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BRIEF REPORT

Epstein-Barr Virus DNA Is Associated With Conjunctival Squamous Cell Carcinomas: A Case-Control Study From Zimbabwe

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Incidence of conjunctival squamous cell carcinoma (cSCC) in Zimbabwe is >30-fold higher than the global average. cSCC risk is notably higher among people with human immunodeficiency virus, implicating impaired immune response and a yet unknown infectious etiology. Formalin-fixed, paraffin-embedded blocks from Zimbabwe, comprising conjunctival precancer (n = 78), invasive cSCC cases (n = 148) and nonmalignant eye lesions (n = 119), were tested for multiple DNA viruses using Luminex bead–based technology. Epstein-Barr virus (EBV) type 1 positivity was strongly associated with cSCC diagnosis (adjusted odds ratio [aOR], 5.6 [95% confidence interval {CI}, 3.0–10.4) and marginally associated with precancer (aOR, 2.1 [95% CI, 1.0–4.5]). On analyzing EBV transcriptional activity with any of LMP1, EBNA1, and BZLF1, RNA transcripts were detected in 5 of 112 controls, 3 of 67 precancers, and 10 of 139 cases and none were associated with conjunctival case status. Our EBV DNA data suggest that EBV may play a role in cSCC. However, the low detection rate of EBV RNA supports further investigation to infer causality.

Keywords. conjunctival lesions; EBV; human herpesvirus 4; viral infections; Zimbabwe.

Conjunctival squamous cell carcinomas (cSCCs) represent a subtype of ocular squamous cell neoplasia (OSSN) arising in the conjunctiva, the connective squamous epithelial tissue that lines the eyelids and covers the sclera (white of the eye) [1]. cSCC disproportionately affects populations from sub-Saharan Africa, the geographic region with the highest prevalence of human immunodeficiency virus (HIV) [2, 3]. A strong association between cSCC and HIV status reported in prior research suggests an underlying infectious etiology for this tumor [4–6]. cSCC rates in Zimbabwe, the location of this report, can be as high as 3.4 per 100 000, which is >30-fold higher than the global average.

Exposure to ultraviolet light is the only identified epidemiological risk factor for cSCC [7] to date, but an infectious etiology has been postulated [8]. Prior investigations into a viral etiology for cSCC have primarily focused on cutaneous human papillomavirus (HPV) genotypes [6, 9, 10], although more recent data [6, 11] suggest an association between a cSCC diagnosis and human herpesvirus 4, known as Epstein-Barr virus (EBV). One study from Zambia recently reported EBV DNA detection rates of 80.3% in 178 tissue samples obtained from OSSNs [11]. However, that study did not include benign lesion samples as a comparator group and combined both conjunctival and corneal tissue in the case group.

In this report, we evaluated presence of viral DNA for multiple human herpesviruses and HPV types in tissue from histologically confirmed conjunctival precancerous lesions, invasive cSCC cases, and a control group of tissue sampled from nonmalignant eye lesions. This report is timely given the upward trend of cSCC diagnoses in Zimbabwe, with an observed 20-fold increase over the last 3 decades [2, 12].

METHODS

Patient Consent Statement

Ethical approvals were received from the Joint Research Ethics Committee for the University of Zimbabwe and Parirenyatwa Hospital (JREC/335/21), Medical Research Council of Zimbabwe (MRCZ/A/2651), and Research Council of Zimbabwe (RCZ 04047). We conducted a case-control study

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that retrieved formalin-fixed, paraffin-embedded (FFPE) blocks from Parirenyatwa tertiary hospital histopathology archives in Harare, Zimbabwe. Informed consent was waivered as only de-identified archived samples were used and participants' contact details were not provided.

Retrieval of Tissue and Laboratory Processing

The retrieved tissue had a diagnosis made between 1 January 2015 and 31 December 2019. The case group was comprised of 148 histologically confirmed cSCC lesions and 78 conjunctival precancerous lesions. Samples were classified as precancerous if they were reported as conjunctival dysplasia or intraepithelial neoplasia (CIN 1–3). FFPE blocks from 119 patients with histologically confirmed benign eye lesions (pterygium, trauma, polyp, cyst, and inflammation) and diagnosed within the same period were included as controls. Eligible controls were matched, when possible, to the combined precancer and cancer case group by sex and by ± 10 years age range. Age, sex, HIV status (when available), histopathology findings, and dates of diagnosis were abstracted. All selected FFPE blocks had histology readings from 2 pathologists at the laboratory in Zimbabwe, as routine practice to assess histology diagnosis variability and ascertain reproducibility. The hematoxylin and eosin slides cut from the blocks were further blindly reread by a third pathologist at Istituto di Ricovero e Cura a Carattere Scientifico – Istituto Tumori 'Giovanni Paolo II' Istituto Tumori Giovanni Paolo ll, Bari, Italy. Of the 322 histology slides that were read by a third pathologist, 78.3% were concordant, 14% lacked adequate tissue for analysis, and 8% were discordant.

