A Real-World Feasibility Study of CareHPV assay, VIA/VILI and Pap Smear as Primary Screening in Rural China

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Abstract

Background: To compare the real-world performance of visual inspection with acetic acid and with Lugol’s iodine (VIA/VILI), cytology and careHPV DNA assay in rural China performed by local health providers.

Methods: Eligible women living in rural areas in Xinmi County, Henan Province were invited to participate in cervical cancer screening program. Enrolled women were randomized into 3 intervention arms, screened by VIA/VILI, pap smears, and careHPV assay respectively. Women had positive primary screening results were referred to colposcopy and/or biopsy. All the clinical and lab work was performed by local health providers. The final diagnoses of histopathology were based on the diagnosing of a senior histopathologist expert from Cancer Hospital, Chinese Academy of Medical Sciences. Questionnaires about the knowledge and attitudes towards the HPV and the screening program of the health providers at village clinics were collected.

Results: 894 women had careHPV DNA test, 552 underwent VIA/VILI and 547 had Pap smears. The positive rates for careHPV assay, VIA/VILI and Pap smears were 10.6%, 18.1%, and 4.9% respectively ($\chi^2=48.647, P<0.001$). The overall CIN2+ detection rate was 0.5%, the CIN2+ detection rate for the three arms were not significantly different (0.7% for careHPV assay, 0.5% for VIA/VILI, 0.2% for pap smear, $\chi^2=1.648, P=0.439$). The knowledge of the health providers about HPV, HPV assay in screening was unsatisfactory. However, their attitudes about implementing HPV assay into the national program were positive.

Conclusion: Implementing careHPV assay in low resource settings and performed by simply trained lab personnel is feasible. For large population screening program, extensive training and good quality control are needed to improve the quality. Education for implementing HPV assay in local health providers is needed.

Keywords: Cervical cancer and precancerous lesions; Population screening; HPV assay; VIA/VILI; Pap smears; Real-world; Feasibility

Introduction

Invasive cervical cancer ranks the fourth most common malignant tumor among women around the world [1], with 85% cervical cancer occurrence and 87% death in less-developed countries and regions, including China. It has been proven that HPV vaccine and organized screening could prevent cervical invasive cancer effectively [2,3]. Establishing a comprehensive primary screening program with cytology in low-resource settings is difficult due to the lack of qualified cytologists. Visual inspection with acetic acid or Lugol’s iodine (VIA/VILI) is recommended for primary screening in low-resource settings by World Health Organization (WHO) since they are simple and low-cost [4]. However, the sensitivity of VIA/VILI to detect cervical intraepithelial neoplasia 2 or worse lesion (CIN2+) in different studies varies greatly due to its subjectivity [5-7]. Currently, HPV assay is recommended as an option for cervical cancer screening. However, most available HPV tests are expensive, require experienced laboratory personnel and high-quality lab conditions, which is difficult to be implemented in many low-resource settings. In recent year, careHPV DNA testing was successfully developed. The accuracy and performance of careHPV DNA testing to detect CIN2+ cervical cancer are better than cytology and much higher than VIA/VILI [8]. In addition, the careHPV test is low-cost and fast.

In the year 2009, the central government launched a Free Cervical Cancer Screening Program for 10 million rural women. Pap smears and VIA/VILI are recommended for primary screening. This national screening program has expanded to cover 10 million rural women annually [9]. Our study aimed to evaluate the real-world feasibility of careHPV DNA assay in low-resource settings, and compare with VIA/VILI and pap smears performed by rural local health providers. Besides, a field-based survey assessing the knowledge and attitudes of the local health providers toward the HPV and integrating HPV assay approach into current cervical cancer prevention programs in low resource settings was conducted.

Materials and Methods

Population

Women living in rural areas of Xinmin County were invited to participate in the cervical cancer screening program during November 2013 and January 2014. Non-pregnant women with no history of CIN, pelvic radiation, or hysterectomy, and could voluntarily provide informed consent were eligible for enrollment. A local health worker

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took the responsibility to explain the study procedure to all the women. The enrolled women were randomized into 3 arms, as shown in Figure 1, and then screened by careHPV DNA assay, Pap smears, or VIA/VILI respectively. Women with any test positive would be referred for colposcopy. The study was approved by the Institutional Review Board Cancer Hospital, Chinese Academy of Medical Sciences (CHCAMS).

