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Infectious Agents and Cancer

Research article

Genital and cutaneous human papillomavirus (HPV) types in relation to conjunctival squamous cell neoplasia: A case-control study in Uganda

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Abstract

Background: We investigated the role of infection with genital and cutaneous human papillomavirus types (HPV) in the aetiology of ocular surface squamous neoplasia (which includes both conjunctival intraepithelial neoplasia (CIN) and carcinoma) using data and biological material collected as part of a case-control study in Uganda.

Results: Among 81 cases, the prevalence of genital and cutaneous HPV types in tumour tissue did not differ significantly by histological grade of the lesion. The prevalence of genital HPV types did not differ significantly between cases and controls (both 38%; Odds ratio [OR] 1.0, 95% confidence interval [CI] 0.4–2.7, p = 1.0). The prevalence of cutaneous HPV types was 22% (18/81) among cases and 3% (1/29) among controls (OR 8.0, 95% CI 1.0–169, p = 0.04).

Conclusion: We find no evidence of an association between genital HPV types and ocular surface squamous neoplasia. The prevalence of cutaneous HPV was significantly higher among cases as compared to controls. Although consistent with results from two other case-control studies, the relatively low prevalence of cutaneous HPV types among cases (which does not differ by histological grade of tumour) indicates that there remains considerable uncertainty about a role for cutaneous HPV in the aetiology of this tumour.

Background

In the years before the HIV epidemic, corneo-conjunctival intraepithelial neoplasia (CIN) and carcinoma (together called ocular surface squamous neoplasia (OSSN)) were
Infectious Agents and Cancer 2008, 3:12

reported to be more frequent in African countries than in Europe and the USA [1-3]. Using data from worldwide cancer registries it has been confirmed that incidence of OSSN increases markedly with proximity to the equator, presumably from increasing solar ultraviolet (UV) radiation [3]. Exposure to UV radiation is an established cause of disease. Lesions occur in sun-exposed areas of the eye [4,5], are associated with solar elastosis [4-7] and have been shown to contain classical UV-induced p53 mutations [8]. The incidence of the tumour increases with increasing levels of ambient solar radiation and associations with sun exposure and past history of skin cancer have been identified in case-control studies [3,9-11]. Additional risk factors may also be important. For example, a polymorphism of TP53 codon 72 has been linked to an increased risk of neoplasia in one study from Uganda including 107 cases and 115 controls [12]. Exposure to dust and ocular trauma have also been suggested as possible risk factors, although evidence is scant [1,13].

Since the 1980s there has been a marked increase in cases of conjunctival neoplasia, mostly in sub-Saharan Africa [14-19]. In Uganda for example, the reported incidence has more than tripled over the last decade [14,16], particularly among younger people and a link with HIV infection was suggested in case reports [20-27]. Case-control studies in several African countries [11,28-33] and cohort studies in the USA [34,35], have confirmed a roughly 10 fold excess risk of the tumour in HIV infected people compared to the uninfected; in Africa the majority of cases are HIV infected [36]. In a recent study of 414 cases in Uganda, 64% of people with conjunctival neoplasia were HIV infected and this applied to intraepithelial as well as to invasive cases [5]. The median CD4+ T lymphocyte count of HIV positive cases at diagnosis has been found in this study to be 111 cells/microL (based on results from 112 HIV infected cases) [5]. Use of antiretroviral therapy has been shown to cause tumour regression in an otherwise inoperable case [37]. A recent report from the USA did not find strong associations with level of immunosuppression in HIV infected people, but the study included only 15 cases of the disease [35]. An excess risk has also been reported among immunosuppressed cancer patients and organ transplant recipients (although the number of cases remains small) [38-42].