DNA was extracted from all FFPE sections using an International Agency for Research on Cancer (IARC) in-house protocol [13]. Viral DNA for 21 mucosal α-HPV and 46 β-HPV genotypes and 3 human herpesviruses (cytomegalovirus [CMV] and EBV type 1 [EBV1] and type 2 [EBV2]) were amplified by multiplex polymerase chain reaction (PCR) using 3 different sets of primers. Two primers for amplifying β-globin were included in each reaction as a control to confirm adequacy of the viral DNA extraction and PCR amplification. β-Globin was commonly detected when running the assays for herpesviruses (n = 318 [92.2%]) and mucosal HPVs (n = 313 [90.7%]), although detection was lower for β-HPVs (n = 201 [58.3%]). Only samples with detectable β-globin (ie, able to adequately assess the quality of extracted DNA) were included in the statistical analyses. Following PCR amplification, viral typing was performed using Luminex bead–based assays (Luminex, Austin, Texas), as described in detail previously [14, 15].

Total RNA was purified from 3 pooled sections of the same tissue block using the Pure Link FFPE Total RNA Isolation Kit (Invitrogen, Carlsbad, California) as described previously [16], and treated with DNase.

Reverse-transcription PCR was carried out using the QuantiTect Virus Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions, and combined to a bead-based Luminex technology for the detection of the following EBV transcripts: latent membrane protein 1 (LMP1), EBV nuclear antigen 1 (EBNA1), and BZLF1 (also known as Zta or Zebra), as well as the ubiquitin C (ubC) transcript for assessing the RNA quality. The primer and probe sequences are available upon request.

All statistical analyses were performed using Stata version 14.0 software. Demographic and clinical characteristics were summarized using mean and standard deviation for age and counts, and percentages for the categorical variables. Logistic regression was performed to test the statistical relationships between virus (with $n > 5$) and case status, first in a univariate analysis and then in a multivariable model, adjusting for sex and age.

RESULTS

A total of 345 tissue specimens were included in the study, comprising 226 cases (78 precancers and 148 invasive cancers) and 119 controls. Although the average age was 48 years in both the case and control group, exact matching was not possible, and a higher percentage of controls were in the <30 years age group compared to cases (16.8% vs 1.3%). No significant differences in sex were observed by case status (Table 1), reflective of the matching design. HIV status was only available for 24% of samples (n = 84), but it was notable that all 84 people with HIV (PWH) were from the case group.

Referring to viral DNA prevalence analyses, the most prevalent virus detected belonged to the herpesvirus group, namely EBV, resulting in 45% and 22% prevalence among cases and controls, respectively. EBV1 was detected more often than EBV2 (41.8% vs 11.2% among cases and 16.1% vs 8.9% among controls) and was statistically significantly associated with case status, even after adjustment for age and sex (adjusted odds ratio [aOR], 4.14 [95% confidence interval {CI}, 2.3–7.5]) (Table 2). When considering conjunctival precancerous lesions separately from invasive cSCC, EBV1 DNA remained strongly associated with an invasive cSCC diagnosis (aOR, 5.58 [95% CI, 3.0–10.4]) and marginally associated with precancer (aOR, 2.1 [95% CI, 1.0–4.5]) (Table 2).

Mucosal HPVs, β-HPVs, and herpesviruses other than EBV were infrequently detected in ≤11% of participants (Supplementary Table 1). For example, β-HPV DNA and CMV DNA were detected in <5 samples per study group, which did not permit robust statistical analyses. HPV-6 DNA detection was inversely associated with case status (aOR, 0.3 [95% CI, .1–.8]) (Supplementary Table 1).

