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Performance of high-risk human papillomavirus DNA testing as a primary screen for cervical cancer: a pooled analysis of individual patient data from 17 population-based studies from China

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Contributors

Y-LQ and F-HZ had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Y-LQ, JLB, JWS and SF organised the original individual studies concept and design. FC and the Cervical Cancer Screening Group in China acquired the raw data. Y-LQ, F-HZ, and MJL analysed and interpreted the data. MJL and FHZ drafted the paper. PEC, JLB, JWS, and SF revised the paper. S-YH and RZ did statistical analyses.

Conflicts of interest

The authors declared no conflicts of interest.

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Summary

Background—Controversy remains over whether high-risk human papillomavirus (HPV) DNA testing should be used as a primary screen for cervical cancer. The aims of our study were to assess whether HPV DNA testing could be applied to cervical-cancer screening programmes in China, as well as other similar developing countries.

Methods—We did a pooled analysis of population-based cervical cancer screening studies done in mainland China from 1999 to 2008 with concurrent HPV DNA testing (Hybrid Capture 2 assay; Qiagen, Gaithersburg, MD, USA), liquid-based cytology (LBC), and visual inspection with acetic acid (VIA). Eligible women were sexually active, not pregnant, had an intact uterus, and had no history of cervical intraepithelial neoplasia (CIN), cervical cancer, or pelvic irradiation. All women positive for any test were referred for colposcopy and biopsy. Cervical lesions were diagnosed by directed or random biopsy. We assessed the diagnostic accuracy of HPV DNA testing for the detection of CIN grade 3 or greater.

Findings—30 371 women from 17 cross-sectional, population-based studies in various parts of China were screened. 1523 women were subsequently excluded because of inadequate HPV DNA specimens or they did not have a biopsy taken, which included women with atypical squamous cells of undetermined significance; low-grade squamous intraepithelial lesion or worse; positive HPV, negative cytology, and missing or positive colposcopy results; and unsatisfactory cytology results. HPV DNA testing had a higher sensitivity of 97.5% (95% CI 95.7–98.7) for detection of CIN grade 3 or worse, and a lower specificity of 85.1% (82.3–87.9), compared with cytology (sensitivity 87.9% [95% CI 84.7–90.7], specificity 94.7% [93.5–96.0]) and VIA (54.6% [48.0–61.2], 89.9% [86.8–93.0]). Sensitivity did not vary by study or age (<35 years, 35–49 years, 50 years); however, specificity did vary with age ($p<0.0001$) and was highest in women younger than 35 years (89.4%; 95% CI 86.1–91.5). An increase in the positive cutoff point from the manufacturer recommended 1 pg/mL to 2 pg/mL led to a decrease in the overall HPV DNA positivity from 16.3% to 13.9% ($p<0.0001$), which could result in a decrease in referral rates, although sensitivity was slightly lower (97.5% to 95.2%). An increase in the cutoff point to 10 pg/mL in women younger than 35 years maintained a high sensitivity 97.7% (95% CI 87.7–99.9) and increased specificity to 93.5% (95% CI 91.9–94.6).

Interpretation—HPV DNA testing is highly sensitive and moderately specific for CIN grade 3 or worse, with consistent results across study sites and age groups—including women younger than 35 years. A rise in the cutoff point might be beneficial for future screening programmes in China, especially when screening women younger than 35 years.

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Introduction

Each year there are nearly half a million cases of cervical cancer worldwide, with more than 273 000 deaths. More than 80% of women diagnosed with cervical cancer live in developing countries.¹ Cervical cancer rates have decreased greatly in developed countries because of the introduction of the conventional Pap smear.² However, many women who live in developing countries do not have access to regular screening for cervical cancer. In these resource-poor regions, creating the infrastructure necessary for a successful Pap smear-based screening programme—which includes sample collection, storage, processing, and interpretation—as well as the necessary quality control and quality assurance systems, can be prohibitively difficult. Moreover, further management and treatment once abnormalities are found are also crucial issues in low-resource countries. Thus, a cervical-cancer prevention programme based on cytology is not often a viable option.²

Since persistent infection with high-risk types of human papillomavirus (HPV) is necessary for the development of cervical cancer and its precursors, cervical-cancer screening with an HPV DNA test has been proposed.³ HPV DNA testing gives an objective result and thus might be easier to implement in developing countries. However, there is still debate over whether HPV DNA testing alone can be used as a primary screen without cytology.^{4–7} Economic, algorithmic, and implementation concerns, which vary between countries, must also be taken into account.

China is the world's most populous country, with about 70% of its population living in rural regions. Most cervical-cancer screening in China is opportunistic and cancer incidence varies throughout the country—incidence is typically highest in rural areas in central China.⁸ Indeed, in rural Shanxi Province, the incidence of cervical cancer is estimated to be as high as 81 cases per 100 000.⁹ In 2009, the Chinese Government launched an ambitious cervical-cancer screening programme: 10 million women living in rural China are to be screened with either visual inspection or, in some regions, Pap smear over 3 years.^{10,11} However, with an estimated 500 million women living in rural China, this is only a small fraction of the women who should be screened for cervical cancer.^{10,11} Since the sensitivity of visual inspection and Pap smear might depend on the experience and training of the health practitioners doing the tests or readings, future large-scale screenings might benefit from a test with objective results, such as HPV DNA testing.

In studies done in rural China,^{12–15} the high-risk HPV DNA test was more sensitive than liquid-based cytology (LBC) and visual inspection. Similarly, studies have shown that HPV DNA testing is more sensitive than conventional cytology.^{16,17} A modelling study in China¹⁸ found that one-time screening at age 35 years would reduce lifetime cervical cancer risk by 15–28%. Cytology-based strategies that required multiple visits were the least effective,

although the most effective at reducing cervical-cancer risk; the most cost effective were HPV DNA-based methods.

