1-2020

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INTERNATIONAL JOURNAL OF CLINICAL VIROLOGY

Research Article

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Submitted: 10 January 2020
Approved: 28 January 2020
Published: 30 January 2020

How to cite this article: Titus M, Ermel A, Moormann A, Cu-Uvin S, Orang'o O, et al. Low sensitivity of the careHPV™ Assay for detection of Oncogenic Human Papillomavirus in cervical samples from HIV-infected and HIV-uninfected Kenyan women. Int J Clin Virol. 2020; 4: 001-005.

DOI: dx.doi.org/10.29328/journal.ijcv.1001006

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Abstract

Background: Human papillomavirus (HPV) infection causes cervical cancer (CC), a common malignancy among Kenyan women. New CC screening methods rely on oncogenic HPV ("high-risk", or HR-HPV) detection, but most have not been evaluated in swabs from Kenyan women.

Methods: HPV typing was performed on 155 cervical swabs from Kenyan women using the Roche Linear Array® (LA) and careHPV™ (careHPV) assays. Detection of 14 oncogenic HPV types in careHPV assay was compared to LA results.

Results: Compared to LA, sensitivity and specificity of careHPV assay was 53.0% and 80.9%, respectively. The sensitivity and specificity of careHPV in swabs from women with cervical dysplasia was 74.1% and 65.2%, respectively. The sensitivity and specificity of careHPV in swabs from HIV-infected women was 55.9% and of 96.4%, respectively. Overall agreements of careHPV assay with LA was substantial.

Conclusion: The results for careHPV assay are promising for oncogenic HPV detection in Kenyan women. The low sensitivity of careHPV for detection of HR-HPV could limit it's benefit as a screening tool. Thus, a full clinical validation study is highly desirable before the careHPV assay can be accepted for cervical cancer screening.

Introduction

Cervical cancer (CC) is one of the most common cancers among women globally [1]. Human papillomavirus (HPV) is the causative agent of CC [2,3]. Of the many HPV types, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, are classified as oncogenic, or "high risk" (HR) types due to epidemiological studies that demonstrated a high degree of oncogenicity [4]. HPV 26, 53, and 66 are classified as probable HR types. HPV 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and 89/CP6108 are considered to be low risk (LR) types for CC development [4].

Most women in Kenya and other sub-Saharan African countries are not screened regularly for CC [5]. For those who are screened, visual inspection with acetic acid (VIA) is nearly always used, but this test lacks sensitivity and specificity for diagnosis of precancerous lesions of the cervix [6-8]. Cytological testing is not available to most women in Kenya. There is a move towards the use of oncogenic HPV

DNA testing as a screening tool for CC in sub-Saharan Africa and other part of the world [9]. HPV detection assays may be suitable for use in CC screening programs in countries with limited resources such as those in sub-Saharan Africa, depending on cost and performance. Such assays potentially include the GeneXpert, Sacace™ HPV Genotypes 14 Real-TM Quant (Quant), careHPV™ (careHPV), and others [10]. In addition, point-of-care HPV tests are of interest due to the potential for decentralizing screening for CC. However, low sensitivity or specificity in detection of oncogenic HPV may lead to mismanagement. Therefore, this study was designed to compare careHPV, a test that potentially could be used in CC prevention programs in sub-Saharan Africa with the Roche Linear Array (LA) assay, which is an HPV test extensively used in epidemiological studies throughout the world, and as such can be considered as a comparative for other HPV tests.

Materials and methods

Study site

Study participants were recruited and enrolled at the Moi Teaching and Referral Hospital (MTRH) in Eldoret, Kenya. MTRH, the largest referral hospital in western Kenya, is located in the town of Eldoret. This hospital has good infrastructure for screening, diagnosis, and treatment of CC. Sample processing and laboratory assays were conducted at the Center for Global Health Research, Kenya Medical Research Institute (KEMRI) in Kisumu, Kenya.

Ethical approval

Ethical approval was obtained from the Kenya Medical Research Institute's Scientific and Ethics Review Unit (KEMRI-SERU) protocol number: KEMRI/SERU/CGHR/052/3322 and Institutional Research and Ethics Review Committee (IREC) protocol number: FAN: IREC 1730 from Moi Teaching and Referral Hospital (MTRH) and Moi University School of Medicine, Eldoret, Kenya.

