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Clinical Performance of Digital Cervicography and Cytology for Cervical Cancer Screening in HIV-infected Women in Lusaka, Zambia

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Abstract

While there is a growing literature on the clinical performance of VIA in HIV-infected women, to our knowledge none have studied VIA enhanced by digital cervicography. We estimated clinical performance of cervicography and cytology to detect cervical intraepithelial neoplasia grade 2 or worse. Sensitivity and specificity of cervicography were 84% (95% confidence interval [CI]: 72%–91%) and 58% (95%CI: 52%–64%). At the high-grade squamous intraepithelial lesion or worse cutoff for cytology, sensitivity and specificity were 61% (95%CI: 48%–72%) and 58% (95%CI: 52%–64%). In our study, cervicography appears to be as good as cytology in HIV-infected women.

Keywords

Cervical cancer; cytology; digital cervicography; HIV/AIDS; screening

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Conflicts of Interest

No conflicts of interest were declared for the remaining authors.

INTRODUCTION

Cervical cytology has helped reduce cervical cancer mortality in the developed world,[1,2] but the lack of trained personnel and limited laboratory and patient-recall infrastructure has hindered implementation of cytology-based screening in much of the developing world. Visual inspection with acetic acid (VIA) is a low-cost alternative that can be performed by non-physician health providers, and has become a popular screening option in resource-constrained countries.[3]

HIV-infected women in developing countries are a high-risk group for cervical cancer, particularly with longer life spans on affordable antiretroviral therapy, but generally have little or no access to quality cervical cancer screening services.[4,5] Cytology and VIA-based screening have been compared in several studies,[6,7] but few have focused on HIV-infected women,[8–10] and none of the studies in HIV-infected women have evaluated VIA enhanced by digital cervicography (DC). DC is an adjunct to VIA and involves digital photography of the cervix, using a commercial brand camera, to allow for magnified visualization of surface morphology, while also facilitating telemedicine support, patient and provider education, and quality assurance of screening.[11]

Zambia has a particularly high burden of cervical cancer, with the second-highest incidence and highest mortality rates in the world.[1,2] The Cervical Cancer Prevention Program in Zambia (CCPPZ), a public-sector initiative, offers nurse-led services with DC with same-day cryotherapy for eligible precancerous lesions, or referral for loop electrosurgical excision procedure (LEEP) treatment for cryotherapy-ineligible lesions.[12,13] Surgical, radiation, and chemotherapy services for management of invasive cervical cancer are offered through Zambian Ministry of Health facilities.

To assess the clinical performance of DC, a resource-appropriate screening technology, as well as cytology in HIV-infected women, we enrolled HIV-infected women in Zambia and calculated the clinical performance of each screening test to detect cervical lesions on histopathology.

METHODS

Participants were enrolled between January 2008 and December 2011 from Matero public health clinic in Lusaka. After counseling by a nurse provider, HIV-infected women were invited to participate in the study if they were non-pregnant by self-report, between 20–45 years of age, and deemed healthy enough to undergo a pelvic examination (assessed by the nurse enrolling for the study and defined as patients who were not bedridden or physically incapacitated and were mobile enough to undergo a pelvic exam without discomfort). Informed consent was obtained from all participants, and a nurse-administered questionnaire was used to collect socio-demographic data.

Trained, experienced nurses performed the study procedures, starting with the collection of cervical specimens for thin layer cytology using a cytobrush (for endocervical sampling) and an Ayres spatula (for ectocervical sampling). Both the cytobrush and spatula were rinsed in PreservCyt™ vials (Cytyc™ Corporation, Marlborough, MA, USA) and stored at room

temperature locally for <4 weeks before batched-shipping to a U.S.-based laboratory for processing, analysis and interpretation by a certified senior cytotechnologist according to the revised (2001) Bethesda classification system. All abnormal slides and 10% of normals were subsequently reviewed by a board certified senior cytopathologist.

Immediately after the collection for cytology, the nurse conducted VIA enhanced by DC, performed by washing the cervix with 5% acetic acid, waiting for 2–3 minutes, and evaluating acetowhite lesions by real-time digital imaging of the cervix.[11] To capture the DC images, the study nurse used a 7–8 megapixel digital camera with 10x optical zoom and a built-in flash. The image was reviewed in real-time, and the results of the DC were recorded as being positive or negative. Next, the nurse performed DC-directed cervical punch biopsies with a 2×4mm tip Tischler biopsy forceps. A biopsy was taken from the lesion that appeared to have the most advanced degree of neoplasia, and from a normal appearing area of the cervical transformation zone. If the cervix had no abnormal area, only a normal area biopsy was taken of the transformation zone; conversely, if the cervix had no normal area, only an abnormal area biopsy was taken. Biopsy specimens were immediately placed in 10% formalin and sent to the pathology department of the University Teaching Hospital in Lusaka, Zambia for review by a United Kingdom-trained, board-certified Zambian senior pathologist. A combined histopathology variable was created to represent the most severe diagnosis from the normal and abnormal areas for each woman.

