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Schistosome Infection is Associated with High-Risk Human Papillomavirus Persistence, Together with Altered Cervicovaginal Microbiota

Crispin Mukerebe[1,2,*], **Alexandra A. Cordeiro**[3], **Christine Aristide**[3], **Soledad Colombe**[3], **Brooke W. Bullington**[3], **Samuel Kalluvya**[4], **Govert J. van Dam**[5], **Claudia J. de Dood**[6], **Paul L.A.M. Corstjens**[6], **Jane K. Maganga**[1], **John M. Changalucha**[1], **Lucy A. Namkinga**[7], **Victor Anacletus Makene**[2], **Myung Hee Lee**[2], **Jennifer A. Downs**[1,2,3]

[1]Mwanza Intervention Trials Unit/National Institute for Medical Research, Tanzania

[2]Department of Molecular Biology and Biotechnology, College of Natural and Applied Sciences, University of Dar es Salaam, Tanzania

[3]Center for Global Health, Weill Cornell Medicine, United States of America

[4]Department of Medicine, Weill Bugando School of Medicine, Tanzania

[5]Leiden University Center for Infectious Diseases, Leiden University Medical Center, The Netherlands

[6]Department of Cell and Chemical Biology, Leiden University Medical Center, The Netherlands

[7]St. Francis College of Health and Allied Sciences, Department of Internal Medicine, Pharmacology and Psychiatry, Tanzania

Abstract

Schistosoma haematobium infection may impair female genital mucosal antiviral defense. We sought to determine whether women with *S. haematobium* infection had higher odds of high-risk human papillomavirus (HR-HPV) persistence, a pre-requisite to cervical cancer. We also examined cervicovaginal dysbiosis, which has been linked to HR-HPV persistence and schistosome infection. In 96 Tanzanian women with baseline and 9–12-month follow-up samples, we performed HPV genotyping, schistosome antigen quantification, and 16S rRNA sequencing. Both *S. haematobium* (Odds ratio (OR): 4.7 [1.3–16.5], p=0.017) and *Gardnerella*-dominant

[*]**Corresponding author:** Crispin Mukerebe, Mwanza Intervention Trials Unit/National Institute for Medical Research, 14, International School Road, Mwanza, Tanzania, crispinmukerebe@yahoo.com.

Authors' contributions

CM: conceptualization, investigation, formal analysis, writing – original draft. AAC: formal analysis, writing – original draft. CA: investigation, project administration. SC: investigation, project administration. BWB: investigation, visualization. SK: supervision. GJvD: supervision, methodology, resources. CdD: investigation, resources. PLAMC: supervision, methodology, resources. JM: conceptualization, interpretation. JC: supervision, interpretation. LN: supervision. VM: supervision. MHL: formal analysis, visualization. JAD: conceptualization, formal analysis, funding acquisition, investigation, methodology, writing – original draft. All authors reviewed and approved the final manuscript for submission.

Conflict of interest

The authors declare no conflict of interest.

This study demonstrates increased odds of persistent high-risk human papillomavirus infection in the cervix of women in Tanzania who had schistosome infection or altered cervicovaginal microbiota, suggesting an elevated risk of cervical cancer in areas where these infections are endemic.

microbiome (p=0.049) were associated with HR-HPV persistence, suggesting these factors may contribute to high cervical cancer rates in Africa.

Keywords

S. haematobium ; high-risk human papillomavirus; cervicovaginal dysbiosis

Introduction

An estimated 100 million girls and women suffer from schistosome infections in Africa [1]. Parasitic *Schistosoma haematobium* and *S. mansoni* worms reside in venules of the urogenital and gastrointestinal tracts and lay eggs that migrate through mucosal tissue, inducing a host immune reaction and secreting proteolytic enzymes that damage tissue. When the genital tract is involved, known as female genital schistosomiasis (FGS), sequelae include mucosal breaches, bleeding, and long-term fibrosis [2]. Further, human and animal studies have demonstrated that schistosomes impair host mucosal anti-viral control, potentially allowing viruses that infect mucosal tissue to persist and flourish [3,4].