However, the clear excess risk of ocular surface epithelial dysplasias among HIV infected people (and among immunosuppressed renal transplant recipients) suggests a role for an underlying infection in the aetiology [43,44]. Although an active search for other new oncogenic infections is ongoing, no new candidate virus (if one exists) has yet been identified [45]. A causal relationship between persistent infection with several (high risk) genital human papillomavirus (HPV) types and cancer of the uterine cervix is established. In non-melanoma skin carcinogenesis, a role has been suggested for cutaneous HPV types from the betapapillomavirus genus. A variety of HPV types has already been identified in some, but not in all, tumour specimens from several small case series and results from case-control studies have, to date, been inconclusive [2]. Here we present results on the association of genital and cutaneous (from the betapapillomavirus genus) HPV types in relation to ocular surface epithelial neoplasias from a case-control study in Uganda, together with a review of published evidence.

Results

Paraffin-embedded biopsy material was available for 81 cases (mean age 35 years) and for 29 controls (mean age 30 years). Among cases, 17 people had lesions graded as CIN (conjunctival intraepithelial neplasia) I, 18 were CIN II, 22 were CIN III and 24 people had an invasive carcinoma. Fifty two cases (64%) were HIV seropositive, 22 (27%) were seronegative and the HIV serostatus was unknown for seven people (9%). Among controls, 15 people had pinguecula, 3 had chronic inflammation, two had a pyogenic granuloma, two had a cavernous angioma and seven had a variety of other diagnoses. Ten controls (34%) were HIV seropositive and 19 (66%) were seronegative (Table 1). There were significantly more HIV seropositive cases than controls (70% (52/74; seven cases had unknown serostatus) versus 34%; p < 0.001).

Table 2 shows the prevalence of genital and cutaneous HPV among controls, stratified by age, sex and HIV serostatus – none of the apparent differences was statistically significant (at the 5% level). Table 3 shows the proportion of cases with evidence of genital or cutaneous HPV DNA in tumour tissue, stratified by the histological grade of the lesion (CIN I – III and invasive carcinoma). The prevalence of genital and cutaneous HPV types did not differ significantly by histological grade of the lesion, but at all grades, the prevalence of genital HPV types was higher than that of cutaneous types. For all tumour grades combined, this difference was statistically significant (38% versus 22%; p = 0.03).

Overall, the prevalence of genital HPV types did not differ between cases and controls (38% [31/81] in cases and 38% [11/29] among controls; OR 1.0, 95% CI 0.4–2.7, p = 1.0). The genital HPV types identified were 6, 11, 16, 18, 31, 33, 35, 45, 51, 52, 66 and two that were unclassifiable. High risk genital types were identified in 13 cases (types 16 [eight people], 51 and 66 [in one person], 18, 35, 51 and 52 [one person each]) and in three controls (types 31 and 33 [two people]). The most frequently detected genital type was HPV 11, which was found in 22 cases and in 10 controls. The prevalence of cutaneous HPV types was 22% (18/81) among cases and 3% (1/29) among controls.
(OR 8.0, 95%CI 1.0–168.5, p = 0.04) and did not differ significantly between HIV infected and uninfected cases and controls (Table 4). The cutaneous HPV types identified were 5, 8, 14, 17, 19, 23, 36, 37, 80, plus 9 that were unclassifiable; HPV 14 was identified in three cases and types 8, 17 and 23 were found in two people each. Evidence of infection with more than one HPV type was identified in tissue from 19 cases and four controls.

Discussion
Our findings demonstrate that both genital and cutaneous HPVs can be found in conjunctival tissue – the genital types were more frequently identified. However, we found no evidence that genital types were associated with ocular surface squamous neoplasia. In relation to cutaneous HPV, results reported here are broadly consistent with those from two other studies – the prevalence was significantly higher among cases than among controls. However, the prevalence of cutaneous HPV was still relatively low among cases and did not differ by histological grade of the lesion.