However, several factors might influence the accuracy of HPV DNA testing. For example, the age of women being tested affects test performance. Previous studies in Europe¹⁹ and North America¹⁶ have shown that HPV testing in women younger than 35 years detects many cases of HPV infection that will regress without treatment, which leads to over-referral in this age group. Additionally, although HPV DNA testing involves a laboratory assay with little interstudy variability and can be automated, it is still operator dependent and relies on appropriate specimen collection, proper transportation to the laboratory, and quality assurance programmes to minimise contamination within the laboratory. All of these factors might result in variation in accuracy. Given the large number of small-size or moderate-size studies of cervical cancer, and the lack of large-scale studies assessing the accuracy and factors affecting the accuracy of HPV DNA testing in China, it is appropriate to investigate them as a pooled analysis.

To address this gap in knowledge, we did a pooled analysis on individual patient data from 10 years of cervical-cancer screening projects, which screened women from both rural and urban areas of China. Although studies on HPV DNA testing have been done with randomised designs and longitudinal outcomes,^{19,20} pooling individual patient data from cross-sectional studies with a common design is still useful and allows more analysis of covariates than pooling published data. We stratified results by age, location, and testing cut-points to determine the best HPV DNA screening algorithms with which to implement cervical-cancer screening programmes in developing countries such as China.

Methods

Participants

From 1999 to 2008, the Cancer Institute and Hospital of the Chinese Academy of Medical Sciences (CICAMS; Beijing, China), in collaboration with the Cleveland Clinic (Cleveland, OH, USA), International Agency for Research on Cancer (IARC; Lyon, France), and PATH (Seattle, WA, USA), screened women in 17 population-based, cross-sectional, cervical-cancer screening studies in four urban and ten rural areas of China, throughout nine provinces. Eligible women were sexually active, not pregnant, had an intact uterus, and had no history of cervical intraepithelial neoplasia (CIN), cervical cancer, or pelvic irradiation. Recruitment for all studies was based on community lists to minimise selection bias. Most women included had never been screened for cervical cancer, and none had been screened in the past 5 years. Women included in the pooled analysis all concurrently received HPV DNA testing (Hybrid Capture 2 [HC2] assay; Qiagen, Gaithersburg, MD, USA), LBC, and visual inspection with acetic acid (VIA). The study methods have been outlined in detail elsewhere.^{13,14,21–28} Written informed consent was obtained from all women. The human subjects review boards of CICAMS, Cleveland Clinic, PATH, or IARC approved these studies.

Procedures

Our pooled analysis used individual patient data from 17 cross-sectional, population-based studies: seven projects in the Shanxi Province Cervical Cancer Screening Study (SPOCCS), five studies in the Screening Technologies to Advance Rapid Testing (START) project, two projects done with the International Agency for Research on Cancer (IARC), the *FastHPV* trial, the HPV and CIN prevalence survey in Jiangsu province, and the HC2 clinical trial.

Investigators screened patients from rural Shanxi province in SPOCCS I,^{13,23–26} II,^{14,27} and III²² from 1999 to 2007 SPOCCS III also expanded to include five provinces or districts: Shanxi, Beijing, Xinjiang, Henan, and Shanghai. In the START Project, women from five rural areas^{12,15,28} were screened from 2003 to 2007 All of them received HPV DNA testing, LBC, and VIA. In some studies all women also received visual inspection with Lugol's iodine (VILI) and colposcopy. The two projects done in cooperation with IARC were done between 2004 and 2005.²¹ In these studies, all women received HPV DNA testing, LBC, VIA, and colposcopy. In the IARC-(2) study, women also received VILI. In 2007, women were screened with direct HC2, careHPV (Qiagen, Hilden, Germany), LBC, VIA, and VILI in the *FastHPV* trial (unpublished). In the HPV and CIN prevalence survey in Jiangsu province in 2008 (unpublished), women aged 18–25 years were screened with HPV DNA testing, LBC, and VIA. In the HC2 clinical trial (unpublished) done in 2008, women received HPV DNA testing, LBC, VIA, and VILI. In SPOCCS I, all women received colposcopy and biopsy. In all other projects, women who tested positive with any screening test received colposcopy and biopsy.

In all studies, carcinogenic HPV DNA testing was done with the high-risk probe set of HC2, which detects 13 carcinogenic HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). All women received physician-collected HPV DNA sampling. About 13 000 women in five studies also did self-sampling for HPV DNA testing in addition to receiving physician-collected HPV DNA sampling. In the *FastHPV* trial and START 2007, *careHPV*, an HPV DNA test that is completed on site and can have results in 3 h, was also done. In 11 of the studies—SPOCCS II, SPOCCS III-(1), SPOCCS III-(3), START 2003, START 2005, START 2006, START 2007, IARC-(2), *FastHPV* trial, the prevalence survey in Jiangsu, and the HC2 trial—HC2 sample testing was done at CICAMS. In the earliest trial, SPOCCS I, HC2 was done at Qiagen (formerly Digene Corporation) in the USA; the remaining studies had HC2 done at local hospitals in China.

All patients underwent LBC (SurePath, BD Diagnostics, Franklin Lakes, NJ, USA or ThinPrep, Hologic, Bedford, MA, USA), and results were graded according to the Bethesda system.²⁹ The cytological classifications were: within normal limits (negative); atypical squamous cells of undetermined significance (ASC-US); atypical glandular cells of uncertain significance (AGC); atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H); low-grade squamous intraepithelial lesion (LSIL); high-grade squamous intraepithelial lesion (HSIL); squamous cell carcinoma (SCC); adenocarcinoma in situ (AIS); or adenocarcinoma.

All studies used VIA as a screen, although six of the studies also used VILI if VIA was negative. Positivity for VIA was defined as distinct, dense, non-moveable acetowhite areas

in the transformation zone near the squamocolumnar junction, visible 1 min after application of 3–5% acetic acid. VILI was done after VIA, and a positive VILI examination was defined as dense, thick, bright mustard-yellow or saffron-yellow areas in the transformation zone next to the squamocolumnar junction. All visual inspection was done by trained Chinese gynaecologists.

Both directed biopsies and four-quadrant punch biopsies were used in these studies. Directed biopsy was used in cases of visible lesions. When the four-quadrant punch biopsies method was indicated, random biopsies were taken at positions of two, four, eight, and ten o'clock depending on the quadrant. In SPOCCS I, all patients received four-quadrant punch biopsies and endocervical curettage. In SPOCCS II, START 2003, and START 2004, all patients with positive visual inspection, HC2, or cytology had four-quadrant punch biopsies as well as endocervical curettage. A virtually painless, 2 mm bronchoscopy biopsy instrument was used for the exocervical biopsies. Histological diagnoses were categorised as negative; CIN grade 1, 2, or 3; SCC; AIS; or adenocarcinoma.