We and others have hypothesized that, through its effects on the genital mucosal immunity, *S. haematobium* infection may promote high-risk human papillomavirus (HR-HPV) persistence, defined as detection of the same HR-HPV genotype in an individual at two time points at least 6 months apart [5]. Persistence of HPV infection in the cervix occurs in ~10–20% of women who acquire HPV [5], and contributes to nearly all cases of cervical cancer. *S. haematobium* eggs are a group I carcinogen causing squamous cell carcinoma of the urinary bladder, but whether and how they contribute to cervical cancer is not well understood. Limited data exist describing HR-HPV prevalence and persistence in the context of FGS, and evidence on their association is mixed. A recent systematic review concluded that, while there may be associations between prevalent HR-HPV or cervical pre-cancer and *S. haematobium,* limited and inconsistent evidence precludes definite conclusions [6]. Additionally, cervicovaginal dysbiosis has been linked to both HPV persistence and schistosome infection [7,8].

To quantify the association of both *S. haematobium* and *S. mansoni* infection with HR-HPV persistence, we analyzed prospectively collected biobanked samples. We assessed schistosome infection overall, and hypothesized *a priori* that *S. haematobium* infection, which preferentially affects the genital tract, would be most strongly associated with HR-HPV persistence. We further leveraged cervicovaginal microbiota data from the same cohort to assess for the association of non-*Lactobacillus*-dominant microbiota with HR-HPV persistence.

Methods

Past prospective study.

Procedures for original data collection between July 2017 and September 2019 have been described [8]. Briefly, women were enrolled into two 12-month cohorts: one from communities endemic with *S. mansoni* and <2% *S. haematobium,* and one from

communities endemic with *S. haematobium* and <2% *S. mansoni.* In each cohort, approximately equal numbers of women with and without schistosome infection were enrolled. Pregnant women were excluded due to the need to sample the cervix.

Baseline sociodemographic and clinical data were recorded. At quarterly visits, we collected blood for voluntary HIV counseling and testing and schistosome circulating anodic antigen (CAA) testing, urine, and stool. Gynecologic examinations included swab collection for sexually-transmitted infection (STI) testing and 16S rRNA sequencing of cervicovaginal microbiota.

To test our primary hypothesis that schistosome infection was associated with HR-HPV persistence, we compared schistosome infection and other genital infections between those with and without HR-HPV. Women with HIV were excluded from analysis given its known association with HR-HPV persistence.

Study definitions.

We defined HR-HPV as the HPV types associated with cervical cancer. These included 12 types consistently classified as high-risk for cervical cancer (HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59), one probable high-risk type (HPV-68), and seven possible high-risk types (HPV-26, HPV-53, HPV-66, HPV-69, HPV-70, HPV-73, and HPV-82) [9,10]. The assay also quantified eight low-risk types: HPV-6, HPV-11, HPV-40, HPV-42, HPV-43, HPV-44, HPV-54, and HPV-61.

We defined schistosome infection as serum CAA ≥30 pg/mL using up-converting reporter particle technology with the dry SCAA20 lateral flow assay performed at the National Institute for Medical Research (NIMR) laboratory in Mwanza [11]. Urine filtration and Kato Katz stool preparations were examined microscopically for schistosome eggs. Women who were CAA positive but microscopy egg-negative were assumed to have the schistosome species most dominant in their community. All participants with eggs or CAA positivity received praziquantel as soon as either was detected.

HPV type testing.

DNA was extracted from baseline and 9- or 12-month (endline) endocervical swabs for retrospective HPV detection and genotyping with the Allplex HPV28 kit (Seegene, Korea) using a CFX96 Dx real-time multiplex PCR system (Bio-Rad Laboratories, USA). We defined HPV persistence as presence of the same HPV genotype at baseline and endline.

STI testing.

Vaginal swabs were tested on-site for *Trichomonas vaginalis* (OSOM® rapid test, Sekisui Diagnostics, USA). Cervicovaginal swabs had DNA extracted by QIAamp DNA mini-kit (Qiagen, Germany), and qPCR to detect *Chlamydia trachomatis* and *Neisseria gonorrhea* DNA was performed using the artus CT/NG QS-RGQ kit and Rotor-Gene Q system (Qiagen). Extractions and PCRs were performed in the NIMR-Mwanza laboratory. STIs were treated free of charge.

16S rRNA sequencing.

We sequenced 16S rRNA from baseline cervicovaginal swabs, as previously described [8]. Briefly, cervicovaginal COPAN ESwabs™ (ThermoScientific, USA), kept at −80°C until analysis, had DNA extracted by phenol/chloroform/isoamyl and the 16S rRNA gene amplified. Libraries were prepared with TruSeq DNA library preparation kit (Illumina, USA) and sequenced on the Illumina MiSeq platform using a paired-end 250×250-bp kit. The DADA2 pipeline was used for amplicon sequence variant grouping [8].

