RESEARCH ARTICLE

Evaluation of Several Screening Approaches for Detection of Cervical Lesions in Rural Shandong, China

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Abstract

Purpose: The study was designed to: (1) investigate the prevalence of high-risk human papillomavirus (HR-HPV) infection and cervical neoplasia; and (2) evaluate clinical performance of visual inspection with acetic acid/ Lugol's iodine (VIA /VILI), Pap smear, high-risk human papillomavirus (HR-HPV) DNA test for detecting cervical intraepithelial neoplasia grade 2 or worse (CIN2+) and (3) explore appropriate screening approach in rural areas of Shandong Province. Materials and Methods: A total of 3,763 eligible women from Yiyuan County in Yimeng mountainous areas of rural Shandong, China, were enrolled and underwent Pap smear, HR-HPV DNA testing by Hybrid Capture 2 (HC2), and VIA /VILI tests. Women positive in any test were referred to colposcopy and biopsy as indicated. Results: The prevalence of HR-HPV infection among all enrolled women was 11.1% and that in healthy women was 9.9%. In total 33 cases of CIN1, 16 cases of CIN2, 6 cases of CIN3 but none of cervical cancer were detected and the crude prevalence of CIN2+ was 0.58%. For detecting CIN2+, the sensitivity of HR-HPV DNA testing, VIA/VILI, Pap smear was 90.9%, 77.3%, 81.8%, respectively. Pap smear had the best specificity of 98.2%, followed by HR-HPV DNA testing with specificity of 89.4%, VIA/VILI had the lowest specificity of 81.2%. Colposcopy referral rate of HR-HPV DNA testing, VIA/VILI, Pap smear was 11.1%, 18.5%, 2.3%, respectively. Conclusions: Our results suggest that HR-HPV DNA testing alone might be appropriate for primary cervical cancer screening in rural low-resource areas of Shandong Province, China.

Keywords: Cervical cancer screening - high-risk human papillomavirus DNA - rural areas - Shandong, China

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Introduction

Cervical cancer is one of the most common cancers among women globally, with most of them (more than 80%) occurring in developing countries (Arbyn et al., 2011; Jemal et al., 2011). The People's Republic of China, as a developing country, contains approximately one fifth of the world's population and has about 64% of population resident in rural areas. The disease burden in rural China is still heavy due to lack of infrastructure and resources necessary for routine Papanicolaou (Pap) smear screening, histological diagnosis, and proper treatment procedures (Shi et al., 2012a). Conventional Pap smear, though reduced cervical cancer incidence and prevalence rates widespread, has its limitations: requiring highly trained personnel, adequately equipped laboratories, and referral systems to communicate results (Massad et al., 2013). Visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI) are two modifications of a direct visual assessment of the cervix. Visual inspection with acetic acid/ Lugol's iodine (VIA /VILI) could be used as primary screening in low-resource settings for their advantages: requiring a lower level of infrastructure, less expensive, immediate result (Sankaranarayanan et al., 2012). High-risk human papillomavirus (HR-HPV) types deoxyribonucleic acid (DNA) test has been taken as an alternative primary screening test considering the fact that cervical cancers and a high proportion of cervical precursors are caused by persistent HR-HPV infection (Schiffman et al., 2011). The Digene Hybrid Capture 2 (HC2) for HR-HPV DNA testing (QIAGEN, Gaithersburg, MD), approved by the Food and Drug Administration, can offer an objective assay for presence of the viruses. Pap smear, VIA, VILI, HR-HPV test have their characteristics and indications in different settings (Longatto et al., 2012a).

While these screening approaches have been evaluated in several studies (Sarian et al., 2005; Gravitt et al., 2010; Longatto et al., 2012b), few studies have reported about the prevalence of HR-HPV infection and cervical neoplasia in rural Shandong Province with different socioeconomic factors. Thus we addressed the following aims among

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women aged 30~65 years in a population-based study in Yiyuan County, located in Yimeng mountainous areas of rural Shandong, China: (1) to investigate the prevalence of HR-HPV infection and cervical neoplasia, (2) to evaluate the performance of VIA /VILI, Pap smear, and HR-HPV DNA testing for detecting cervical intraepithelial neoplasia grade 2 or worse (CIN2+), and explore an appropriate screening approach in rural areas of Shandong Province, (3) to provide free cervical cancer screening service for women in rural Yiyuan County.