Patients with cervical intraepithelial neoplasia (CIN) grades 2 or 3 on biopsy underwent therapeutic LEEP. Women with evidence of invasive cancer on biopsy were immediately referred to the University Teaching Hospital (UTH) in Lusaka for further management.

Clinical and pathology data were entered into a Microsoft Access™ (Redmond, WA, USA) database and cleaned using Microsoft Excel™ and SAS™ version 9.2 (SAS Institute Inc., Cary, NC, USA). SAS and Open Epi (www.openepi.com) were used to calculate the point estimates and 95% confidence intervals (95% CI) of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of DC and cytology. DC results were dichotomized as positive and negative, while cytology results were dichotomized at three clinically-relevant cut-offs: atypical squamous cells of undetermined significance or worse (ASC-US+), low-grade squamous intraepithelial lesions or worse (LSIL+), or high-grade squamous intraepithelial lesions or worse (HSIL+).

Ethical approval for this study was obtained from the University of Zambia Biomedical Research Ethics Committee and the University of Alabama at Birmingham Institutional Review Board (affiliation of CIDRZ at the time of this study).

RESULTS

We enrolled 303 women into the study; all women were screened by both cytology and DC, and had histopathology results from a punch biopsy. The median age was 32 years, 10.6% had completed high school, and 61.8% were married (Table 1). A total of 86.4% were antiretroviral-experienced, and 56.5% had a baseline CD4+ count <200 cells/mm^3.

Half of all women (50.5%) screened positive by DC, and nearly half (45.5%) of all women had HSIL+ (Table 1). Using the most severe histopathologic diagnosis from the individual biopsy results for each woman, 63.7% of women had CIN1 or worse (CIN1+), 20.1% had CIN2+, and 10.9% had CIN3+ lesions (Table 1).

The sensitivity of DC for identifying CIN2+ was 84% (95% CI: 72% – 91%) and the specificity was 58% (95% CI: 52% – 64%) (Table 2). The sensitivity estimates of cytology for identifying CIN2+ were as follows: HSIL+, 61% (95% CI: 48% – 72%); LSIL+, 90% (95% CI: 80% – 95%); ASC-US+, 100% (95% CI: 94% – 100%). The specificity estimates of cytology for identifying CIN2+ were: HSIL+, 58% (95% CI: 52% – 64%); LSIL+, 35% (95% CI: 29% – 41%); ASC-US+, 13% (95% CI: 10% – 18%). The PPVs were low (23% – 33%) for both tests, while the NPVs were correspondingly high (86% – 100%). A similar pattern of results was observed at the CIN3+ diagnostic threshold on histopathology (Table 2).

DISCUSSION

We have demonstrated that among HIV-infected women in Zambia, the point estimates for sensitivity of DC to detect CIN2+ and CIN3+ lesions were higher than those of cytology at the HSIL+ cutoff. While previous studies have reported that VIA has higher sensitivity than cytology for both HIV-uninfected women[6,7] and HIV-infected women,[8–10] our study is the first to provide estimates of the clinical performance of DC.

The sensitivity point estimate of DC for CIN2+ that we report (84%) is slightly higher than three previous studies of HIV-infected women that reported 65% – 80% sensitivity for unaided VIA.[8–10] The specificity point estimate of DC for CIN2+ that we report (58%) lies near the lower end of the range (51% – 83%) reported for unaided VIA in these studies.[8–10] The specificity point estimate of cytology for CIN2+ that we report (58%) is slightly lower but comparable to that of Mabeya et al. (66%),[9] while both are substantially lower than that reported by Sahasrabuddhe et al. (83%).[8] Our lower specificity of cytology could be because our histopathology gold standard was based solely on punch biopsy specimens. Punch biopsies are small, and in women who screen DC positive the punch biopsies could lead to under-ascertainment of the true amount of cervical disease if the lesion is not adequately sampled in the (relatively small) punch biopsy specimen. Our histopathology specimens, and that of Mabeya et al., were from punch biopsy alone, while those of Sahasrabuddhe et al. were based on real-time colposcopically-guided cervical punch biopsies, endocervical curettage, and LEEP, which result in a more extensive sampling of at-risk areas on the cervix.