Screening and data collection

The primary screening was done at the township level hospital. On the day of recruiting, eligible women signed the informed consent were given an identity number and assigned to one of the study arms randomly by a pre-set computer program. The pap smears specimens were graded by a local pathologist according to Bethesda 2001 classification system. Atypical Squamous Cells of Undetermined Significance (ASC-US) or worse lesion were defined as abnormal cytology. In VIA/VILI, 5% acetic acid were applied to the cervix through embedded cotton swap and then observed after 1 min. If no aceto-whitening was found, then the cervix was swabbed with 5% iodine solution. VIA or VILI exam abnormal women were referred to colposcopy. The careHPV specimen was collected with careHPV cervical sampler into Digene collection media (DCM) and sent to the lab in Xinmi Maternal and Children Health Care Hospital. A local lab assistant was trained by a senior technician from CHCAMS for two days, then the assay was run by the local lab assistant alone. In careHPV test results, represented as a ratio of viral load expressed in Relative Light Units (RLU), compared with a positive control set at 1 pg/mL. Questionnaires of women were collected from the health providers at the village level.

Colposcopy was performed by local doctors. Endocervical curettage (ECC) was performed in a case of the invisible transformation zone. Colposcopy-guided directed biopsies were performed if an abnormal epithelial area on the cervix was observed. Pathological slides were prepared by local doctors. To ensure the accuracy of clinical diagnosis, pathological results were reviewed by a senior pathologist from CHCAMS as the final diagnosis.

Statistical analysis

Microsoft Access 2010 software was used for data input and management. Double entry validation and logical consistency check were performed. SPSS 23.0 were used for data analysis. Mean and the standard deviation (SD) was calculated for age at screening. Normality test and homogeneity of variance test were performed to detection the characteristics of age distribution. Kruskal-Wallis Test was performed to compare the age of the three arms. Bonferroni test was used to compare the difference between every two groups. A proportion was calculated for a categorical variable. Women were stratified by age (<34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64). The Cochran-Armitage trend test was used to detect the trend of the positive rate of primary screening results along with the increasing of age group. P<0.05 was considered statistically significant.

Results

Screening

A total of 1,993 women younger than 64 years old participated in the screening studies. Among them, 894 women were randomized into careHPV DNA screening, 552 women were screened by VIA/VILI, and 547 women were screened by pap smears. The average age with SD was 44.1 ± 7.84 years for all women, and the age range was 21 to 64. The average age with SD for women screened by careHPV assay, VIA/VILI, pap smears were 44.5 ± 8.01, 43.6 ± 8.72, and 44.0 ± 6.51, respectively. No statistically significant difference was found between the age of the three arms (P=0.135).

The age-stratified number of cases, positive rates were presented in Table 1. For women who had the careHPV assay, 95 (10.6%) were found HPV-positive. Among women had abnormal VIA/VILI, 100 (18.1%) women were found abnormal, and 97.0% (97/100) were a low-grade suspicious lesion, the other 3.0% (3/100) women were a high-grade suspicious lesion. For women who had pap smears, 4.9% (27/547) of them found ASC-US or worse (ASC-US+) cytology, 81.5% (227/277) of them were ASC-US, and 18.5% (52/277) were low-grade squamous intraepithelial lesions (LSIL). The difference between the primary screening positive rates shown statistical significance (χ²=48.647, P<0.001), careHPV DNA testing was higher than pap smears (χ²=14.180, P<0.001) but lower than VIA/VILI (χ²=16.408, P<0.001). As shown in Figure 2, the positive rate for careHPV DNA testing was significantly increasing with age (χ²=13.473, P trend<0.001), while for VIA/VILI the positive rate was decreasing with age (χ²=10.818, Ptrend=0.001). No statistically significant difference of the follow-up rate was found among the three arms (careHPV 84.2% vs. VIA/VILI 73.0% vs. pap smear 77.5%, χ²=4.398, P=0.111). In total, 5 CIN1 cases, 8 CIN2 cases, and 2 CIN3 cases were found from the 172 women. The overall detection rate of CIN2+ was 0.5%. The detection rates of CIN2+ was 0.7% (6/894) for HPV assay, 0.5% (3/552) for VIA/VILI, and 0.2% (1/547) for pap
In the presented study, we found that in a real-world screening program in rural China, the CIN2+ detection rate of careHPV was higher than the conventional pap smear and VIA/VILI, though the difference was not statistically significant. If all women with positive careHPV DNA assay, VIA/VILI, and Pap Smears results at primary screening, stratified by age groups.

