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*Care*HPV cervical cancer screening demonstration in a rural population of north India

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ABSTRACT

Objective: To compare cervical *care*HPV screening in a rural community setting with other methods of cervical screening for the detection of high-grade cervical intra-epithelial neoplasia (CIN).

Study design: Cross-sectional study. All ever-married women aged 30–59 years surveyed in an administrative area of Uttar Pradesh, India were targeted for screening by *care*HPV (cervical and vaginal samples), Pap test and visual inspection of the cervix following application of acetic acid (VIA). Women who screened positive were referred for colposcopy and the results were confirmed histologically. Sensitivity, specificity and predictive values for the detection of histological CINII+ and CINIII+ were assessed for each screening test.

Results: Sixty-five percent (5032/7704) of the women invited for cervical screening agreed to participate in the study. Screen-positive rates for cervical *care*HPV, vaginal *care*HPV, Pap test and VIA were 3%, 2%, 3% and 6%, respectively. Data for women who did not complete all screening modes, women lost to follow-up and women with missing histological results were excluded before data analysis, resulting in a final sample size of 4658. Cervical *care*HPV had high sensitivity (85%) for the detection of CINIII+ lesions and moderate sensitivity (53%) for the detection of CINII+ lesions. Sensitivities for the detection of CINIII+ and CINII+ were 54% and 41% for vaginal *care*HPV, 62% and 44% for Pap test, and 8% and 22% for VIA, respectively.

Conclusion: Cervical *care*HPV testing is superior to VIA and Pap test for the detection of high-grade CIN in a rural community setting.

Introduction

Human papillomavirus (HPV) is a causal factor for cervical cancer, and persistence of HPV oncogenic types has been shown to be necessary for the development of cervical intra-epithelial neoplasia (CIN) and cervical cancer [1,2]. The diagnostic accuracy of HPV testing in primary cervical screening in non-randomized studies was summarized in a systematic review which concluded that HPV testing by the Hybrid Capture II (HCII) test and polymerase chain reaction is substantially more sensitive but significantly less specific for the detection of prevalent CINII+ compared with cytology [3]. A review of randomized clinical trials (RCTs) also indicated that screening strategies based on HPV testing were more sensitive than cytology for the detection of CINIII+ [4]. Another review suggested that HPV testing should be adopted worldwide, especially in low-resource settings where the burden of cervical cancer is greatest [5]. To the authors' knowledge, very few large-scale observational studies and only two large-scale RCTs on HPV screening for cervical cancer have been conducted in India. A multicentre cross-sectional study in India evaluated the accuracy of HPV testing as primary screening for the detection of cervical neoplasia, and found a varying range of sensitivities [6]. Other studies have also evaluated HPV testing for the detection of cervical neoplasia [7–9]. A study conducted in the Osmanabad district in India to measure the effect of a single round of HPV testing found a definite association between HPV testing and incidence of and mortality due to cervical cancer [10]. A cluster RCT of visual assessment, cytology and HPV screening for cervical cancer in rural India demonstrated that the detection rates by HPV testing were similar to those for cytology despite greater investment [11].

In the search for an affordable HPV test, the *care*HPV test was developed by PATH in collaboration with Qiagen (Formerly

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Digene) as a rapid batch assay to detect the DNA oncogenic types of HPV based on Digene's Hybrid Capture. The *care*HPV test is a low-cost, less time-consuming HPV-DNA test. The clinical accuracy of the *care*HPV test was tested in a cross-sectional setting in rural China, and the results were similar to those obtained for the HCII test. The *care*HPV test was therefore considered to be a promising primary screening method for cervical cancer prevention in low-resource settings [12]. A multicentre *care*HPV demonstration study was subsequently undertaken with the aim of demonstrating the feasibility of *care*HPV screening in various rural–urban settings, and comparing the *care*HPV test with other screening alternatives such as cervical cytology and visual inspection of the cervix following application of acetic acid (VIA). As India does not have a national screening facility, there is an urgent need to study feasible screening models for the country. As such, one of the four centres included in the multicentre demonstration study was based in a rural area in north India. The results from this centre are reported in the present article.