Strengths of our study include the number of women enrolled, leading to relatively precise estimates of test performance characteristics. In addition, all women had a punch biopsy taken, and while biopsy placement was guided by DC impression, biopsies were also obtained from normal appearing areas of the cervix. Thus, histopathology was obtained regardless of DC or cytology test results, and we have minimized (if not eliminated) any verification bias that can result from only performing histopathology on screen-positive women.

Our clinical performance point estimates suggest that DC is as good as or better than cytology for identifying cervical lesions in our population of HIV-infected women, while the relatively lower specificity point estimate of DC (58%) likely leads to overtreatment and/or over-referral of women who, based on the CCPPZ clinical protocol, require excisional biopsy (LEEP) or diagnostic biopsy. The program scale-up in CCPPZ has used the advantage of the reasonably high sensitivity of DC,[14] while overtreatment with cryotherapy is a lesser concern because this treatment modality has been shown to be a safe and acceptable treatment method.[15] Nevertheless, the integration of other screening tests, such as point-of-care human papillomavirus DNA or E6 tests, either individually or in combination with DC, may improve both the sensitivity and specificity of cervical cancer screening in HIV-infected women, and thus merit investigation.

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Table 1

Socio-demographic and clinical characteristics of participants

Age (years), n	302
Median, IQR	32.0 (27.5, 37.0)
Education, n	302
High school not completed	270 (89.4)
High school completed	32 (10.6)
Marital status, n	152
Not married	58 (38.2)
Married	94 (61.8)
Employment, n	301
Not employed outside the home	92 (30.6)
Formal sector	36 (12.0)
Informal sector	85 (28.2)
Other	88 (29.2)
Monthly household income, n	301
Less than KR500	21 (7.0)
KR500 or more	280 (93.0)
Number of lifetime partners, n	298
Median, IQR	3.0 (2.0, 4.0)
Age at sexual debut (years), n	303
Median, IQR	18.0 (16.0, 19.0)
Gravidity, n	288
Median, IQR	3.0 (2.0, 4.0)
Condom use with regular partner, n	297
Never	137 (46.1)
Ever	160 (53.9)
ART history, n	279
ART-Naïve	38 (13.6)
ART-Experienced	241 (86.4)
Baseline CD4+ (cells/mm^3), n	294

<200	166 (56.5)
200–350	84 (28.6)
>350	44 (15.0)
Previous Pap smear, n	300
Never	300 (100)
Ever	0 (0)
Digital Cervicography, n	303
Negative	150 (49.5)
Positive	153 (50.5)
Cytology, n	303
Normal	32 (10.6)
ASC-US	49 (16.2)
ASC-H	10 (3.3)
LSIL	74 (24.4)
HSIL	115 (38.0)
Cancer	23 (7.6)
Histopathology, n	303
Normal	110 (36.3)
CIN1	132 (43.6)
CIN2	28 (9.2)
CIN3	27 (8.9)
Cancer	6 (2.0)

Numbers in parentheses are percentages unless otherwise indicated.

IQR, interquartile range; KR, Zambian rebased kwacha (KR500 ~ $95 USD); ART, antiretroviral therapy; ASC-US, atypical squamous cells of uncertain significance; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia.

Table 2

Clinical performance of DC and cytology, with combined histopathology result as the reference standard

	True +	False +	True −	False −	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
CIN2+ threshold on histopathology								
DC positive	51	102	140	10	84% (72–91)	58% (52–64)	33% (26–41)	93% (88–96)
HSIL+	37	101	141	24	61% (48–72)	58% (52–64)	27% (20–35)	86% (79–90)
LSIL+	55	157	85	6	90% (80–95)	35% (29–41)	26% (21–32)	93% (86–97)
ASC-US+	61	210	32	0	100% (94–100)	13% (10–18)	23% (18–28)	100% (89–100)
CIN3+ threshold on histopathology								
DC positive	28	125	145	5	85% (69–93)	54% (48–60)	18% (13–25)	97% (92–99)
HSIL+	21	117	153	12	64% (47–78)	57% (51–62)	15% (10–22)	93% (88–96)
LSIL+	32	180	90	1	97% (85–100)	33% (28–39)	15% (11–21)	99% (94–100)
ASC-US+	33	238	32	0	100% (90–100)	12% (9–16)	12% (9–17)	100% (89–100)

CIN, cervical intraepithelial neoplasia; CI, confidence interval; DC, digital cervicography; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of uncertain significance.

A “+” denotes “or greater;” e.g., CIN2+ denotes a biopsy result of CIN2 or greater.