A comprehensive review of the published literature identified 12 case reports or case series in which the prevalence of HPV in tumour tissue from patients with ocular surface squamous neoplasia was investigated [46-57]. Eleven studies tested for HPV 16; seven also looked for evidence of infection with HPV 18; four studies also included HPV 6 and/or 11, one looked at HPV 2 and in one study the specific genital HPV type was not specified. Only three studies included more than 20 cases, the largest having 38. The prevalence of detectable HPV varied from 0% to 93% (summarised in Table 5) – much of this variation might be explained by the differing laboratory methodologies employed across individual studies. Sixteen case-control studies were identified and are summarised in Table 6, together with results from this investigation [7,11,30,58-70]. With the exception of one study, in which HPV type was not specified, all of the studies investigated HPV 16; nine also investigated HPV 18 and 5 investigated HPV 45. There is considerable heterogeneity in results. For example, in relation to HPV 16, four studies demonstrated a positive association and eleven showed no association with ocular surface squamous neoplasia.

Table 1: Distribution of cases and controls by age, sex and HIV serostatus

| Age   | Percentage of cases (n) | Percentage of controls (n) |
|-------|-------------------------|---------------------------|
| 15–28 | 27% (22)                | 38% (11)                  |
| 29–32 | 27% (22)                | 31% (9)                   |
| 33–70 | 46% (37)                | 31% (9)                   |

| Sex   | Percentage of cases (n) | Percentage of controls (n) |
|-------|-------------------------|---------------------------|
| Male  | 44% (36)                | 48% (14)                  |
| Female| 56% (45)                | 52% (15)                  |

| HIV serostatus | Percentage of cases (n) | Percentage of controls (n) |
|----------------|-------------------------|---------------------------|
| Negative       | 27% (22)                | 66% (19)                  |
| Positive       | 64% (52)                | 34% (10)                  |
| Unknown        | 9% (7)                  | 0% (0)                    |

None of the apparent differences in prevalence of HPV by age, sex or HIV sero-status was statistically significant.

Table 2: The proportion of controls with evidence of infection with HPV, stratified by age, sex and HIV serostatus

| All HPV | Genital HPV | Cutaneous-HPV |
|---------|-------------|---------------|
| Age     |             |               |
| 15–28   | 27% (3/11)  | 27% (3/11)    | 9% (1/11)     |
| 29–32   | 33% (3/9)   | 33% (3/9)     | 0% (0/9)      |
| 33–70   | 56% (5/9)   | 56% (5/9)     | 0% (0/9)      |

| Sex     |             |               |
|---------|-------------|---------------|
| Male    | 29% (4/14)  | 29% (4/14)    | 0% (0/14)     |
| Female  | 47% (7/15)  | 47% (7/15)    | 7% (1/15)     |

| HIV serostatus | Percentage of cases (n) | Percentage of controls (n) |
|----------------|-------------------------|---------------------------|
| Negative       | 32% (6/19)              | 32% (6/19)                | 0% (0/19)     |
| Positive       | 50% (5/10)              | 50% (5/10)                | 10% (1/10)    |

| TOTAL          | 38% (11/29)             | 38% (11/29)               | 3% (1/29)     |

Table 3: The proportion of cases with evidence of infection with HPV, stratified by histological grade of tumour

| All HPV | Genital HPV | Cutaneous-HPV |
|---------|-------------|---------------|
| CIN I   | 47% (8/17)  | 35% (6/17)    | 29% (5/17)    |
| CIN II  | 56% (10/18) | 50% (9/18)    | 28% (5/18)    |
| CIN III | 45% (10/22) | 27% (6/22)    | 23% (5/22)    |
| Invasive| 42% (10/24) | 42% (10/24)   | 13% (3/24)    |

| TOTAL          | 47% (38/81)  | 38% (31/81)   | 22% (18/81)   |

1. $\chi^2$ (trend) = 1.9; p = 0.2
Infectious Agents and Cancer 2008, 3:12

(five studies failed to identify HPV 16 in either the cases or controls). In most studies, type-specific methods of HPV detection were used and so the types shown in the tables were the only ones that were tested for.

Only three studies (including this one [68,69]) investigated cutaneous HPV types – each demonstrated a significantly higher prevalence of cutaneous HPV in cases as compared to controls (summarised in Table 7). Two of the three studies examined the prevalence according to histological grade of tumour (this study and reference 69) and no association was demonstrated in either.