Materials and Methods

Ethical considerations

The study protocol was approved by the Institutional Review Boards at Qilu Hospital of Shandong University. Written informed consent was obtained by signature or thumbprint.

Recruitment and data collection

From June to October in 2010 year, totally 3763 women were enrolled in this project. Women aged 30-65 years were considered eligible if they were married or had previous sexual intercourse; had a cervix; had not been previously diagnosed with cervical cancer; were not pregnant; were physically able to undergo routine cervical cancer screening; were able to provide informed consent. Before all clinical study procedures, eligible women were given a presentation including an explanation of informed consent, the aim of this project, risk and benefits of participation, knowledge about HPV infection and cervical cancer prevention, encouragement for participation. Following the presentation, women who agreed to participate provided a signature or thumbprint on the printed consent form. After consent, women responded to a brief questionnaire designed to collect information on demographics, socioeconomic factors, reproductive history and contact information. These women also underwent a gynecological examination, including a conventional Pap smear and collection of cervical cells in sample transport medium for HR-HPV DNA testing by HC2. Thereafter, VIA /VILI test were performed.

Pap smear and interpretation

After removing any obscuring mucus from the cervix with a cotton swab, cervical cells were collected using an Ayre's spatula and endocervical brush, smeared onto a glass slide and fixed in ethanol. Slides were stained according to standard protocols, and reviewed by a local cytopathologist and external cytopathologist (senior experts from Qilu Hospital). Pap smears results were categorized according to the 2001 Bethesda System (Solomon et al., 2002). For analysis, the results equal or worse than atypical squamous cells of undetermined significance (ASCUS) were considered positive.

HR-HPV DNA testing and interpretation

The HR-HPV DNA testing was done by HC2, using cervical cell swabs, as previously described in detail (Kjaer et al., 2008). Briefly, cervical cell swabs were collected using HC2 kit brushes, and placed into 1 ml of Digene standard transport medium. Samples were stored at -20°C and sent to Qilu Hospital for analysis. The samples were analyzed only for the presence of 13 HR-HPV types namely 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. The results were classified positive if relative light unit coefficient (RLU/CO) was equal to or greater than 1.0 RLU/CO.

VIA /VILI methods and interpretation

After sample collection for Pap smear and HC2, 5% acetic acid was applied on the cervix through embedded cotton. The cervix was examined by naked eyes with a bright lamp after 1 minute. Thereafter use of acetic acid, Lugol's iodine was also applied on the cervix through embedded cotton. Immediately after, the cervix was observed in the same manner. Results of VIA and VILI were classified as normal, abnormal, and suggesting cancer according to the examiner's visual impression. Examiners have been trained to classify their visual impression according to the Atlas of Visual Inspection. Abnormal or suggesting cancer in VIA or VILI was classified positive.

Colposcopy and biopsy

Women who had at least one positive screening test were referred to colposcopy. All of examinations were performed by experienced and certified colposcopists who were aware that referred patients had at least one positive screening test, but were masked to the specific test results. Any suspicious lesions were subjected to directed biopsy for histological confirmation. Endocervical curettage (ECC) was performed for diagnosis if the entire squamocolumnar junction (SCJ) could not be visualized or a lesion extended into the endocervical canal. All biopsies were read by local pathologists, and reviewed by an expert pathologist from Qilu Hospital who was blinded to the original diagnosis. Histological diagnosis were categorized following the classification system as normal, inflammation/cervicitis, squamous metaplasia, cervical intraepithelial neoplasia Grade1, 2, or 3 (CIN1, CIN2, or CIN3), microinvasive cancer, squamous cervical cancer (SCC), adenocarcinoma in situ(AIS), and cervical adenocarcinoma. Histology results were considered gold standard diagnosis and true disease status. Women with the results CIN2+ were treated by Loop Electrosurgical Excision Procedure (LEEP) or Cold Knife Conization (CKC) or hysterectomy.