On analyzing the EBV transcriptional activity in EBV DNA–positive samples with any of LMP1, EBNA1, and BZLF1, RNA transcripts were detected in 5 of 112 controls, 3 of 67 precancers, and 10 of 139 cases (Table 2). A total of 4 samples (3

Table 1. Demographic Characteristics of All Participants, Stratified by Case Status

Characteristic	cSCC Cases[a] (n = 226)			Controls[b] (n = 119)	*P* Value
	All	Precancer (n = 78)	Cancer (n = 148)	All	
Age, y					**.82**
Mean (SD)	**47.7 (12.4)**	**48.2 (12.4)**	**47.5 (12.5)**	**48.1 (18.9)**	
<30	**3 (1.3)**	**2 (2.6)**	**1 (0.7)**	**20 (16.8)**	**<.001**
30–39	**52 (23.0)**	**15 (19.2)**	**37 (25)**	**26 (21.9)**	
40–49	**96 (42.5)**	**31 (39.7)**	**65 (43.9)**	**19 (16.0)**	
≥50	**75 (33.2)**	**30 (38.5)**	**45 (30.4)**	**54 (45.4)**	
Sex[c]					**.16**
Female	**119 (53.1)**	**38 (48.7)**	**67 (45.9)**	**72 (61.0)**	
Male	**105 (46.9)**	**40 (51.3)**	**79 (54.1)**	**46 (39.0)**	
HIV status					
Known HIV positive	**84 (37.2)**	**17 (21.8)**	**67 (45.3)**	**0 (0)**	
Unknown	**142 (62.8)**	**61 (78.2)**	**81 (54.7)**	**119 (100)**	
Histology classification among cases					
Low-grade	**13 (5.8)**	**13 (16.7)**	…	…	
High-grade	**65 (28.8)**	**65 (83.3)**	…	…	
Invasive	**148 (65.5)**	…	**148 (100)**	…	
Histology classification among controls					
Pterygium	…	…	…	**81 (68.1)**	
Inflammation	…	…	…	**23 (19.3)**	
Trauma	…	…	…	**12 (10.1)**	
Polyp	…	…	…	**1 (0.8)**	
Cyst	…	…	…	**2 (1.7)**	

Data are presented as No. (%) unless otherwise indicated. Where there are missing *P* values, the variable is presented as descriptive and no *P* value was calculated; where *P* values are provided, they compare all controls versus all cases.

Abbreviations: cSCC, conjunctival squamous cell carcinoma; HIV, human immunodeficiency virus; SD, standard deviation.

[a]Cases are defined as histologically confirmed cSCC (precancer and invasive cSCC).

[b]Controls are defined as histologically confirmed benign lesions; pterygium, inflammation, cyst, polyp, and eye trauma.

[c]Three participants had missing data on sex.

cases and 1 control) were excluded due to invalid RNA as evidenced by negative UbC messenger RNA results. LMP1 RNA was not detected in any precancer specimens and was not associated with invasive cSCC (Table 2), even after adjusting for age and sex (aOR, 1.06 [95% CI, .27–4.08]). Similarly, BZLF1 RNA was not associated with case status, after adjusting for age and sex (precancer: aOR, 1.84 [95% CI, .36–9.48]; invasive cSCC: aOR, 1.77 [95% CI .43–7.33]). None of the specimens tested positive for EBNA1 RNA. Overall, none of the EBV DNA–negative randomly selected specimens (n = 35) tested positive for EBV transcripts.

DISCUSSION

This is the largest study, to our knowledge, to report a strong association of EBV1 DNA with cSCC and precancerous lesions versus a noncancerous lesion comparison group. Our findings are consistent with the recent study from Zambia that detected a high rate of EBV DNA in 105 histology-confirmed invasive and 38 precancerous lesions [11]. They concluded that EBV DNA and EBNA1 protein in all the grades of preinvasive and, especially, invasive OSSN suggested a causal role of EBV. However, they did not include a noncancerous lesion comparison group. Our findings also expand on a smaller prior study of 67 cases, of which 22 were invasive cSCC, and 55 benign conjunctival tissue samples from Uganda [6] that reported significant associations between EBV DNA types 1 and 2 combined and malignant conjunctival lesions (aOR, 12.0 [95% CI, 4.3–33.5]).

Our data do not support an association of mucosal and β-HPVs with conjunctival precancer or cSCC lesions, despite these viruses being the primary focus of prior investigations [6, 9, 10]. Although we detected CMV in cSCC cases (n = 12: 3 PWH and 9 with unknown HIV status) but not in controls (n = 0), the limited sample size makes the association with cSCC unclear, warranting future investigations.

Our study had incomplete HIV data, thus limiting our ability to assess EBV and cSCC associations by HIV status. Previously, cSCC has been reported to be strongly associated with HIV infection [5, 6], including an up to 20-fold increased risk of developing cSCC (aOR, 21.5 [95% CI, 16.3–28.4]) in PWH in South Africa [5]. Additional studies with complete HIV status and more comprehensive HIV clinical data on degree of immunosuppression are needed to elucidate whether HIV is an effect modifier of the EBV–cSCC association. Our study was also limited by the availability of fewer controls than cases, thus inhibiting a perfect match by sex. Although the mean age was similar

Table 2. Logistic Regression–Derived Unadjusted and Adjusted Odds Ratios for the Association Between Epstein-Barr Virus DNA and RNA Detection, and Case Status