Statistical analysis.

We compared characteristics between those with and without HR-HPV persistence using logistic regression or Fisher's Exact test if any cell count was <5. Multivariable models were not pursued to maintain an appropriate events-per-variable ratio (>10) and reduce risk of overfitting. For microbiota analysis, we used procedures described previously, including filtering out rare taxa (<0.1% of relative abundance (RA) or detected in only a single sample) prior to downstream analysis [8]. Observed microbiota for each participant were classified into community types [12]. The distribution across community types by HR-HPV persistence status was assessed by Fisher's Exact test. We compared RA and alpha diversity (supplemental) by HR-HPV persistence using the rank-sum test. Analyses used R version 4.4.2.

Ethics.

Ethical approval was obtained from the National Institute for Medical Research (NIMR/HQ/R.8a/Vol.IX/2446), Weill Cornell Medicine (#1612017800), and Bugando Medical Centre/Catholic University for Health and Allied Sciences (CREC/171/2017). All participants provided written informed consent.

Results

Within the initial cohort of 147 women, 96 without HIV co-infection were followed beyond 6 months and had paired baseline and endline samples for HPV genotyping. The mean age was 32.7+/−9.2 years, 75% were married, and mean years of schooling were 5.7+/−3.1. Among these 96, 63 (66%) had any HPV type detected at baseline, of whom 51 (81%) had HR-HPV. The most frequent HR-HPV types were HPV-35, HPV-39, and HPV-68. Among those who had HR-HPV at baseline, 12 had persistence of the same HPV type at endline. HR-HPV types that persisted were HPV-16, HPV-26, HPV-31, HPV-35 (n=2), HPV-45 (n=2), HPV-52, HPV-53 (n=3), HPV-56, and HPV-73. One woman had persistence of three genotypes and all others had one. There were no differences in sociodemographic characteristics between women with versus without HR-HPV persistence including age, age at first sex, and recent contraceptive use (Supplementary Table 1).

Thirty-nine women (41%) had schistosome infection at baseline compared to 21 women (22%) at endline after quarterly testing and treatment. There were no differences in rates of baseline HR-HPV infection, or overall HPV infections, between women with and without baseline schistosome infection. Endline schistosome infection was strongly associated with HR-HPV persistence on univariable analysis (OR=4.7 [1.3–16.5], p=0.017). Gonorrhea and

chlamydia infections tended to be more common among those with HR-HPV persistence (Figure 1A).

Baseline cervicovaginal microbiota were characterized in 86 women (90%). The RA of bacterial genera is depicted in stacked composition bar graphs (Figure 1B). Persistent HR-HPV was associated with shifts in the distribution of community types (p=0.026); women with persistent HR-HPV more frequently had *Gardnerella* dominance (33% versus 8% of women, p=0.049), and although not significant, *Lactobacillus* dominance was less common (zero versus 26%, p=0.11). The RA of *Gardnerella* was also higher in this group (31% versus 13%, p=0.031). The predominant *Lactobacillus* species identified was *L. iners* (2.6% versus 25.8%, p=0.069); all other *Lactobacillus* species had mean RAs <1.5%.

On a pre-specified sub-analysis to examine potential contributions of schistosome infection by species, the odds of HR-HPV persistence remained elevated among women with schistosome infection living in *S. haematobium* endemic communities (OR=2.7 [0.4–5.0], p=0.020, n=42), but did not differ between those with and without schistosome infection living in *S. mansoni* endemic communities (n=54).

Discussion

To our knowledge, this is the first study to document a robust increased odds of HR-HPV persistence in women with schistosome infection. Our group has previously reported altered cervicovaginal microbiota in schistosome infections [8], and the finding that cervicovaginal dysbiosis was also associated with HR-HPV persistence in our cohort further strengthens the veracity of our data given well-known linkages of dysbiosis with HR-HPV acquisition, persistence, and cervical dysplasia [7] Understanding factors that drive HPV persistence is critical to improving cervical cancer prevention worldwide. This is particularly important in sub-Saharan Africa, where cervical cancer incidence and mortality are the world's highest [13]. Further, the high diversity of HPV types in Africa will lead to ongoing circulation of HR-HPV types even with wide use of prophylactic HPV vaccines [13]. To advance this discussion, we propose a causal pathway for contributors to HR-HPV persistence among women with schistosome infections.