Our study combined individual raw data from the studies and estimated pooled sensitivity and specificity for the detection of high-grade lesions or worse. In all the studies, the clinical results and other test results were masked from the laboratory personnel that did the HPV analyses, and cytopathologists and histopathologists did the reviews and made diagnoses without knowledge of the specific results of other tests. Specific results of the screening tests were masked from colposcopists, but they were aware that one of the tests was positive. In most studies, cytology and biopsy results were read at CICAMS, although some biopsies were read by local pathologists. Cytology results in six studies and biopsy results in 11 studies were reviewed by international experts.

To exclude verification bias, we established criteria for final diagnoses and included all participants for gold standard verification. The gold standard diagnosis was biopsy. However, women with no biopsy results, but negative or ASC-US on cytology and negative for HPV DNA, were deemed to be true negatives (very low risk for high-grade lesions) on the basis of findings from SPOCCS that there was only one CIN grade 2 case and no CIN grade 3 or worse cases of those women (one [0–07%] of 1511). Women with negative cytology, positive HPV DNA but negative colposcopy, and who had unavailable biopsy results, were deemed negative or CIN grade 1 with the expectation that most women would not have high grade disease. Women were judged as having incomplete data if they had no biopsy, but fell in one of the categories ASC-US and HPV positive; LSIL or worse (including ASC-H, LSIL, HSIL, AGC, AIS, adenocarcinoma, and SCC); HPV positive, negative cytology, and missing or positive colposcopy; unsatisfactory cytology results; or inadequate HPV testing results (specimen not sufficient for HC2 test).

Statistical analysis

We assessed the accuracy of HPV DNA testing for the detection of CIN grade 2 or worse and grade 3 or worse. Women with incomplete data were excluded from the analyses. Sensitivities were pooled with the fixed-effect model, and specificities were pooled with the random-effect model since interstudy heterogeneity was statistically significant. We used forest plots to display the variations of sensitivity and specificity in the individual studies

and pooled measures. Q test and I^2 test were used to assess the heterogeneity between studies. Sensitivities, specificities, positive predictive values, and negative predictive values in different age groups (15–34, 35–49, and 50–59), regions (rural and urban), and cutoff points were also calculated. Pooled-analyses were done with Meta-Disc 1.4 (Meta-analysis of Diagnostic and Screening Tests, version 1.4).³⁰

To assess whether the established criteria for women without biopsy results have any effect on the accuracy of HPV DNA testing, we stratified the women without biopsy results into subgroups according to the results of HPV DNA testing, LBC, and colposcopy, and then calculated the estimated number of CIN grade 2 or worse and grade 3 or worse that might have been missed in each subgroup using the probability of CIN grade 2 or worse and grade 3 or worse generated from SPOCCS I (where all women had biopsies) as the weights. The corrected accuracy was computed with the estimated number of cases where CIN was grade 2 or worse and grade 3 or worse.

Risk ratios and their 95% CIs were calculated to assess the association between an increase in cutoff point for a positive HPV DNA test and the risk of a high-grade lesion. The group in which the cutoff was less than 1 pg/mL was used as the control group, and it was compared with other groups of 1 to less than 2 pg/mL, 2 to less than 4 pg/mL, and 4 to less than 10 pg/mL.

We used χ^2 tests compare the differences in HPV DNA testing accuracy between age groups and the differences of HPV prevalence in different pathology or cytology grades. Continuous variables were examined by calculating the means, medians, and SDs. These statistical analyses were done with Statistical Package for the Social Sciences version 13.0.

Role of the funding source

All three sponsors supported FHZ, MJL, SYH, and RZ in the design of the pooled study, data analysis, data interpretation, and writing of the report. YLQ, FHZ, and SYH had access to the raw data. The sponsor had no access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the flow of study participants. 30 371 women from 17 population-based studies were screened, of these 1523 women were excluded. The mean age of included women was 39.8 years (SD 6.8, range 17–59; table 1). The proportion of women aged 17–29 years was 6.3% (1807 of 28 848 women), 30–34 years was 12.7% (3654 women), 35–49 years was 74.4% (21 471 women), and 50–59 years was 6.6% (1916 women). Most women were from rural areas (90.9%; 26 232 women), with 2616 (9.1%) from urban areas. Only 3369 women (11.7%) had attended senior high school or above, 13 508 (46.8%) had attended junior high school, 9048 (31.4%) had attended primary school, and 2919 (10.1%) were illiterate. Almost all of the women screened were married (98.4%; 28 384 women). The women had a median of three pregnancies (range 0–16; IQR two to four) and two livebirths (range 0–14; IQR two to three). The mean age of sexual debut was 19.9 years (SD

2.6) with later onset in urban (22.8 years, SD 3.2) compared with rural areas (19.6 years, SD 2.3). 21.3% of rural women (5592 of 26 232), reported two or more sexual partners, and 15.5% of urban women (404 of 2612; four women with missing data) reported the same. The mean age of women excluded from the analysis was 39.0 years (SD 7.3) and had the same number of pregnancies and live births as those included. 1322 (86.8%) of the 1523 women excluded were from rural areas and 201 (13.2%) were from urban areas. Among included women, there were 439 cases (1.5%) of CIN grade 2, 429 cases (1.5%) of CIN grade 3, and 51 cases (0.2%) of invasive cervical cancer.

4691 (16.3%) of the 28 848 women included in our analysis tested positive for carcinogenic HPV DNA. Women in urban areas had a lower prevalence of HPV DNA (7.9%; 206 of 2616) compared with women from rural areas (17.1%; 4485 of 26 232; $\chi^2=148.60$; $p<0.0001$). One exception was a rural area in Xinjiang Province, in which the population is predominately Muslim Uygur, which had a particularly low HPV DNA prevalence of 6.9% (61 of 879). Overall, the peak of high-risk HPV positivity was 17.7% (3810 of 21 471) in women aged 35–49 years. In rural women, positivity similarly peaked at 18.4% (3734 of 20 330). However, in urban women, prevalence was highest in those younger than 35 years at 9.5% (110 of 1152).