EBV DNA and RNA tested	Controls (n = 112)	Precancer (n = 67)	Cancer (n = 139)
Any EBV			
Positive	25 (22.32)	22 (32.84)	71 (51.08)
Negative	87 (77.68)	45 (67.16)	68 (48.92)
Unadjusted OR (95% CI)	Ref	1.70 (.86–3.35)	**3.63 (2.09–6.33)**
Adjusted OR by sex and age (95% CI)	Ref	1.82 (.92–3.62)	**3.92 (2.22–6.91)**
EBV type 1			
Positive	18 (16.07)	18 (26.87)	68 (48.92)
Negative	94 (83.93)	49 (73.13)	71 (51.08)
Unadjusted OR (95% CI)	Ref	1.92 (.92–4.02); $P = .08$	**5.00 (2.73–9.15)**
Adjusted OR by sex and age (95% CI)	Ref	**2.13 (1.00–4.51); $P = .05$**	**5.58 (2.99–10.42)**
EBV type 2			
Positive	10 (18.93)	6 (8.96)	18 (12.95)
Negative	102 (91.07)	61 (91.04)	121 (87.05)
Unadjusted OR (95% CI)	Ref	1.00 (.35–2.90)	1.52 (.67–3.43)
Adjusted OR by sex and age (95% CI)	Ref	.98 (.34–2.85)	1.41 (.62–3.23)
Any EBV RNA			
Positive	5 (4.46)	3 (4.48)	10 (7.19)
Negative	107 (95.54)	64 (95.52)	129 (92.81)
Unadjusted OR (95% CI)	Ref	1.00 (.23–4.34)	1.66 (.55–5.00)
Adjusted OR by sex and age (95% CI)	Ref	1.31 (.28–6.08)	2.18 (.66–7.17)
LMP1 RNA			
Positive	4 (3.57)	0 (0)	5 (3.6)
Negative	108 (96.43)	67 (100)	134 (96.4)
Unadjusted OR (95% CI)	Ref	0 (0)	1.01 (.26–3.84)
Adjusted OR by sex and age (95% CI)	Ref	0 (0)	1.06 (.27–4.08)
BZLF1 RNA			
Positive	4 (3.57)	3 (4.48)	6 (4.32)
Negative	108 (96.43)	64 (95.52)	133 (95.68)
Unadjusted OR (95% CI)	Ref	1.27 (.27–5.84)	1.22 (.34–4.43)
Adjusted OR by sex and age (95% CI)	Ref	1.84 (.36–9.48)	1.77 (.43–7.33)

Data are presented as No. (%) unless otherwise indicated. Only EBV β-globin–positive samples were included in this analysis (n = 318; 112 controls, 67 precancer [low-grade and high-grade] and 139 cancer [conjunctival squamous cell carcinoma] samples).

Abbreviations: BZLF1, BamHI Z fragment leftward open reading frame 1; CI, confidence interval; EBV, Epstein-Barr virus; LMP1, latent membrane protein 1; OR, odds ratio.

for both groups, sex distribution may have been biased. Therefore, we adjusted for both sex and age in our analysis.

It is biologically plausible that EBV can lead to malignancy, as it is classified as a group 1 carcinogen by IARC and has been previously linked to human cancers including nasopharyngeal carcinoma and various lymphoid malignancies [17]. The more pronounced association of EBV DNA with conjunctival precancer and cancer lesions in our study suggests a possible dose-response association between EBV DNA detection and degree of conjunctival squamous cell carcinogenesis. The detection of EBV DNA supported our hypothesis that EBV, an established oncogenic virus for various malignancies, might play a significant role in conjunctival cancer development. However, the lack of association with EBV RNA warrants further investigations to strengthen this inference. It is worth highlighting that BZLF1 is known to turn EBV from latent cycle to lytic cycle [18] and was the most detected RNA transcript in our study. Furthermore, BZLF1 has previously been observed in EBV-related tumors such as Burkitt lymphoma [19], thus indicating the need for further investigation of its association in conjunctival lesions. We recommend performing prospective studies, using snap-frozen cancer tissues, to optimize detection of EBV RNA and oncogenic protein expression, for any causal inferences to be made. Although our study does not directly assess EBV presence within malignant cells, identifying contributing viruses is a key step toward designing early detection strategies. In the long term, this will avoid both the morbidity associated with severe ocular surgical procedures and the potential detrimental impacts upon household economic security. These data contribute toward design of future experiments to determine the oncogenic potential of EBV among eye lesions, which we could not perform in this study.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization (IARC/WHO), the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the IARC/WHO.

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