Data analysis

Women were considered to have a normal cervix or negative result if: *i)* all screening tests were negative; *ii)* any screening test was positive but colposcopy revealed no lesion; or *iii)* any screening test and colposcopy was abnormal, but histological results were normal/inflammation. Women were considered as cases of cervical diseases if histological results were CIN2 or worse. Crude estimates of diagnostic accuracy were biased due to non-random exclusion of women who did not have the opportunity for full diagnostic verification (Mahé and Gaffikin, 2005). Diagnostic accuracy statistics including sensitivity, specificity, and positive/negative predictive

values (PPV/NPV) and 95% confidence interval (CI) were calculated for detecting CIN2+ with each Pap smear, VIA/VILI and HPV testing. As previously described (Denny et al., 2000), we calculated crude sensitivity, that is the ratio of the number of test positive, disease positive women to the total number of women identified with disease. This measure is roughly equivalent to sensitivity, but does not require that the biopsy be applied to all women examined or verification bias be corrected. We calculated the crude specificity in the same way as previously reported (Denny et al., 2000), that is the ratio of the number of test negative, disease negative women to the total number of women free of disease. Pearson's chi-square (χ^2) test or Fisher's exact test or Yates' continuity correction chi-square test were used to assess differences in prevalence of HPV infection by age and disease grade and differences in sensitivity and specificity for CIN2+ results. Multiple test comparisons were compared using Bonferroni adjusted χ^2 test. The diagnosis agreement between local cytopathologist and experts from Qilu Hospital was measured using kappa statistics. All analyses were conducted using the SPSS for Windows Version 16.0 statistical package (SPSS Inc., Chicago, IL).

Results

Demographic characteristics

A total of 3763 eligible women were enrolled in the study (Table 1). The median age was 40 years with 1438 (38.2%) in the age group 40-49 years. A total of 2317 (61.6%) women had one or two childbirths, 1392 women (37.0%) reported three or more births. Only 78 (2.1%) women were illiterate, most of women (95.1%) had received primary or middle school education.

Overview of screening and diagnostic procedures

As is shown in Figure 1, among 3763 women, 417 (11.1%, 95%CI: 10.1–12.1) women were detected positive in HR-HPV DNA testing, 698 (18.5%, 95%CI: 17.3–19.8) women were defined as positive in VIA/VILI test, 87 (2.3%, 95%CI: 1.8–2.8) women were detected positive in Pap smear (i.e. equal or worse than ASCUS). Of the 3763 Pap smears that were taken, 3734 (99%) were classified as being "satisfactory for evaluation". We considered the few unsatisfactory Pap smear results as Pap negative rather than repeating Pap smear, which will not be feasible logistically in rural areas. Total 1031 (27.4%) women with positive results in any test were referred to colposcopy, of these, 654 women had indication for biopsy and considered as negative for CIN2+. In the referred group, 377 (10.0%) women underwent biopsy and pathological diagnosis. We detected a total of 33 CIN1 cases, 16 CIN2 cases , 6 CIN3 cases and none of cervical cancer.

Prevalence HPV infection and cervical disease

Among 3763 women with HR-HPV DNA testing by HC2 results, the prevalence of was 11.1% (Table2). Though there was no statistical difference of HR-HPV

Table 1. Demographic Characteristics of the Women

Characteristics	Number	Percentage
Participants	3763	
Age (years)		
30-39	1824	48.5
40-49	1438	38.2
50-59	439	11.7
≥60	62	1.6
Total number of childbirth		
0	54	1.4
1-2	2317	61.6
≥3	1392	37.0
Education		
Illiterate	78	2.1
Primary	1673	44.5
Middle	1904	50.6
High	108	2.8