HPV DNA prevalence increased with the severity of verified disease status ($\chi^2=7734.36$, $p<0.0001$): 11.2% (3022 of 26 945) in normal, 79.7% (784/984) in CIN grade 1, 95.0% (417 of 439) in CIN grade 2, 97.4% (418 of 429) in CIN grade 3, and 98.0% (50 of 51) in SCC or ADC. Most women with histology results of CIN grade 2 or worse tested positive by HPV DNA screening (table 2).

Figure 2 shows the sensitivities and specificities of the high-risk HPV DNA test by study for CIN grade 2 or worse (figure 2A) and grade 3 or worse (figure 2B). Overall, the sensitivity of the HPV DNA test was high; sensitivity varied little by geographical location, with 16 of 17 locations having sensitivities of 95% or above for CIN grade 3 or worse. Only one study, START 2005, had a lower sensitivity in the 11 CIN grade 3 or worse cases at this site. If we exclude this study, there was little effect on the pooled sensitivity for CIN grade 3 or worse (98.1%, 95% CI 96.4–99.1) as well as for grade 2 or worse (97.0%, 95.6–98.0), with p values for heterogeneity of 0.958 for CIN grade 3 or worse and 0.820 for grade 2 or worse. Specificity varied significantly between locations for both CIN grade 2 or worse and CIN grade 3 or worse ($p<0.0001$). Positive predictive values also differed significantly between studies, ranging from 2.3% to 31.6% ($p<0.0001$) for CIN grade 3 or more severe, and 10.5% to 47.4% ($p=0.001$) for grade 2 or more severe (data not shown). Negative predictive values were uniformly high (data not shown).

For reference, we estimated the overall clinical performance for VIA and cytology in our pooled study. The sensitivity of VIA was lower than HPV DNA testing at 54.6% (range 14.3–85.7; 95% CI 48.0–61.2) for CIN grade 3 or worse and 48.0% (12.5–70.2; 42.1–53.9) for grade 2 or worse. The specificity was 89.9% (69.9–97.5; 86.8–93.0) for CIN grade 3 or worse and 90.4% (70.0–98.2; 87.3–93.5) for grade 2 or worse. For test positivity at LSIL or worse, the sensitivity of cytology was 87.9% (50.0–100.0; 84.7–90.7) for CIN grade 3 or worse and 80.5% (55.6–90.0; 77.8–83.0) for grade 2 or worse. The specificity was 94.7%

(90.8–99.4; 93.5–96.0) for CIN grade 3 or worse and 95.8% (92.4–99.7; 94.7–96.9) for grade 2 or worse. Furthermore, when we assessed 8663 women with biopsy results only, sensitivities of HPV, cytology, and VIA for CIN grade 3 or worse and grade 2 or worse did not change (data not shown). However, among this referral population, HPV positivity was 50.7% (4390 of 8663) at 1.0 pg/mL, cytology positivity was 22.3% (1905 of 8531) at LSIL or worse and 39.3% (3350 of 8531) at ASC-US or worse, and VIA positivity was 25.3% (2188 of 8657). The test positivity for all tests were higher in this subset than in the general population— HPV 16.3% (4691 of 28 848); cytology 6.6% (1905 of 28 716) at LSIL or worse, and 16.0% (4599 of 28 716) at ASC-US or worse; VIA 10.8% (3122 of 28 815).

Urban regions had similar sensitivity (100.0%, 95% CI 80.5–100.0) and higher specificity (92.7%, 87.8–97.6) for CIN grade 3 or worse, compared with rural areas (97.4%, 95.5–98.7; 84.3%, 81.5–87.2) (webappendix). Overall, sensitivity for HPV testing did not vary with age (table 2; CIN grade 3 or worse $p=0.810$, grade 2 or worse $p=0.432$). Specificity, however, significantly differed between age groups ($p<0.0001$). Specificity was higher among women younger than 35 years compared with women aged 35–49 years and older than 50 years (table 2). This pattern was also noted in rural women, where specificity was highest among women younger than 35 years (89.0%, 95% CI 85.1–90.9; webappendix). However, in urban areas, specificity was highest in women aged 35–49 years (94.1%, 90.1–98.1) and 50 years or older (94.1%, 90.9–96.4), and was lowest in women younger than 35 years (91.0%, 85.4–96.6; webappendix). Overall, positive predictive value was generally highest in women aged 35–49 years; negative predictive value was uniformly high in all age groups (table 2 and webappendix).

Figure 3 shows the accuracy of HPV DNA testing at various relative light unit/cutoff (RLU/Co) values in all women and different age groups by receiver operating characteristic curves. There was a slight decrease in sensitivity for CIN grade 3 or worse when increasing the positive RLU/Co cutpoint from 1.0 pg/mL to 2.0 pg/mL for the HPV DNA (97.5% to 95.2%, McNemar test $p=0.001$; figure 3B). There was also a corresponding increase in specificity, from 85.1% to 87.5% (McNemar test $p<0.0001$), an increase in positive predictive value from 10.0% to 11.4% ($\chi^2=4.85$, $p=0.030$), and a significant decrease in the overall HPV DNA positivity—which correlates with referral rate—from 16.3% to 13.9% (McNemar test $p<0.0001$). However, raising the cutpoint above 2.0 pg/mL resulted in significantly decreased sensitivities without much gain in specificity or positive predictive value. Similar results were noted at the CIN grade 2 or worse cutpoint (figure 3A). Furthermore, when increasing the cutoff to 10 pg/mL, sensitivity in all age groups significantly decreased (97.5% to 89.0% for CIN grade 3 or worse, and 96.3% to 87.1% for grade 2 or worse), although specificity (85.1% to 90.9% for grade 3 or worse, and 86.4% to 92.1% for grade 2 or worse) and positive predictive value (10.0% to 14.1% for grade 3 or worse, and 18.9% to 26.5% for grade 2 or worse) increased.

