% of cases (293/300) and for 91% of the same quadrant in the right eye (246/271) of controls (OR = 6.4, 95% CI 2.5–16.1). The findings were evident in HIV infected and uninfected people (Table 5). T5

Table 4. Factors identified on clinical examination of the nasal quadrant of the unaffected eye of cases with ocular surface squamous neoplasia and of the nasal quadrant of the right eye in controls

	Number of cases/controls	Odds ratio (95% confidence intervals
Allergy		
No	300/266	1.0
Yes	0/6	–
Hyperaemia		
No	261/234	1.0
Yes	39/38	0.7 (0.4–1.2)
Pigmentation		
No	60/57	1.0
Yes	240/215	1.2 (0.8–2.0)
Pinguecula		
No	7/25	1.0
Yes	293/246	6.4 (2.5–16.1)
Pterygium		
No	293/263	1.0
Yes	7/9	0.5 (0.2–1.4)

Note: these analyses were restricted to the 295 controls recruited from the ophthalmology clinic; for the majority, the results of ocular examination were recorded. Odds ratios adjusted for age, sex, HIV serostatus and district of residence.

Discussion

A primary aim of this study was to identify underlying infectious factors in the aetiology of OSSN. Therefore, the collection of biological material from cases and from controls, in which presence of infection can be measured, was considered of paramount importance. However, results in relation to HPV remain unclear (and are published elsewhere)[2] and since no other infection (if there is one) has been identified, we have as yet, made no further use of any of this material. Since associations between oncogenic infections and the cancers they cause tend to be strong, coupled with the inherent practical difficulties of recruiting people in resource-poor settings, our choice of control group was made on pragmatic grounds. The inclusion of people with "other eye diseases," together with the need to boost the proportion of HIV infected people in the comparison group (nearly half of whom came from only 1 centre), may have biased our findings and we acknowledge that this is the principle weakness

Table 5. Selected risk factors for ocular surface squamous neoplasia, stratified by HIV serostatus

	HIV seronegative		HIV seropositive	
	Number of cases/controls	Odds ratio (95% confidence intervals	Number of cases/controls	Odds ratio (95% confidence intervals
Previous injury to affected eye (cases), or any eye in controls				
No	96/523	1.0	174/197	1.0
Yes	10/23	2.0 (0.9–4.6)	15/4	3.4 (1.0–11.3)
Hours spent in direct sunlight/day				
1 hr	42/286	1.0	94/116	1.0
2–4 hrs	44/213	1.7 (1.1–2.8)	85/76	1.6 (1.0–2.7)
5+ hrs	20/53	2.2 (1.1–4.2)	13/10	1.3 (0.5–3.5)
		χ^2(trend) = 5.9, $p = 0.02$		χ^2(trend) = 2.8, $p = 0.1$
Pinguecula				
No	3/14	1.0	4/11	1.0
Yes	106/174	4.4 (1.0–16.8)	189/72	7.3 (2.2–24.4)

Note: numbers do not always add to the total because of missing values. Odds ratios adjusted for age, sex and district of residence. Analyses of clinical variables were restricted to the 294 controls who were recruited from the ophthalmology clinic and who therefore had an ocular examination.

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J_ID: Z3Q Wiley Ed. Ref. No.: 09-1121.R2 Customer A_ID: IJC25040 Date: 13-January-10 Stage: Page: 5

of the work presented here. However, extensive sensitivity analyses outlined above demonstrate the robustness of key findings, which are also supported by other published studies and are evident in HIV infected and uninfected people. Of particular note, is the lack of any evidence (other than an association with HIV) suggesting underlying infection as a possible cause.

Results presented here in relation to self-reported time spent in direct sunlight and occupation lend further support to the importance of exposure to solar ultraviolet radiation as a cause of OSSN. Lesions occur in sun-exposed areas of the eye,[5,6] are associated with solar elastosis and have been shown to contain classical UV-induced p53 mutations.[5–9] The incidence of the tumor increases with increasing levels of ambient solar radiation and associations with sun exposure and past history of skin cancer have also been identified in other case-control studies.[1,10–12] These findings are perhaps unsurprising given the similarity of this disease with cutaneous squamous cell carcinoma, for which UV exposure is an established cause.[13]

Exposure to dust and ocular trauma have been suggested as possible risk factors for OSSN, although, until now, evidence was scant and based only on case reports.[14,15] We found an increased risk in association with a self-report of prior trauma to the affected eye; this is the first time the risk has been identified in an observational epidemiological study. It is important to note, however, that it was an exposure that was relevant for only 8% of cases and that further information on the precise nature of the previous eye injury was not available. In addition, the possibility of bias, due to better recall of trauma in subjects with OSSN than in controls, should also be considered.

In 1979, Clear *et al.* examined 234 conjunctival biopsies in Africans from Malawi. They speculated that solar keratosis, pinguecula and pterygium are present as a continuous spectrum of the same pathological process, eventually leading to carcinomatous change in a small proportion of affected individuals.[7] Pinguecula and to a lesser extent pterygium have been linked to exposure to solar UV in subsequent studies, although the evidence relating to the nature of that association remains relatively sparse.[16,17] Although common among cases and controls, the association between the presence of pinguecula and risk of OSSN is evident, with 98% of cases (all but 7 people) having clinically identified pinguecula in the contra-lateral eye, as compared to 91% of controls. Conversely, pterygium was relatively rare in both cases and controls and no associations with OSSN were identified. Of note however, is that diagnoses of pinguecula and pterygium were made on clinical grounds alone; there was no histological verification.

In summary, in this—the largest case-control study of OSSN ever conducted—we confirm associations with exposure to solar ultraviolet radiation and with the presence of pinguecula and report a role for previous ocular trauma in the aetiology of the disease. We did not identify any socioeconomic or demographic factors that might point to an underlying infectious cause (other than infection with HIV), although the identification of such an infection is an area of on-going research.

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