There is substantial variation in HPV prevalence rates between different studies, which may have arisen, in part, because of differences in patient selection, sample taking, preparation and storage and detection method. Even for PCR as a detection system, there are many variables that influence the sensitivity and specificity and so could impact on the reported prevalence. This review was not done to draw attention to these differences, but rather to show that there is no consistent evidence for a causal association between HPV and OSSN. In addition, however, it should be noted that the total

| Study [Reference] | Detection method | Number HPV positive/total (%) | HPV type |
|------------------|------------------|-------------------------------|----------|
| McDonnell et al, 1987 [46] | In situ hybridisation (ISH) | 0/28 (0%) | HPV 2, 6, 16, 18 |
| McDonnell et al, 1989 [47] | PCR | 1/1 (100%) | HPV 16 |
| Lauer et al, 1990 [48] | PCR | 4/5 (80%) | HPV 16 |
| Odrich et al, 1991 [49] | PCR | 2/2 (100%) | HPV 16 |
| McDonnell et al, 1992 [50] | PCR | 33/38 (87%) | HPV 16 |
| Tuppurainen et al, 1992 [51] | ISH and PCR | 0/4 (0%) | HPV 6, 11, 16 and 18 |
| Serna et al, 1995 [52] | PCR | 1/9 (11%) | HPV 16 |
| Nakamura et al, 1997 [53] | ISH and PCR | 2/8 (25%) | HPV 16 |
| Toth et al, 2000 [54] | PCR | 5/23 (9%) | HPV types not specified |
| Eng et al, 2002 [55] | PCR | 0/20 (0%) | HPV 6, 11, 16, 18 |
| Moubayed et al, 2004 [56] | ISH | 12/14 (86%) | HPV 16 |
| Reszec and Sulkowski, 2005 [57] | PCR | 1/11 (9%) | HPV 16 |
number of cases and controls studied in this and in other studies, remains relatively small.

Results reported here are also broadly similar to those from case-control studies investigating the role of HPV in the aetiology of cutaneous squamous cell carcinoma (SCC) [71,72]. Moderate associations between cutaneous HPV types and cutaneous SCC have been identified, but doubt remains about whether this is causal. It has been suggested that the increased serorecognition of HPV among cases as compared to controls may arise as a result of tumour formation [73]. Some support for this view comes from a recent small prospective study, in which the seroprevalence of antibodies against the L1 antigen of 38 HPV types among 39 cases of cutaneous squamous cell carcinoma (SCC) for whom plasma was collected prior to diagnosis (incident) and 80 controls was examined [72]. Fifteen cases having already developed SCC at blood collection (prevalent) were also tested. There were no statistically significant differences in the seroprevalence of antibodies against any of the HPV types examined between incident cases and controls, nor was there a difference in the seroprevalence of multiple infections. However, consistent with results from published case-control studies, the seroprevalence against many cutaneous HPV types was higher among prevalent cases than among either incident cases or controls. This might suggest that if HPV is involved in the aetiology of cutaneous squamous

| Study [Reference] | Prevalence of cutaneous HPV (number/total) | Odds Ratio (95% Confidence Interval) and p value |
|-------------------|--------------------------------------------|-----------------------------------------------|
| Case              | Control                                    |                                              |
| Ateenyi-Agaba et al, 2004 [68] | 86% (18/21) | 35% (7/20) | 12.0 (1.7–84.9), p = 0.002<sup>1</sup> |
| Tornesello et al, 2006 [69] | 17% (15/86) | 0% (0/63) | ∞ (2.5–∞), p = 0.002<sup>2</sup> |
| de Koning et al [this study] | 22% (18/81) | 3% (1/29) | 8.0 (1.0–168.5), p = 0.04 |

1. For comparative purposes, the unadjusted odds ratio is shown
2. Estimated using Fisher exact test
Infectious Agents and Cancer 2008, 3:12