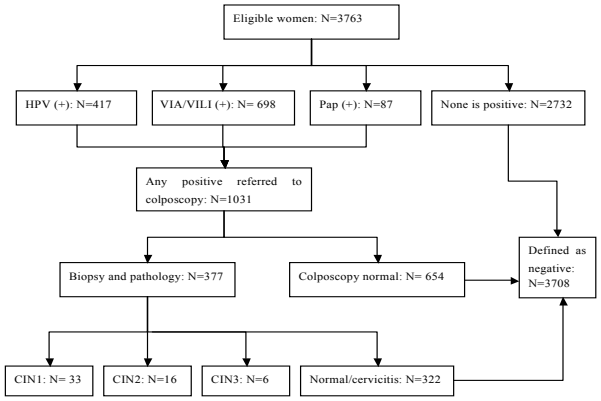

Figure 1. Overview of the Screening and Diagnostic Procedures

Table 2. Distribution of HPV Infection in Ages and Disease Grades

Variables	Number	HPV positive cases	HPV infection rate (%)
Total	3763	417	11.1
Age (years)			
30-39	1824	205	11.2
40-49	1438	168	11.7
50-59	439	40	9.1
60-65	62	4	6.5
Cervix			
Normal/cervicitis	3708	370	9.9
CIN1	33	27	81.8
CIN2	16	14	87.5
CIN3	6	6	100

Table 3. Test Positive Cases by 3 Tests in Different Cervical Grades

	Screening tests		
Final diagnosis	HR-HPV DNA test	VIA/VILI	Pap smear
Negative(N=3708)	370	658	50
CIN1(N= 33)	27	23	19
CIN2(N=16)	14	12	12
CIN3(N=6)	6	5	6
< CIN2(N=3741)	397	681	69
CIN2+(N=22)	20	17	18
Total number	417	698	87

*HPV DNA: human papillomavirus DNA; CIN: cervical intraepithelial neoplasia; CIN2+: CIN2 or worse; VIA: visual inspection with acetic acid; VILI: visual inspection with Lugol's iodine

Table 4. Clinical performance of the 3 Screening Tests for Detection of CIN2+

Screen tests	Clinical performance of tests				
	Sensitivity(95%CI)	Specificity(95%CI)	PPV	NPV	Colposcopy referral rate
HR-HPV DNA	90.9(78.9-99.9)	89.4 (88.4-90.4)	47.9	99.9	11.1
VIA/VILI	77.3(59.8-94.8)	81.2 (80.6-83.0)	24.4	99.8	18.5
Pap smear	81.8(65.7-97.9)	98.2 (97.7-98.6)	20.7	99.8	2.3

*PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval; CIN: cervical intraepithelial neoplasia; CIN2+: CIN2 or worse; HPV DNA: human papillomavirus DNA; VIA: visual inspection with acetic acid; VILI: visual inspection with Lugol's iodine

Table 5. Pap Smears Results of Local and External Cytopathologist

Final diagnosis	Local diagnosis		In total
	Positive	Negative	
Positive	83	4	87
Negative	40	3636	3676
In total	123	3640	3763

*Kappa=0.78; Local diagnosis were determined by local cytopathologist, final diagnosis were dependent on expert cytopathologist from Qilu Hospital. The results equal or worse than atypical squamous cells of undetermined significance (ASCUS) were considered positive

DNA prevalence between age categories, the HR-HPV infection rate in age from 60 to 65 years was the lowest. HR-HPV prevalence in CIN groups, ranging from 81.8% to 100%, was significantly different from that in normal/cervicitis with 9.9% positive rate. But the differences between CIN grades were not significant statistically. The crude prevalence of CIN2, CIN3, CIN2+ was 0.42%, 0.16%, 0.58% , respectively , without considering the 'true positive' cases in the defined negative group that could be detected if the entire enrolled population had underwent colposcopy and biopsy.

Clinical performance of the three screening tests

Test positive cases by 3 tests are reported in Table 3. Of the defined negative group (N=3708), the most cases (658) were detected positive in VIA/VILI test, that were false positive cases, while only 50 positive cases were detected in Pap smear test. Among the CIN2+ (N=22, including 14 CIN2 and 6 CIN3) group, the positive cases (i.e. true positive case) in HC2, VIA/VILI, Pap smear test was 20, 17, 18, respectively.