Subjects and methods

This study was conducted in a tehsil (county) of Uttar Pradesh, India by the Institute of Cytology and Preventive Oncology of the Indian Council of Medical Research in collaboration with the Program for Appropriate Technologies of Health (PATH), Seattle, USA. The other centres in the multicentre study were in Hyderabad (India), Uganda and Nicaragua. The study had a cross-sectional design, and the target sample size was 5000 women for each centre. The total duration of the study was three years, and it commenced at the centre in Uttar Pradesh in September 2010. Project staff (e.g. auxiliary nurse midwives (ANMs) and social workers) and existing healthcare workers from the government infrastructure, including ANMs and accredited social health activists from the National Rural Health Mission, Government of India, were trained in motivational aspects to raise community awareness and invite women for screening. At the screening centre, women were counselled and the procedure was explained. All the health workers and medical officers received one week of training using audiovisuals and one month of 'hands on' training for the visual test methods and Pap smear collection. Laboratory technicians received *care*HPV training for one week in three sequential steps. In the first step, the laboratory technician observed while the trainer conducted the entire test. In the second step, the laboratory technician performed the test side by side with the trainer. In the third step, the laboratory technician performed the test independently under the trainer's observation.

Before the initiation of screening, a baseline survey of ever-married women was performed at each health centre through a door-to-door survey conducted by health workers in order to identify women aged 30–59 years and invite them for screening. Flip charts, information brochures and pamphlets were used when inviting women to participate. Women who had undergone a total hysterectomy, or who had been diagnosed with cancer or pre-cancer, were excluded from the study. Menstruating women were excluded temporarily. Pregnant women were eligible to participate in the study 12 weeks after the end of their pregnancy. Eligible women were screened by ANMs after written informed consent was received.

First, a vaginal *care*HPV specimen was taken by the woman herself after an ANM at the screening centre explained how to do so, with the help of a pictorial chart. If a woman refused to take a sample herself, a vaginal sample was collected by the ANM. This was followed by speculum examination of the woman in the lithotomy position after insertion of a non-lubricated bivalve speculum with the help of a torch with white light (halogen bulb), collection of a *care*HPV sample by brush from the cervix, and collection of a Pap smear sample by Ayres spatula. Finally, the ANM performed VIA and women with positive results were referred immediately for colposcopy-directed biopsy. Other women were called back after 15 days to collect their Pap smear and HPV results. Any women who received positive screening results were referred for colposcopy if they had not been referred earlier due to positive VIA results.

For *care*HPV, a ratio of viral upload (expressed in relative light units (RLU)) to a positive control set at 1 pg/ml-cut off (CO) was considered positive if the RLU/CO value was $\geq$1.0. The Bethesda system was used for the assessment of Pap smears [13]. A finding of atypical squamous cells of undetermined significance (ASCUS) or more was considered to be a positive screening result. The cervix was inspected visually after the application of 5% acetic acid with a cotton swab, with sufficient time (1 min) allowed for colour change in the transformation zone. The observation of white colour against the pinkish background of normal epithelium was considered to be a positive screening result for VIA. Colposcopic diagnosis was made in accordance with the guidelines of the International Agency for Research on Cancer (IARC) [13]. Biopsy/endocervical curettage was performed wherever necessary. Women with histological CINI+ were referred for treatment in accordance with the IARC guidelines [13]. Cryotherapy was given by eligible doctors at the health centre: patients requiring surgery and radiotherapy were referred to a tertiary care hospital.

The quality of screening tests was controlled by training and retraining the ANMs. Quality control of colposcopy was achieved by training and retraining the doctors working on the project and by on-site visits by a senior colposcopist. Quality control of the pathology reports for biopsy was achieved by cross-checking reports by an external quality control pathologist. All women were counselled regarding the importance and need for follow-up. The modes of contact were via telephone conversations and home visits. At least three attempts were made to contact women before declaring them as lost to follow-up. The treated women were followed up for 12 months, and re-examined with colposcopy and Pap test to observe the effectiveness of treatment and any possible recurrence. Withdrawal of participants at any stage during the study was monitored, and the reason for withdrawal was noted.

Detection of histological CINII+ or CINIII+ was assessed using sensitivity, specificity, positive and negative likelihood ratios (ratios of sensitivity and specificity to false positivity and false negativity, respectively), and predictive values. Data analysis was performed using Statistical Package for the Social Sciences Version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Of the 7761 women invited for cervical screening, 5032 (65%) agreed to participate in the study. Baseline characteristics for age, marital status, menstrual history and the presence of previous health problems including cancer were obtained. The mean (standard deviation) age of all women screened was 37.9 (7.5) years. Table 1 shows the flow of women screened by various modes and their subsequent outcome at various levels up to confirmatory diagnosis. Biopsy was performed on 62–83% of cases who screened positive by various modes. Women who did not complete all screenings, women lost to follow-up and women with missing histological results were excluded, resulting in a final sample size of 4658 (93%). Further analysis was performed on the data of these 4658 women. In total, 4537 (97%) women were married. Menstrual history was regular in 3852 (83%) women and irregular in 805 (17%) women. None of the women had any health risks that could influence the results.

Table 2 shows age-specific positive screening results by cervical and vaginal *care*HPV, Pap test and VIA for 4658 women. Table 3