Study population, design, specimen collection and processing

De-identified dry cervical swab specimens, collected by a gynecologist or general physician/nurse during pelvic examination at Chandaria Cancer Centre-MTRH and Academic Model Providing Access to Healthcare (AMPATH) clinics were stored at -80°C at the AMPATH Reference Laboratory until a sufficient number for HPV testing was achieved. Swab specimens were transported on dry ice to the KEMRI laboratory and stored at -80°C awaiting HPV testing. The archived frozen cervical swabs collected from women presenting at MTRH for CC screening (n = 283, aged 20-48 years) were used for HPV testing. Cervical swab specimens were not randomly selected, but were chosen based on availability. The cervical swab specimens were used directly without further processing for the careHPV™ testing as per the manufacturer's instructions while DNA was extracted from the swabs for LA testing.

DNA extraction

Swab samples were eluted into 1 mL of 1X phosphate buffered saline (PBS) and stored at -20°C awaiting DNA extraction. DNA was isolated from the samples using Qiagen DNA extraction kit following the manufacturer's protocol (Qiagen, Hilden, Germany). Briefly, DNA was extracted from 250 µL swab specimens in 1X PBS, washed in 750 µL wash buffer AW2 (provided in the Qiagen DNA extraction kit) and 750 µL absolute ethanol and finally eluted in 120 µL of buffer AVE (provided in the Qiagen DNA extraction kit). Purified samples were stored at -20°C until HPV detection/genotyping was performed.

HPV detection and genotyping

The Roche Linear Array (LA) (Roche, Branchburg, NJ, USA) detects 37 HPV types including 20 HR-HPV genotypes and 17 low risk (LR) HPV genotypes [11]. Briefly, 450 base pair fragments from the HPV L1 region were amplified from purified DNA samples by polymerase chain reaction (PCR), followed by hybridization using a reverse line blot system as previously described [12]. Genotypes identified in the LA assay include HPV types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, IS39 and CP6108.

The careHPV™ (careHPV) (Qiagen, Gaithersburg, MD, USA) is an assay that does not differentiate specific HPV genotypes, but detects the presence and absence of one or more of the 14 HR-HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) as a group. The careHPV assay utilizes an antibody-bound paramagnetic bead technique to qualitatively detect one or more of these 14 high-risk HPV types. HPV detection was performed according to the careHPV assay instruction manual provided.

Briefly, a supplied lysate buffer was added to the specimens, and HPV DNA was denatured through the addition of the denaturing solution supplied with the careHPV kit. Hybridization was then performed with full-length, specific and complementary RNA to form HPV DNA/RNA complexes. Magnetic micro-particle solid support was then added, which is coated with anti-DNA-RNA hybrid antibodies that captures DNA-RNA hybrids, allowing separation and removal of unbound nonspecific material. Alkaline phosphatase-linked anti-hybrid antibody was then added to bind and detect the captured HPV DNA/RNA hybrid mixtures. Washing was performed to remove unbound alkaline phosphatase conjugate. The light intensity generated by the reaction of a chromogenic substrate reflects the amount of HPV DNA present in the sample. The ratio of relative light unit (RLU) to the mean of RLU of the minimum positive control (RLU/CO) was used for detection. A sample was declared positive for HPV DNA if a reading of ≥0.5 pg/mL was observed.

Statistical analysis

The Buderer formula for sample size calculation was used to determine the appropriate number of samples for this study

[13]. The formula is designed to evaluate diagnostic tests by assessing the ability of a test to screen for disease, using parameters such as sensitivity, specificity, and predictive values. Statistical analysis was performed using MedCalc software version 15.6.1 (MedCalc Software, Mariakerke, Belgium). Data from 155 samples tested by the two assays were used for evaluation of the virologic performance of the careHPV assay. The 14 HR-HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) that are detected by two assays were considered for the analysis. The LA assay was used as the comparative test to calculate the virologic sensitivity and specificity of the careHPV assay. The kappa and McNemar statistic were used to analyze the concordance of the careHPV assay against LA in the detection of HPV genotypes. Kappa values were interpreted as poor/slight agreement (0.00 - 0.20), fair agreement (0.21 - 0.40), moderate agreement (0.41 - 0.60), substantial agreement (0.61 - 0.80), or almost perfect agreement (0.81 - 1.00) [14]. A McNemar test p-value of <0.05 indicates significant discordance between results determined by the two assays.

Results and discussion

Demographic characteristics of the study population

The mean age of the 283 women from whom specimens were obtained was 35 years (range 20 to 48 years). DNA was successfully extracted from 281 samples using the Qiagen DNA extraction kit; two samples yielded inadequate DNA when quantified by NanoDrop™ 2000 (Thermo Fisher Scientific, Wilmington, DE, U.S.A.). the NanoDrop™ 2000 detection limit was 2 to 15,000 ng/µL, therefore sample with DNA concentration less than 2 ng/µL were excluded from subsequent analysis. These 281 samples were then analyzed for 37 specific HPV types using LA.