Figure 2 depicts at least three plausible mechanisms by which schistosome infections may exacerbate cervical HPV persistence. First, egg migration through the genital mucosa–which occurs both in *S. haematobium* and *S. mansoni* infection–disrupts the genital epithelial barrier, altering mucosal gene expression [3]. Second, migration of immunogenic eggs evokes a type 2 immune environment, with concomitant decreases in type 1 anti-viral responses, both in mucosa and systemically [3,4]. This altered type 2 environment has been associated with increased infectivity of HIV and reactivation of herpesvirus in *S. mansoni* infection [3,4]. Notably, genital mucosal cytokine alterations are also linked with HPV persistence [14]. Third, we documented that cervicovaginal dysbiosis, marked by high microbial diversity or *Lactobacillus* deficiency, was associated with schistosome infection [8]. A meta-analysis of >100,000 women and robust human and animal data indicate that cervicovaginal dysbiosis potentiates HPV persistence and is itself potentiated by HPV [7]. Together, these data highlight the multiple genital mucosal effects of schistosome infection

that may enhance HPV persistence. Future larger studies could use mediation analysis to test these pathways and quantify effects.

We report no association of *S. haematobium* with HR-HPV prevalence, suggesting that *S. haematobium* does not affect susceptibility to HR-HPV but could alter viral clearance. Our data contrast with data from Zimbabwe in which women with FGS (defined as cervical lesions or eggs in the genital tract), versus women without, had more prevalent baseline HR-HPV, but not more persistent HR-HPV among the subset of 37 women (69%) examined after 5 years [15]. We posit that the study's low follow-up and nonspecific definition of FGS may explain its discrepant finding. We performed systemic antigenic detection of active *S. haematobium*, which does not guarantee genital tract involvement, and still found significant differences in genital mucosal HR-HPV persistence. This suggests that systemic *S. haematobium* infection involves the genital tract, whether through direct effects of eggs or indirect immune modulation, more frequently than previously recognized. Interestingly, soil-transmitted helminth infections in the gut have also been associated with increased cervical HPV prevalence and altered cervical cytokines [16].

This study has strengths and limitations. The relatively small size precluded multivariable analysis and potentially lowered power to detect other associations of HR-HPV. Furthermore, we could not establish the impact of anti-helminth treatment on HR-HPV persistence since all women were treated whenever schistosome infection was diagnosed. The association of endline schistosome infection with HR-HPV persistence may be because women with endline schistosome infection despite quarterly testing and treatments had greater schistosome burden and/or exposure. Key strengths include this study's hypothesis-driven testing and our finding that HR-HPV was associated with dysbiosis, consistent with other studies. Additionally, point estimates indicating higher HR-HPV persistence among individuals with chlamydia and gonorrhea underscore the reliability of our data.

In conclusion, our findings offer novel evidence that vaginal dysbiosis in schistosome-endemic settings may facilitate HR-HPV persistence. Our data suggest that *S. haematobium* infection may contribute to HR-HPV persistence, and increase the risk of cervical cancer, in areas in which these infections overlap.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A

Genital Tract Finding	No HR-HPV persistence	HR-HPV persistence	p-value	Odds ratio [95% CI]
Genital infections	**n=84**	**n=12**		
Schistosome infection at baseline	34 (40%)	5 (42%)	0.85	1.1 [0.4-3.5]
Schistosome infection at endline	15 (18%)	6 (50%)	**0.017**	**4.7 [1.3-16.5]**
Chlamydia infection	6 (7%)	2 (18%)	0.24	**
Gonorrhea infection	3 (4%)	1 (9%)	0.41	**
Trichomonas infection	22 (27%)	1 (8%)	0.28	**
Cervicovaginal microbiota	**n=77**	**n=9**		
Community type (baseline)			**0.026**	**
CT 1-2¥ (*Lactobacillus* dominant)	20 (26%)	0		
CT 3 (*Gardnerella* dominant)	6 (8%)	3 (33%)		
CT 4 (Mixed microbial communities)	51 (66%)	6 (67%)		
Gardnerella dominance (baseline)*	6 (8%)	3 (33%)	**0.049**	**
Relative abundance of *Gardnerella* at baseline (% median [IQR])	13% [5,25]	31% [16,35]	**0.031**	**

*dominance defined as >50% **no odds ratio calculated; Fisher's Exact test used
¥Includes combination of CT1 (non-*L. iners Lactobacillus* dominant, n=1) and CT2 (*L. iners* dominant, n=19)