Table 1: careHPV DNA assay, VIA/VILI, and Pap Smears results at primary screening, stratified by age groups.

| Age        | N  | Negative (95%CI) | Positive (95%CI) | Normal (95%CI) | Abnormal (95%CI) | NILM (95%CI) | ASC-US+ (95%CI) |
|------------|----|-----------------|------------------|----------------|------------------|-------------|----------------|
| <34        | 102| 95.3 (91.3, 99.3) | 5.0 (4.7, 5.7)   | 77.5 (73.4, 81.7) | 25.0 (23.0, 27.0) | 23.0 (21.3, 24.7) | 17.5 (16.7, 18.3) |
| 35-39      | 105| 93.8 (89.3, 98.2) | 6.3 (6.0, 6.7)   | 83.3 (75.1, 91.6) | 16.7 (16.0, 17.4) | 16.7 (16.0, 17.4) | 16.7 (16.0, 17.4) |
| 40-44      | 166| 90.2 (85.9, 94.5) | 9.8 (9.5, 10.4)  | 78.3 (70.5, 86.1) | 23.7 (22.3, 25.1) | 23.7 (22.3, 25.1) | 23.7 (22.3, 25.1) |
| 45-49      | 222| 89.9 (86.1, 93.0) | 10.1 (9.4, 11.9) | 81.7 (74.7, 88.6) | 18.3 (17.4, 19.3) | 18.3 (17.4, 19.3) | 18.3 (17.4, 19.3) |
| 50-54      | 137| 84.6 (79.0, 90.1) | 15.4 (14.9, 21.0) | 80.0 (74.9, 92.6) | 14.0 (13.4, 20.6) | 14.0 (13.4, 20.6) | 14.0 (13.4, 20.6) |
| 55-59      | 50 | 79.4 (69.4, 89.4) | 20.6 (16.6, 24.6) | 94.8 (87.3, 100.0) | 2.0 (1.0, 12.7) | 2.0 (1.0, 12.7) | 2.0 (1.0, 12.7) |
| 60-64      | 17 | 89.5 (75.7, 100.0) | 10.5 (0.0, 24.3)  | 100.0 (100.0, 100.0) | 0.0 (0.0, 0.0) | 0.0 (0.0, 0.0) | 0.0 (0.0, 0.0) |
| Total      | 799| 89.4 (87.4, 91.4) | 10.6 (8.6, 12.6)  | 81.9 (78.7, 85.1) | 18.1 (14.9, 21.3) | 18.1 (14.9, 21.3) | 18.1 (14.9, 21.3) |

Discussion

In the presented study, we found that in a real-world screening program in rural China, the CIN2+ detection rate of careHPV was higher than the conventional pap smear and VIA/VILI, though the difference was not statistically significant. If all women with positive questionnaires, the CIN2+ detection rate of careHPV assay was not significantly different. However, their attitudes about implementing HPV assay into the national program were positive that 79.2% of them were completed. If all women with positive HPV results, the HPV DNA positive rate of careHPV assay, VIA/VILI, and Pap Smear were not significantly different (χ2=1.648, P=0.439).

Questionnaire survey

In total, 24 health providers from the villages clinics who were responsible for organizing eligible women finished the questionnaires. 45.8% (11/24) of them finished high school and the other 54.2% (13/24) finished the college education. The average years of being working in the village clinics were 15.8 years. As shown in Table 2, all the health providers have heard of HPV, but the knowledge about HPV and cervical cancer was unsatisfactory since more than half (58.3%) of them thought that all HPV genotypes could cause cervical cancer and 75.0% thought genital bacterial infections could cause cervical cancer. For the knowledge of cervical cancer screening, VIA/VILI and pap smears were better known as the primary screening tests due to the high awareness about the screening program. The knowledge about HPV assay as the primary screening was unsatisfactory that nearly 30% of them thought that HPV-positive equals to cervical cancer and they were unaware of the recommend HPV screening frequency for HPV-negative women. However, their attitudes about implementing HPV assay into the national program were positive that 79.2% of them were completed agree. The most concerned issue for them was the cost of HPV assay.
Table 2: Knowledge and attitudes about HPV and HPV screening for cervical cancer of local health providers.

| What advantages do you think of HPV DNA testing? | Easy to collect samples | 16 (66.7) | 8 (33.3) |
|--------------------------------------------------|-------------------------|-----------|---------|
| girls were more educated, which was consistent with previous studies. Previous studies have shown that the prevalence of HPV positivity is similar among women in rural and urban settings [25-27]. However, these studies have been limited to small samples and have not considered the impact of socioeconomic factors.

Conclusions

In conclusion, we found that the prevalence of HPV positivity is similar among women in rural and urban settings. However, these studies have been limited to small samples and have not considered the impact of socioeconomic factors. We believe that further research is needed to explore the factors that influence the prevalence of HPV positivity in women in rural China.

Future Directions

Future research should focus on the prevention and control of cervical cancer in rural areas. Initiatives should be taken to increase public awareness about cervical cancer and its prevention. We believe that the adoption of HPV screening in rural China would be a significant step towards reducing the incidence of cervical cancer in the country.

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