The possibility that the presence of a tumour facilitates detection of antibodies against HPV is supported by the findings of Favre et al (2000), who reported a higher seroprevalence of HPV-5 among patients with burns or with proliferative cutaneous autoimmune diseases than among controls [74]. Patients with psoriasis, involving abnormal keratinocyte differentiation and proliferation, have also shown a high HPV-5 seroprevalence [75]. This is thought to arise as a consequence of cell proliferation in the skin providing an environment that favours viral replication, resulting in a rise in antibodies against the relevant HPV type. Similarly, there is debate concerning the results obtained from studies using tests for cutaneous HPV DNA. The prevalence of HPV DNA was significantly lower in tumour biopsies than in swabs of the tested lesion [76]. Furthermore, evidence of cutaneous HPV DNA has been found to be both highly prevalent and persistent in the healthy population [77]. It is possible that the results reported here reflect a similar situation. However, there is now some preliminary evidence from studies of molecular mechanisms, suggesting that HPV might interact with ultra-violet radiation disturbing apoptotic pathways and leading to cell immortalization [78]. Transforming properties of E6 and E7 proteins of some cutaneous HPV types have also been described (reviewed in reference [71]). It remains to be established what role, if any, HPV plays in the pathological processes that lead to the development of both conjunctival and cutaneous squamous cell neoplasia.

It should be noted that the relatively high percentage of samples with unclassified cutaneous HPV types could represent infections with novel types of which only subgenomic amplicons have been sequenced [79]. However, the other possibility is that these were infections with low copy numbers of one of the 25 tested cutaneous HPV types allowing only for general detection and not the identification of specific types. With the broad spectrum SPF10 PCR – DEIA (see Methods section) more than 50 HPV types can be detected. It cannot, therefore, be excluded that the two cases with an indeterminate genital HPV result actually represent a cutaneous HPV type. The SPF10-LiPA25 system amplifies a small fragment from 65 base pairs and is therefore very suitable for the testing of paraffin-embedded, formalin-fixed samples. Although the conjunctiva represent mucosal tissue, the detection of genital HPV types in 40% of the HIV seronegative cases and in 32% of the HIV seronegative controls was unexpected. This finding indicates that the natural history of HPV and their tissue tropism is not fully understood.

Conclusion
We find no evidence of an association between genital HPV types and ocular surface squamous neoplasia. The prevalence of cutaneous HPV was significantly higher among cases as compared to controls. Although consistent with results from two other case-control studies, the relatively low prevalence of cutaneous HPV types among cases (which does not differ by histological grade of tumour) indicates that there remains considerable uncertainty about a role for cutaneous HPV in the aetiology of this tumour.

Methods
Participants
From November 1995 to May 2001 in country-wide clinics, anyone with a suspect corneo-conjunctival lesion was offered removal and histology, and enrolment in a follow-up study with home visits. HIV serology was also offered after pre-test counselling. Lesions were photographed and details of the eyes and general health were recorded and analysed in EPI INFO version 6. Those who subsequently turned out to have lesions other than ocular surface squamous neoplasia were used as a control group in the analyses of HPV.

Consent and ethical approval
Information about the disease, its treatment and HIV testing was given in private in vernacular by counsellors, and consent confirmed by signature or thumbprint. The study was approved by the Science and Ethics Committee of the Uganda Virus Research Institute, and by the Uganda National Council for Science and Technology.

Serology and histopathology
Venous blood was taken and screening tests for HIV antibodies done, with confirmation at the Uganda Virus Research Institute (two enzyme immunoassay tests in parallel, with Western blot if required). Biopsies went to St Thomas’ Hospital London for histopathology. CIN was classified (by SBL) into 3 stages according to one, two or three thirds thickness being dysplastic; invasive tumours were diagnosed when the epithelial basement membrane was breached.

HPV typing
HPV analyses were performed on DNA isolated from formalin-fixed, paraffin-embedded specimens. Chances of contamination during the cutting of the sections were minimised by discarding the initial section that was cut to remove any environmental contamination which had occurred while blocks were stored and by changing cryostat blades in between sections. DNA was extracted from the sections in a cabinet which had been UV-treated to remove any contaminating DNA. Additionally, 15 negative DNA isolation controls were included. For both the
infectious agents and cancer

Infectious Agents and Cancer 2008, 3:12

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Page 7 of 9

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