B

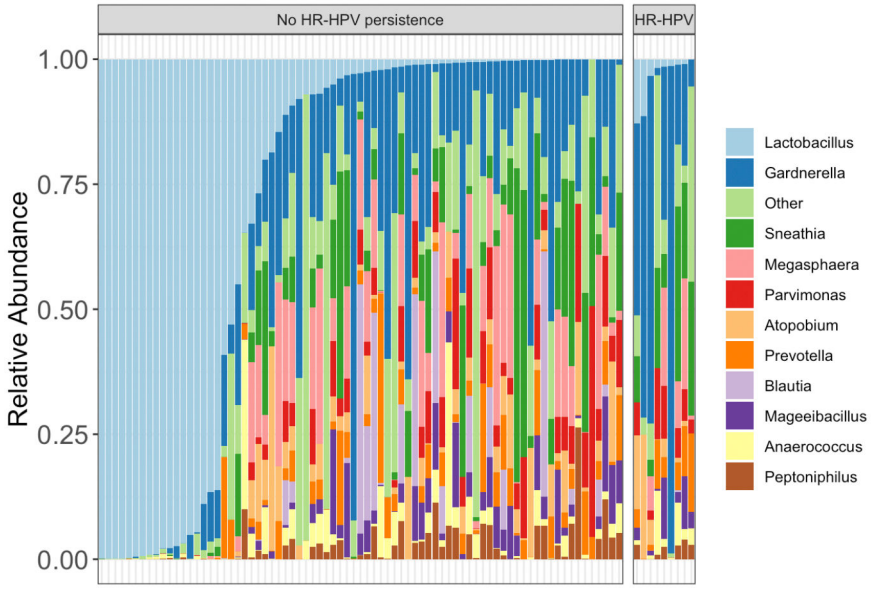

Figure 1. Genital tract infections and cervicovaginal microbiota in women with and without persistent HR-HPV.

(A) Genital infections associated with HR-HPV persistence.

(B) Relative abundance of cervicovaginal microbiota in women without persistent HR-HPV (left side) and with persistent HR-HPV (right).

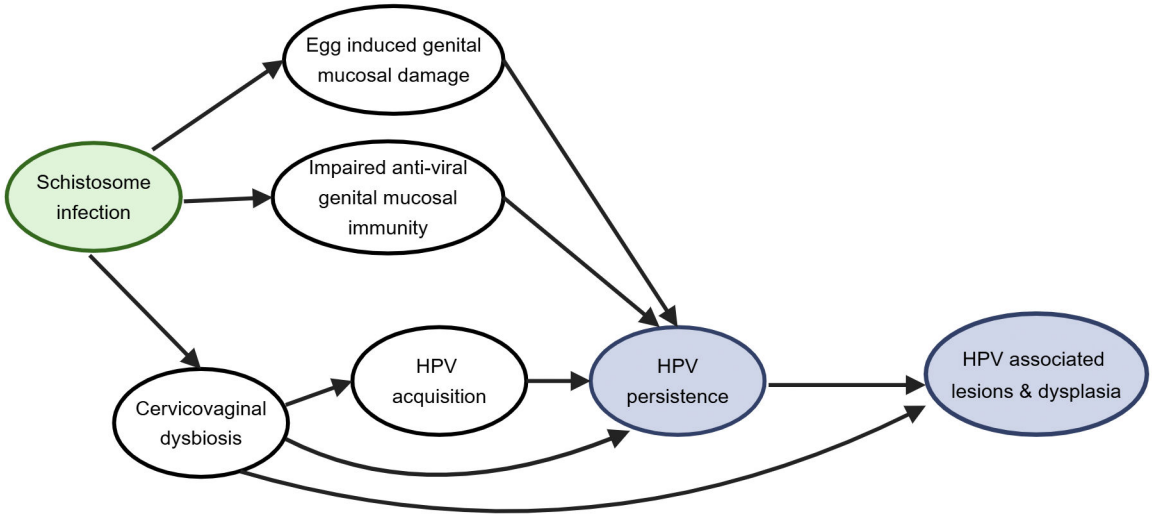

Image created with BioRender.com and with guidance from Textor J et al, Int J Epi 2016 and DAGitty.net.

Figure 2.

Proposed directed acyclic graph for factors contributing to HPV persistence and dysplasia in the setting of schistosome infections.