In women younger than 35 years, sensitivity remained high at 97.7% (95% CI 87.7–99.9) for CIN grade 3 or worse lesions when HPV positivity was set at 10 pg/mL. The corresponding specificity was 93.5% (91.9–94.6), with a proportion of positive HPV tests of 7.2%. This pattern was not present in women aged 35 years or older where, after the 2.0 pg/mL cutpoint, sensitivity decreased significantly from 95.0% (95% CI 92.5–96.8) at the 2.0

pg/mL cutpoint to 88.1% (84.7–91.0) at the 10 pg/mL cutpoint (McNemar χ^2 test $p < 0.0001$). Heterogeneity tests for different studies were also done on the cutpoint of 2.0 pg/mL and 10.0 pg/mL, which showed that there were still no significant differences of sensitivity ($p > 0.05$; data not shown).

Table 3 shows the risk ratios for CIN grade 3 or worse at various RLU/Co values. The risk ratios of CIN grade 3 or worse increased with higher cutpoint levels, with RLU/Co values from 1.0 pg/mL to less than 2.0 pg/mL having 33.0 times more risk (95% CI 14.5–75.1) of CIN grade 3 or worse versus less than 1.0 pg/mL, although 10.0 pg/mL or greater had 331.5 times increased risk (186.5–589.1). For the 2.0 pg/mL to less than 4.0 pg/mL and the 4.0 pg/mL to less than 10.0 pg/mL ranges, the risk ratios for CIN grade 3 were similar: 62.9 (28.9–136.7) and 64.6 (30.4–137.4), respectively.

Table 4 shows the corrected HC2 accuracy for the detection of CIN lesions grade 2 or worse and grade 3 or worse by age groups after estimating the number of CIN lesions in women without biopsy results. After the correction, an additional 84 CIN grade 2 or worse and 27 grade 3 or worse were estimated to be detected. The overall sensitivity of HC2 decreased by 1.2% for CIN grade 2 or worse and increased by 0.1% for grade 3 or worse, and specificity decreased by 1.0% for CIN grade 2 or worse and grade 3 or worse. For different age groups, sensitivity decreased for CIN grade 2 or worse and increased for grade 3 or worse, and specificity decreased for both grade 2 or worse and grade 3 or worse. The changes of sensitivity and specificity had no clinical significance.

Discussion

Findings from our pooled analysis show that HPV DNA testing is a highly sensitive and moderately specific test for CIN grade 2 or worse and grade 3 or worse lesions across various locations and ages in the Chinese population. We also found that increasing the cutoff for test positivity to 2.0 pg/mL might reduce referral rates without reducing the sensitivity of the test, especially when screening women younger than 35 years. To our knowledge, our pooled study is the largest analysis of cervical-cancer screening methods performed in China (panel). Our study sites ranged from rural to urban regions, in many provinces of China. The high accuracy of the tests was consistent throughout the various study sites with no significant difference in sensitivity throughout the sites. Only one study, START 2005, done in the rural region of Gansu Province, had a lower sensitivity. Gansu Province is a low-resource area and there might have been sampling error due to less experienced physicians. Furthermore, the operator doing the HC2 testing for this study was newly trained and inexperienced, which might have contributed to the low sensitivity. VIA's overall sensitivity in our pooled study was quite low (54.6%) with a broad range from 14.3% to 85.7% for CIN grade 3 or worse and high specificity (89.9%) among different sites. Compared with HPV DNA testing, cytology had a lower sensitivity (87.9%) and higher specificity (94.7%), the sensitivity also varied among different sites, ranging from 50.0% to 100.0% for CIN grade 3 or worse. The variable performance of VIA and cytology highlight the difficulties in achieving reliable screening on the basis of these tests. However, the higher HPV positivity in the women with biopsies simply shows that HPV has a higher referral rate than VIA and cytology when applied as a primary screen.

We also found that HPV DNA test sensitivity did not differ greatly among women in different age groups, which is consistent with previous studies.¹⁶ However, one of our major findings is that, in our population, HPV DNA testing had high specificity in women younger than 35 years compared with older women. The same high specificities were noted in women aged 15–29 years (specificity for CIN grade 2 or worse was 91.6% and for grade 3 or worse was 90.9%) and 30–34 (specificity for grade 2 or worse was 89.7%, and for grade 3 or worse was 88.6%). These findings contrast with previous studies, which found a low specificity in younger women.^{16,18,31–33}

A probable explanation for the high comparative specificity in younger women is the natural history of HPV infection in China compared with other countries. In other countries, the lower specificity in younger women is explained by the higher rate of transient infections in younger women compared with older women. Indeed, in women in Europe and North America, the peak of HPV infection happens in women in their 20s, with a steady decrease in prevalence as age increases.¹⁶ However, our study found that the peak of HPV infection in Chinese women is in those aged 35–44 years. This peak was also noted in previous studies in China,^{21,34} which might be related with the late onset of sexual activity among this population. Since women in this age group have a higher rate of infection in China and about 80% of HPV infections are cleared within a year,³⁵ this group could be testing positive more often for infections that will not lead to cancerous lesions, causing the specificity in this age group to decrease. Conversely, the lower rate of HPV infection in young women in our population might explain the high specificity in this age group. Although the HPV DNA test is not recommended as a primary screening test in young women in other countries, the high sensitivity and specificity of HPV DNA testing in young Chinese women suggest that a different strategy might be applicable in China. Considering our small sample of women aged 15–29 years, 1807 women (6.3% of all included participants), and the very low prevalence of CIN grade 2 (16 women) and grade 3 (nine) in this population, we can only recommend that HPV DNA testing be used for women older than 30 years.

Notably, specificity also rises in the older than 50 years age group as HPV DNA prevalence decreases. The positive predictive value in women aged 35–49 years is higher than for women in other age groups, although the positive predictive value for women younger than 35 years is lower, suggesting the respectively high and low rate of precancerous and cancerous lesions in the women aged 35–49 years and younger than 35 years.

We found that sensitivity did not vary greatly by location, but specificity did vary, with higher specificities in urban areas. The possible reason is that the HPV prevalence is higher in rural than urban regions. Another possible reason is that the skill level of the doctors doing the biopsy might vary, especially as urban doctors tend to have more experience with biopsies.