The careHPV assay permits the use of cervical swab samples directly without extracting DNA From the 283 archived samples, 179 archived left-over samples had sufficient crude material for HPV testing using the careHPV assay. Of 179 samples tested with careHPV, 155 had valid results, and 24 (13.4%) had invalid results.

Comparison of HPV DNA detection among the assays

As indicated above, the cervical swabs from these women were not randomly selected, but were convenience samples. Analysis was performed on 155 swab samples that were tested by LA and had a valid careHPV result. Of these 155 swabs, 105 (67.7%) were from women with normal VIA examinations (with less risk of developing CC) and 50 (32.3%) were from women who had abnormal VIA examinations (who are at high risk of developing CC). Regarding HIV status, 93 of 155 swabs (60.0%) were from women were HIV-uninfected and 62 (40.0%) were from women who were HIV-infected. The mean age of these women who contributed the 155 swabs was 35 years.

Overall test performance of carehpv compared to linear array

The Linear Array enables type-specific detection of 37 HPV types. For the purpose of this study, Linear Array results were designated as positive only if one of the 14 HR-HPV types also included in the careHPV was detected. Of the 155 samples that were tested by LA, 66 (42.6%) were positive for 14 HR-HPV detectable careHPV. Fifty-two (33.5%) of 155 swab samples assayed by careHPV were positive for 14 HR-HPV.

Compared to LA, outcomes for the careHPV assay for 14 HR HPV type detection (one or more of these types detected) were: sensitivity = 53.0%, specificity = 80.9%, PPV = 67.3% and NPV = 69.9%, (McNemar test, p = 0.061) (Table 1). Concordance between the careHPV assay and LA was 0.349. Among swab samples from 105 women with normal VIA, the outcomes for 14 HR-HPV types detection in the careHPV assay were: sensitivity = 27.8%, specificity = 86.4%, PPV = 62.5% and NPV = 59.4% (McNemar test, p = 0.015) (Table 1). For swab samples from 50 women with abnormal VIA, these values were: sensitivity = 74.1%, specificity = 65.2%, PPV = 71.4% and NPV = 68.2% MnNemar test, p = 1.000). The concordance between the careHPV assay and LA in samples from women with normal VIA and abnormal VIA were 0.269 and 0.394, respectively (Table 1).

For swab samples from 93 women who were HIV-uninfected, the outcomes for 14 HR-HPV type detection for the careHPV assay were: sensitivity = 50.0%, specificity = 73.8%, PPV = 50.0%, and NPV = 73.8% (McNemar test, p = 1.000). For samples from 62 women who were HIV-infected, the outcomes for 14 HR HPV type detection for the careHPV assay were: sensitivity = 55.9%, specificity = 96.4%, PPV = 95.0%, and NPV = 64.3% (McNemar test, p = 0.001) (Table 2). The careHPV assay showed concordance values with LA in HIV-uninfected and HIV-infected women of 0.172 and 0.458 respectively (Table 2).

Table 1: Performance characteristics of the careHPV™ Assay for the detection of 14 high risk HPV types compared to Linear Array Assay in all swabs (n = 155) and among swabs from women with normal or abnormal VIA examinations.

careHPV Assay	Overall population: n = 155	VIA-normal: n = 105	VIA-abnormal: n = 50
Sensitivity % (CI)	53.0 (40.3 - 65.4)	27.8 (16.5 - 41.6)	74.1 (53.7 - 88.9)
Specificity % (CI)	80.9 (71.2 - 88.5)	86.4 (75.7 - 93.6)	65.2 (42.7 - 83.6)
PPV % (CI)	67.3 (55.9 - 77.0)	62.5 (40.6 - 81.2)	71.4 (51.3 - 86.8)
NPV % (CI)	69.9 (63.8 - 75.4)	59.4 (48.9 - 69.3)	68.2 (45.1 - 86.1)
Kappa	0.349	0.269	0.394
McNemar test P-value	0.061	0.015	1.000

Sensitivity, Specificity, Positive and Negative Predictive Values, McNemar test and Kappa Values of careHPV Assays against Linear Array in overall population and among VIA-normal and VIA-abnormal women. VIA is visual inspection with acetic acid. CI is 95% confidence interval. High-Risk HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 considered during analysis.