The clinical performance characteristics of the 3 screening tests are reported in Table 4. The sensitivity of HC2 HPV DNA testing, VIA/VILI, Pap smear for detecting CIN2+ was 90.9%, 77.3%, 81.8% respectively. There was no significant difference between tests statistically ($p>0.1$). Pap smear had the best specificity of 98.2%, followed by HR-HPV DNA testing with specificity of 89.4%, VIA/VILI had the lowest specificity of 81.2%. The specificities were different significantly in statistics ($p<0.001$). As for colposcopy referral rate, Pap smear had the lowest referral rate of 2.3%, VIA/VILI possessed the highest referral rate of 18.5% compared with moderate 11.1% referral rate of HR-HPV DNA test ($p<0.05$). HR-HPV DNA test had the highest PPV of 47.9% and Pap smear had the lowest PPV of 20.7%, while VIA/VILI had the moderate PPV of 24.4%. These tests had NPV of above 99%, the differences of NNP in these 3 tests were not significant.

Evaluation of cytological results by local pathologist

The agreement between the local and external (Qilu Hospital) cytopathologist was evaluated by kappa statistic (Table 5): the agreement was 98.8% and $\varkappa$=0.78. The final diagnosis was determined by cytopathologist from Qilu Hospital. The results equal or worse than atypical squamous cells of undetermined significance (ASCUS) were considered positive. Of 123 positive results by local diagnosis, only 83 cases were confirmed as positive, 40 cases were overdiagnosed. Of 3640 negative results by local cytopathologist, 4 cases were diagnosed as positive.

Discussion

The present research was designed to provide cervical cancer screening service and evaluate the clinical performance of several screening approaches for the detection of cervical neoplasia in rural areas of Shandong Province, China. It was conducted in Yiyuan County of Yimeng mountainous areas, a typical county of many resource-poor settings in Shandong.

To the present study, we found that the prevalence of HR-HPV infection in this region among all enrolled women was 11.1% and that in healthy women was 9.9%. The prevalence of HR-HPV infections in healthy women was similar to that (9.61%) reported in littoral region of Shandong Province (Yuan et al., 2011), also similar to 9.2% of global average (Clifford et al., 2005), but somewhat lower than that (15-22% range) observed in studies of other provinces in China (Dai et al., 2006; Wu et al., 2007; Sun et al., 2010; Wang et al., 2014). We detected total 16 cases of CIN2 and 6 cases of CIN3 but none of cervical cancer. The prevalence of cervical precancerous disease (CIN2+), i.e. high-grade squamous intraepithelial lesion (HSIL) was 0.58%, obviously lower than 3.7%, the estimate prevalence of HSIL in women aged 30-54 years in a pooled summary (Shi et al., 2012a). We noted that most of women (63%) had two or less childbirths. Considering the fact that parity number is an important factor on development of cervical cancer, we assumed the lower prevalence of CIN2+ was related to the strict one-child family policy in Shandong Province (Huang, 1982; Hesketh et al., 2005). The uncorrected verification bias may also account for this lower prevalence of CIN2+. On the other hand, the low number of cases detected in our study perhaps reflects an underdiagnosis of disease. The case definition was based on histological confirmation of CIN2+ by colposcopically-directed biopsy (CDB). This is a flawed reference standard and likely to miss a substantial proportion of CIN2+ lesions (Jeronimo and

Schiffman, 2006).

VIA screening is the simplest method of screening with the cost estimate for $2.64 per test in China and greatest relative ease of use (Shi et al., 2012b). The approach does not require high technology and has been demonstrated to reduce the deaths of women in developing countries (Wright and Kuhn, 2012). In our study, the sensitivity of VIA/VILI was 77.3% (95%CI: 59.8–94.8), similar to previous report (Chen et al., 2012). However, several weaknesses of VIA and VILI have been revealed, particularly the high rate of false-positive cases, which may lead to substantial number of colposcopy (Pimple and Shastri, 2014). The colposcopy referral rate of VIA/VILI in this study was 18.5%, leading to loss of follow-up and resource waste. It has been reported that a strong decline in the sensitivity of the VIA test in women aged 40 years or older (Li et al., 2009), showing the relatively poor performance.