We found greatly increased risks for high-grade lesions with increasing cutpoint and that increasing the cutpoint for a positive HPV DNA test might improve test accuracy. When the HPV DNA positivity cutpoint was raised from the manufacturer recommended 1.0 pg/mL to 2.0 pg/mL, the percentage of test positives decreased from 16.3% to 13.9%, which should result in a reduced rate of referral to colposcopy by 15% in practice, without a significant

decrease in the clinical sensitivity for CIN grade 3 or worse. Increasing the specificity of the test would enhance the cost-effectiveness of the test since fewer women would be unnecessarily referred for further workup. Our findings accord with a recent study from the UK³⁶ with a similar HPV prevalence (15.6%), which also found improved clinical performance when the cutpoint was raised to 2.0 pg/mL. Another recent study from the Netherlands,³⁷ with a lower HPV prevalence (5.1%), found that HPV DNA testing alone did not result in better performance at various cutoffs compared with HPV DNA testing as a primary screen with a cytology triage. In women younger than 35 years, raising the cutpoint to 10.0 pg/mL maintained a high sensitivity for CIN grade 3 or higher. These findings were not replicated for CIN grade 2 or above. As some lesions that seem to be CIN grade 2 might regress to normal, especially in young women,³⁸ the use of a higher cutpoint for lesions that are CIN grade 3 or above might be beneficial in this population.

In our study, women received colposcopy and biopsy if they were positive for the HPV DNA test, LBC, or visual inspection. Their final diagnosis was based on biopsy results that included four-quadrant punch biopsies, if available. In some studies all women received colposcopy, but a stratified analysis showed that the colposcopy protocol did not significantly affect sensitivity and specificity results (data not shown). Also, if women had no biopsy results because they were negative or ASC-US on cytology and negative for HPV DNA, they were assumed to be negative. The high quality of disease verification in our study gives an explanation to contrasting findings from an African and Indian pooled analysis,³⁹ which showed a high sensitivity for VIA (82.9% for CIN grade 3 or worse) and a low sensitivity for HPV DNA testing (68.4% for grade 3 or worse) and Pap smear (56.1% for grade 3 or worse).³⁹ In this study, colposcopy and colposcopy-directed biopsy was used as their gold standard, which could lead to gold standard misclassification and falsely inflate the sensitivity of visual-based screening methods such as VIA, since both colposcopy and VIA miss the same lesions.²⁵ By contrast, our studies required several screening tests to be negative to be deemed negative and four-quadrant punch biopsy was used when no colposcopically suspect lesion was seen. These methods decrease gold standard misclassification.

Nonetheless, we recognise it is a limitation that we cannot do disease ascertainment in the entire population, but the bias affects all tests, not just HPV testing. Despite the limitation, our findings are internally consistent and HPV DNA testing is much more sensitive than the other tests. Moreover, further correction had little effect on estimates of the accuracy of HPV DNA testing. Additionally, we computed an approximated specificity as proposed in a conceptual paper⁴⁰ that usually yields values very similar to the real specificity in screening situations and does not suffer from verification bias. The approximated specificities were nearly equal to those reported here (data not shown). This strongly supports that the specificities presented in our report are very close to the true specificities.

We stratified by age group to reduce confounding and were able to see similar higher sensitivities of HPV DNA test in various age groups. However, since many cervical-cancer screening studies included in our analysis primarily focused on middle-aged women, our population is weighted toward this age group. Moreover, with about 19% of our population being younger than 35 years and less than 3% younger than 25 years, caution is needed

when generalising the results to young women. Considering the correlation of age-specific HPV prevalence with HPV testing performance, our findings are applicable primarily to the Chinese population.

In the USA, HPV DNA testing is recommended as an adjuvant to cervical cytology screening.⁴¹ In China, women who live in urban regions have access to opportunistic screening for cervical cancer, which includes cytology or HPV DNA testing. However, women who live in rural areas, which might lack cytopathologists, often receive less infrastructure-heavy methods of screening, such as visual inspection. Many women are unable to access cervical-cancer screening at all. Although the Chinese Government has begun to close this gap with its cervical-cancer screening programme, which aims to screen 10 million rural women, there are still many women who will remain unscreened.^{10,11} As future programmes expand to reach China's 500 million rural women,^{10,11} choosing the best screening test is of utmost importance since only one or few screens in a lifetime might be achievable.

Our study found the HPV DNA test to be a highly accurate screening test across various locations and age groups in China with optimum screening accuracy at the 2.0 pg/mL cutpoint. Our findings also show that the HPV test can be used in women in China younger than 35 years with high sensitivity and specificity—mainly in women aged 30–34 years. Raising the cutpoint to 10.0 pg/mL will still maintain high sensitivity and specificity. With its high accuracy and applicability to various age groups and regions in China, as well as the recent development of a fast HPV DNA testing method,¹² which is simple, affordable, accurate, and would allow screening results to be available on the same day of visit, the HPV DNA test is a viable option for large scale cervical-cancer prevention screening programmes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Panel: Research in context**Systematic review**

We searched for and then reviewed published articles on the performance of HPV DNA testing in cervical-cancer primary screening with PubMed. HPV DNA testing has been assessed in cross-sectional studies, randomised trials, and metaanalyses. Studies were mainly from developed countries; few were from developing countries such as China. We selected methodologically rigorous studies done in China for our pooled analysis to establish whether high-risk HPV DNA testing could be used as a primary screening test for cervical cancer.

Interpretation

Our findings add to the evidence that HPV DNA testing is a sensitive and specific test, and sufficient clinical benefits would be achieved by adjusting the positive cutpoint to optimise clinical performance for all ages. The consistent high accuracy of HPV DNA testing across various locations and ages in an unscreened Chinese population provides the first evidence that HPV DNA testing could be a viable option for large scale cervical-cancer prevention screening programmes in China.

Figure 1. Flow chart of study participants

HPV=human papillomavirus. ASC-US=atypical squamous cells of undetermined significance. LSIL=low-grade squamous intraepithelial lesion.