Table 2: Performance characteristics of the careHPV Assay compared to the Linear Array Assay for detection of 14 High-Risk HPV among in all swabs (*n* = 155) from HIV-uninfected or HIV-infected women.

careHPV Assay	HIV-uninfected: *n* = 93	HIV-infected: *n* = 62
Sensitivity % (CI)	50.0 (31.9 – 68.1)	55.9 (37.9 – 72.8)
Specificity % (CI)	73.8 (60.9 – 84.2)	96.4 (81.7 – 99.9)
PPV % (CI)	50.0 (31.9 – 68.1)	95.0 (75.1 – 99.9)
NPV % (CI)	73.8 (60.9 – 84.2)	64.3 (48.0 – 78.5)
Kappa	0.172	0.458
McNemar test *p* - value	1.000	0.001

Sensitivity, Specificity, Positive and Negative Predictive Values, McNemar test and Kappa Values of careHPV Assay against Linear Array among HIV-uninfected and HIV-infected women. HIV is human immunodeficiency virus. CI is 95% confidence interval. High-Risk HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 considered during analysis.

Persistent infection with HR-HPV is a risk factor for development of precancerous cervical lesions, which progress to CC in a subset of women. In sub-Saharan Africa, CC screening programs are limited and diagnosis is often made at late stages when treatment is ineffective. Thus, efforts have been made towards finding tools that are acceptable options for HPV detection and CC screening [15-18]. The careHPV assay demonstrated good virologic specificity compared to LA but was less sensitive than LA for the detection of 14 HR-HPVs in overall cervical swab samples. The lower sensitivity of careHPV for detection of HR-HPV could possibly be attributed to the cutoff point of approximately 5000 copies of HPV DNA/mL compared to 300-3000 copies/mL for LA (Sandri *et al.*, 2006). The sensitivity of careHPV was 53% for detection of HR-HPV in our study, a figure comparable to 55% reported in Burkina Faso [16,17]. Despite the overall low sensitivity of careHPV assay among all samples, its virologic sensitivity was somewhat better (74.1%) in samples from women with abnormal VIA results. The concordance of careHPV and LA was 0.35 in overall swab samples, which is slightly higher compared to 0.25 reported the HARP study in Burkina Faso and South Africa [17].

The performance of the careHPV assay in VIA-abnormal cervical swab samples in women from western Kenya demonstrate that this assay can potentially be used as a point care test and in initial cervical cancer (CC) screening in low- and middle-income countries (LMICs) or may be combined together visual inspection with acetic (VIA). Given that both (careHPV and VIA) assays are relatively cheap and simple tests to be used. Most of the CC screening strategies such as cytologic and HPV screens are designed for developed countries unlike LMICs where the gaps in health access are prevalent and resources are scarce. To bridge these gaps, a paradigm shift is needed, and low-cost screening tests like careHPV test may offer a potential solution that may lead to earlier interventions and a reduction in overall cervical cancer rates upon referral for cytologic examination and follow-ups.

Potential limitations of this study include the small sample size and, in a few cases, inadequate DNA material to assay all swabs. Furthermore, limited sample size did not permit a comparison of the assays based on the different stages of the lesions; (CIN) I, II, III and invasive carcinoma. Finally, samples used in this study were archived samples and therefore not representative of the use of HPV testing in a real-world screening environment.

In conclusion, the virologic performance characteristics of careHPV assay in detection of HR-HPV in cervical swabs from Kenyan women with abnormal VIA results demonstrate that this assay might offer an option for CC screening. Low sensitivity of careHPV in detection of HR-HPV could limit it's benefit as a screening tool, however. Further studies are needed to test these assays in real life situations to determine their utility in detecting HR-HPV and underlying cervical dysplasia, and ultimately preventing cervical cancer.

Acknowledgment

The authors thank all our colleagues at Kenya Medical Research Institute-University of Massachusetts Medical (KEMRI-UMMS) for their contribution in HPV testing and writing assistance, and the University of Nairobi (Kenya Aids Vaccines Initiative Institute of Clinical Research) (KAVI-ICR) for allowing us to perform the careHPV assay in their laboratory.

Funding this study was provided by the National Cancer Institute (U.S.A.), 5U54CA190151-02, (D. Brown, P. Loehrer, O. Omenge). Titus M. was a recipient of the U54 mentorship fellowship.

Conflicts of Interest

Dr. Brown receives research funding from Merck and Co., Inc., and has received compensation for consulting and lectures. The other authors declare no conflicts of interest.

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