Pap smear or cytology is the most common screening method in developed areas and decreased the incidence of advanced cervical cancer and associated mortality (Mukakalisa et al., 2014). However, Pap smears are challenging to perform in developing countries because the process requires high-quality laboratories, qualified lab technicians and trained cytopathologists, which may not be available in developing countries (Bradley et al., 2006). In our study, Pap smear had the highest specificity of 98.2% and moderate sensitivity of 81.8%. Another research reported similar corrected sensitivity of 80.2% for detecting HSIL (Moy et al., 2010). The overall agreement between the local and external (Qilu Hospital) cytopathologists was satisfactory. Notably, however, among the positive results of local diagnosis, almost half of them were false positive. The results of Pap smear are subjective and affected by variation in the technical skills of the gynecologists and pathologists. Scholars had identified VIA, and HPV DNA test as recommended alternatives to Pap smears in developing countries (Maine et al., 2011).

The HR-HPV DNA testing by HC2 detected the most CIN2+ cases and had the moderate specificity of 89.4% and colposcopy referral rate of 11.1%. For women in rural areas, they may just have once or twice cervical cancer screening in their lifetime. So a strategy with high sensitivity might be preferable at the cost of specificity loss. However, low specificity could result in the over-referral of women and limit overall screening coverage (Moy et al., 2010). HPV DNA testing has some limitations, including expensive cost requiring a laboratory, and at least 7 hours needed to process. The alternative to HR-HPV DNA testing in low-resource-setting countries is careHPV, which is promising as a primary screening method for cervical cancer prevention in low-resource regions (Qiao et al., 2008), resulting in a reduction of morbidity and mortality of cervical cancer. Though PPV and NPV are affected by the prevalence of a disease, they can provide a different perspective for the performance of screening test in a specific population. HR-HPV DNA testing had the highest PPV for CIN2+ (47.9%), followed by Pap smear (20.7%), VIA/VILI (24.4%).

The differences in the performance of the screening test in different populations as reported may be attributed by variation in the technical skills of the personnel, as well as differences in demographic characteristics of the populations screened. Considering the overall performance of 3 screening tests, our results indicate that HR-HPV DNA testing by HC2 alone might be appropriate for low-resource areas and countries. These findings align with the conclusion by Alliance for Cervical Cancer Prevention (ACCP) that HPV-DNA should become the standard test in developing countries, as well as a systematic review (Nahvijou et al., 2014). For HPV-positive women, cytology triage may be considered in settings with adequate infrastructure, whereas VIA triage may be suitable in settings with limited infrastructure (Muwonge et al., 2014).

We acknowledge that our study has limitations with respect to verification bias; women who resulted negative in all tests were not referred to colposcopy and did not receive random biopsy. Therefore, our results may overestimate the clinical sensitivity of the tests and underestimate the prevalence of cervical lesions. However, among the women with any positive results, we highly encouraged gynecologist to take a biopsy even if only a slight abnormality was observed during colposcopy. Furthermore, HR-HPV DNA testing was performed on all women together with VIA/VILI and Pap test; it is very likely that most women with CIN2+ were detected.

Our study has several strengths. Firstly, we provided free cervical cancer screening for women in rural Yiyuan County. Secondly, propagation and education about cervical cancer prevention contributed to compliance among women, unlike the report that non-compliance was a barrier for screening (Gravitt et al., 2010). Finally, this project was a population-based study and three screening tests were performed on each woman to compare directly clinical performance of screening approaches for detection of cervical neoplasia, which was not possible in large community randomized trials.

In conclusion, our results suggest that HR-HPV DNA testing alone might be appropriate for cervical cancer screening in rural low-resource areas of Shandong. It is important to emphasize performance of the screening tests, but the screening test is only one component of the population-based program required to reduce cervical cancer incidence and mortality. Effort to extend cervical cancer prevention strategies, HPV vaccine inoculation, precancerous lesion screening and treatment to Chinese women should be made, making cervical cancer be the first cancer eliminated (Qiao, 2010).

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