Figure 2. Forest plots of pooled and individual study sensitivities and specificities

Plots show the sensitivity and specificity for CIN grade 2 and worse (A) and CIN grade 3 and worse (B). 95% CIs of each study are represented by a horizontal line, and the point estimate is represented by a square. The size of the square corresponds to the weight of the study in the pooled analysis. The diamond represents the overall estimate. Two vertical lines around the diamond represent the CI of the overall estimate. SPOCCS=Shanxi Province Cervical Cancer Screening Study. START=Screening Technologies to Advance Rapid Testing. IARC=International Agency for Research on Cancer. HPV=human papillomavirus. HC2=Hybrid Capture 2. CIN=cervical intraepithelial neoplasia.

Figure 3. Receiver operating characteristic curves

Curves show the detection of CIN grade 2 and worse (A) and CIN grade 3 and worse (B).

AUC=area under the curve. CIN=cervical intraepithelial neoplasia.

Table 1

Characteristics of pooled studies

Study year; location	Number screened	Age (years)	Screening tests	Follow-up procedure	Histology or cytology location and review
SPOCCSI 1999; Xiangyuan County, Shanxi Province	1997	35–45	HC2 (self, physician), fluorescence test, LBC, VIA, colposcopy	All women received four-quadrant biopsies and ECC under colposcopy	CICAMS, blinded international review
SPOCCS II 2001–02; Xiangyuan and Yangcheng County, Shanxi Province	8497	35–50	HC2 (self, physician), LBC, VIA, AFB	Positive VIA, self-test or physician-test for high-risk HPV, or an abnormal AFB, or a positive Pap test (ASC-US or worse); 4-quadrant biopsies and ECC	CICAMS
SPOCCS III-(1) 2006; Xiangyuan County, Shanxi Province	884	16–54	HC2 (self, physician), LBC, VIA	Positive VIA or positive self-HC2 (colposcopy and directed biopsy, ECC if necessary); positive physician-collected HC2 or ASC-H or worse on LBC (colposcopy and 4-quadrant biopsies, ECC if necessary)	CICAMS; blinded international review (only histology)
SPOCCS III-(2) 2006; Beijing City	795	16–54	HC2, LBC, VIA	Positive VIA (colposcopy and directed biopsy, ECC if necessary); positive physician-collected HC2 and ASC-US on LBC or ASC-H or worse (colposcopy and 4-quadrant biopsies, ECC if necessary)	Peking University People's Hospital, blinded international review and CICAMS review
SPOCCS III-(3) 2006; Ximi, Henan Province	879	16–54	HC2 (self, physician), LBC, VIA	Same as SPOCCS III-(1)	CICAMS, blinded international review (only histology)
SPOCCS III-(4) 2006; Yutian County, Xinjiang Uygur Autonomous Region	883	16–54	HC2 (self, physician), LBC, VIA	Same as SPOCCS III-(1)	CICAMS, blinded international review (histology); People's Hospital of Xinjiang Uygur Autonomous Region, blinded CICAMS review (cytology)
SPOCCS III-(5) 2007; Shanghai city	774	16–54	HC2, LBC, VIA	Positive VIA (colposcopy and directed biopsy, ECC if necessary); positive physician-collected HC2 or ASC-H or worse (colposcopy and four-quadrant biopsies, ECC if necessary)	Shanghai, blinded international and CICAMS review (for cytology, blinded CICAMS review only)
START 2003 2003; Xiangyuan County, Shanxi Province	2005	30–49	HC2, LBC, VIA	Positive VIA, HC2 positive, or ASC-H or worse on LBC (colposcopy and four-quadrant biopsies and ECC)	CICAMS, blinded international review
START 2004 2004; Xiushui County, Jiangxi Province	2499	30–49	HC2, LBC, VIA, VILI, colposcopy	Positive VIA, VILI, or colposcopy (four-quadrant biopsies and ECC); negative VIA or VILI but HC2 positive, or ASC-H or greater on LBC (repeat colposcopy and four-quadrant biopsies and ECC)	Jiangxi, blinded international and CICAMS review
START 2005 2005; Wudu County, Gansu Province	2053	30–49	HC2, LBC, VIA, VILI	Positive VIA or VILI (colposcopy and directed biopsy, and ECC if necessary); negative VIA or VILI but HC2 positive, ECC if necessary	Gansu Cancer Hospital, blinded

Study year; location	Number screened	Age (years)	Screening tests	Follow-up procedure	Histology or cytology location and review
				ASC-H or worse on LBC (colposcopy and 4-quadrant biopsies and ECC)	international and CICAMS review (histology); CICAMS, blinded international review (cytology)
START 2006	2500	30–49	HC2, LBC, VIA, VILI, colposcopy	Same as START 2005	CICAMS; blinded international review
START 2007	2530	30–54	HC2, careHPV, LBC, VIA, colposcopy	Positive VIA or colposcopy (directed biopsy, and ECC if necessary); negative VIA but HC2 or careHPV positive or ASC-H or worse on LBC (repeat colposcopy and four-quadrant biopsies and ECC if necessary)	CICAMS, blinded international review
IARC-(1)	1137	15–59	HC2, LBC, VIA, colposcopy	Positive colposcopy (directed biopsy, and ECC if necessary); negative colposcopy, but HC2 positive and ASC-US, or LSIL or worse on LBC (repeat colposcopy with directed biopsies, and ECC if necessary)	Shenzhen, blinded CICAMS review
IARC-(2)	745	15–59	HC2, fluorescence test, LBC, VIA, VILI, colposcopy	Positive colposcopy or fluorescence test (directed biopsy and ECC if necessary); negative colposcopy, but HC2 positive and ASC-US, or LSIL or worse on LBC (follow-up 1 year later)	Yangcheng County Cancer Hospital, blinded international and CICAMS review (for histology, blinded CICAMS review only)
<i>Fas</i> HPV trial	818	30–50	HC2, careHPV, LBC, VIA, VILI	Either VIA or VILI or careHPV was positive (colposcopy and directed biopsy, and ECC if necessary); VIA and VILI and careHPV were negative, or colposcopy was negative, but HC2 positive or LSIL or worse on cytology (four-quadrant biopsies, and ECC if necessary)	CICAMS
Prevalence survey	316	18–25	HC2, LBC, VIA	Positive VIA (colposcopy and directed biopsy, and ECC if necessary); negative VIA but ASC-H or worse on LBC (colposcopy and four-quadrant biopsies, and ECC if necessary); negative VIA but HC2 positive and ASC-US or better on LBC (colposcopy and directed biopsy, and ECC if necessary)	CICAMS
HC2 trial	1059	30–59	HC2, LBC, VIA, VILI	Positive VIA or VILI: directed biopsy, and ECC if necessary; negative VIA or VILI but HC2 positive and ASC-US, or ASC-H or worse on LBC (colposcopy and four-quadrant biopsies, and ECC if necessary); either HC2 positive or ASC-US on LBC (directed biopsy, and ECC if necessary)	CICAMS

SPOCCS=Shanxi Province Cervical Cancer Screening Study. HC2=Hybrid Capture 2. LBC=liquid-based cytology. VIA=visual inspection with acetic acid. ECC=endocervical curettage. CICAMS=Cancer Institute and Hospital of the Chinese Academy of Medical Sciences. AFB=Amperand's fluorescent biomolecular markers. ASC-US=atypical squamous cells of undetermined significance. ASC-H=atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion. VILI=visual inspection with Lugol's iodine. START=Screening Technologies to Advance Rapid Testing.

Table 2
Accuracy of HPV DNA testing for detection of CIN grade 2 or worse and grade 3 or worse

	<35 years	35–49 years	50 years	All ages	χ^2 ; p value
Sensitivity					
CIN grade 3 or worse	43/43 (100.0, 91.8–100.0)	398/410 (97.1, 94.9–98.5)	27/27 (100.0, 87.2–100.0)	468/480 (97.5, 95.7–98.7)	∞; 0.818 (Fisher's exact)
CIN grade 2 or worse	99/102 (97.1, 91.6–99.4)	736/767 (96.0, 94.3–97.2)	50/50 (100.0, 92.9–100.0)	885/919 (96.3, 94.9–97.4)	∞; 0.432 (Fisher's exact)
Specificity					
CIN grade 3 or worse	4843/5418 (89.4, 86.1–91.5)	17 649/21 061 (83.8, 81.0–86.6)	1653/1889 (87.5, 83.2–90.7)	24 145/28 368 (85.1, 82.3–87.9)	115.34; <0.0001
CIN grade 2 or worse	4840/5359 (90.3, 88.2–92.5)	17 630/20 704 (85.2, 82.6–87.7)	1653/1866 (88.6, 85.1–92.2)	24 123/27 929 (86.4, 83.8–89.0)	104.72; <0.0001
Positive predictive value					
CIN grade 3 or worse	43/618 (7.0, 5.1–9.3)	398/3810 (10.4, 9.5–11.5)	27/263 (10.3, 6.9–14.6)	468/4691 (10.0, 9.1–10.9)	8.95; 0.011
CIN grade 2 or worse	99/618 (16.0, 13.2–19.2)	736/3810 (19.3, 18.1–20.6)	50/263 (19.0, 14.5–24.3)	885/4691 (18.9, 17.8–20.0)	3.78; 0.151
Negative predictive value					
CIN grade 3 or worse	4843/4843 (100.0, 99.9–100.0)	17 649/17 661 (99.9, 99.9–100.0)	1653/1653 (100.0, 99.8–100.0)	24145/24145 (100.0, 100.0–100.0)	∞; 0.139 (Fisher's exact)
CIN grade 2 or worse	4840/4843 (99.9, 99.8–100.0)	17 630/17 661 (99.8, 99.8–99.9)	1653/1653 (100.0, 99.8–100.0)	24 123/24 157 (99.9, 99.8–99.9)	5.99; 0.050

Data are n/N (%; 95% CI). HPV DNA positivity at relative light unit/cutoff values of 1 pg/mL or greater. CIN=cervical intraepithelial neoplasia.

Table 3

Risk ratios for developing CIN grade 3 or worse at various relative light unit/cutoff values

	N	CIN grade 3 or worse (%)	Risk ratio (95% CI)
<1 pg/mL	24 157	12 (0.05)	1 (..)
1 to <2 pg/mL	681	11 (1.6)	33.0 (14.5–75.1)
2 to <4 pg/mL	462	14 (3.0)	62.9 (28.9–136.7)
4 to <10 pg/mL	514	16 (3.1)	64.6 (30.4–137.4)
>10 pg/mL	3019	427 (14.1)	331.5 (186.5–589.1)
Total	28 833	480 (1.7)	

CIN=cervical intraepithelial neoplasia.

Table 4

Uncorrected and corrected accuracy of HPV DNA testing by age groups

	CIN grade 2 or worse		CIN grade 3 or worse	
	Sensitivity	Specificity	Sensitivity	Specificity
<35 years				
Uncorrected	97.1 (91.6–99.4)	90.3 (88.2–92.5)	100.0 (91.8–100.0)	89.4 (86.1–91.5)
Corrected	94.8 (90.3–98.0)	88.3 (87.4–89.1)	100.0 (100.0–100.0)	87.2 (86.3–88.1)
Difference	2.3	2.0	0.0	2.2
35–49 years				
Uncorrected	96.0 (94.3–97.2)	85.2 (82.6–87.7)	97.1 (94.9–98.5)	83.8 (81.0–86.6)
Corrected	95.0 (93.3–96.3)	84.5 (84.0–85.0)	97.2 (95.4–98.5)	83.1 (82.6–83.6)
Difference	1.0	0.7	–0.1	0.7
50 years				
Uncorrected	100.0 (92.9–100.0)	88.6 (85.1–92.2)	100.0 (87.2–100.0)	87.5 (83.2–90.7)
Corrected	97.5 (92.1–99.9)	86.8 (85.3–88.3)	100.0 (100.0–100.0)	85.7 (84.0–87.2)
Difference	2.5	1.8	0.0	1.8
Total				
Uncorrected	96.3 (94.9–97.4)	86.4 (83.8–89.0)	97.5 (95.7–98.7)	85.1 (82.3–87.9)
Corrected	95.1 (93.6–96.3)	85.4 (85.0–85.8)	97.6 (95.9–98.6)	84.1 (83.7–84.5)
Difference	1.2	1.0	–0.1	1.0

Data are % (95% CI). HPV DNA positivity at relative light unit/cutoff values of 1 pg/mL or greater. CIN=cervical intraepithelial neoplasia.