Optical coherence tomography with higher specificity than Papanicolaou cytology in patients with high-risk human papillomavirus: a prospective cohort study

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Abstract

Objective To assess triage of HPV-positive women by optical coherence tomography (OCT), with or without HPV16/18 genotyping, compare with cytology. Design A prospective cohort study. Setting The Second Xiangya Hospital in China. Population 813 participants with high-risk HPV(hrHPV)-positive and cervical cytology results received OCT before colposcopy between 1 March 2021 and 1 October 2021. Methods OCT examinations were performed on an outpatient basis. Cytological and histological results during follow-up were obtained from the Department of Pathology at the Second Xiangya Hospital. Main outcome measures OCT and cytology results were compared with the pathological results to calculate sensitivity, specificity, and immediate CIN3+ risk. The advantages and disadvantages of OCT and cytology triage of hr-HPV-positive women were compared. Results HPV16/18 genotyping with OCT triage has a specificity of CIN3+ lesions [61.1%; 95% CI, 57.6%-64.6%], CIN2+ [66.0%; 95% CI, 62.4%-69.6%]. HPV16/18 genotyping with cytology triage has a specificity of CIN3+[44.0%; 95% CI, 40.4%-47.6%], CIN2+ [47.0%; 95% CI, 43.2%-50.8%]. The OCT triage has a higher specificity and positive predictive value(PPV) compared to the cytology with a significant difference. The OCT triage has a similar immediate CIN3+ risk compared to the cytology. Conclusion The combination of OCT and HPV triage (both genotyping and non-genotyping) is feasible in terms of immediate CIN2+/CIN3+ risk, and the OCT triage strategy reduces the number of colposcopies and improves the specificity and positive predictive value of the test compared to the cytological triage strategy.

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Main outcome measures OCT and cytology results were compared with the pathological results to calculate sensitivity, specificity, and immediate CIN3+ risk. The advantages and disadvantages of OCT and cytology triage of hr-HPV-positive women were compared.

Results HPV16/18 genotyping with OCT triage has a specificity of CIN3+ lesions [61.1%; 95% CI, 57.6%-64.6%], CIN2+ [66.0%; 95% CI, 62.4%-69.6%]. HPV16/18 genotyping with cytology triage has a specificity of CIN3+ [44.0%; 95% CI, 40.4%-47.6%], CIN2+ [47.0%; 95% CI, 43.2%-50.8%]. The OCT triage has a higher specificity and positive predictive value (PPV) compared to the cytology with a significant difference. The OCT triage has a similar immediate CIN3+ risk compared to the cytology.

Conclusion The combination of OCT and HPV triage (both genotyping and non-genotyping) is feasible in terms of immediate CIN2+/CIN3+ risk, and the OCT triage strategy reduces the number of colposcopies and improves the specificity and positive predictive value of the test compared to the cytological triage strategy.

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Keywords Cervical cancer, cervical intraepithelial neoplasia, human papillomavirus, screening, Optical coherence tomography

Tweetable abstract OCT for triage of hrHPV+ is of added value for cytology of women for colposcopy.

Introduction

Globally, cervical cancer continues to be one of the most common cancers among females, being the fourth most common after breast, colorectal, and lung cancer[1].{Sung, 2021 #49} In China, like in many other countries, we have phased out cytology as the primary cervical cancer screening test and replaced it with primary HPV testing. However, the highly transient nature of HPV infection results in a low specificity of this test, and the usual solution is to use cytology for hrHPV-positive patients to avoid unnecessary colposcopy. The specificity of cervical cytology is 42.9%-66.8% for cervical cancer screening in hr-HPV patients[2, 3].

Optical coherence tomography (OCT) is an imaging technique that uses near-infrared light interferometry to measure the intensity of backscattered light. OCT was first used to visualize cervical lesion tissue in 1999. At that time, Pitris first examine cervical specimens in vitro[4]. Then Escobar PF performed the first in vivo examination and established a method for lesion differentiation in 2004[5]. The sensitivity and specificity of the OCT test varied considerably with the procedure in subsequent trials. With the pathology of cervical intraepithelial neoplasia of grade 2 or worse (CIN2+) as the gold standard, the sensitivity and specificity of Escobar PF's study were 56% and 59%, respectively[6]. The sensitivity and specificity of Liu Z's study were 32% and 93% in 2010.[7] Gallwas attempted to establish a more accurate classification of lesion results from OCT images in 2010. His measurements had a sensitivity of 86% and a specificity of 64%[8]. The instruments used in the above experiments had a longitudinal resolution of 10μm-20μm and a transverse resolution of 15μm-25μm. 2018 Zeng used an optical coherence microscopy instrument with a longitudinal resolution of ˜1.8 μm and a transverse resolution of ˜3.5 μm in an in vitro setting with a sensitivity of 80% and a specificity of 89%[9]. They finally established the OCT method for differentiating cervical lesions. 2021 Ren performed a multicentre trial using an OCT instrument with an axial resolution of <5μm and a transverse

resolution of <10μm. They measured sensitivity of 84.9% and a specificity of 85.7%.[9] With the improvement of technology, OCT showed high diagnostic efficiency in evaluating cervical tissue.

In this study, we first want to determine whether HPV combined with OCT screening is effective in the outpatient environment. Secondly, we need to know whether further triage with OCT is more attractive than TCT for hrHPV-positive patients.

Methods

Study Population and Clinical Procedures

The study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University (ethics number LYF2021026). A total of 4419 women attending the gynecology outpatient clinic were invited to participate in the study at the outpatient department of Xiangya Second Hospital from 1 March 2021 to 31 September 2021. All participants signed an informed consent form. Inclusion criteria were as follows: women with sex life voluntarily participated and provided informed consent. Exclusion criteria were as follows: women with total hysterectomy or other reasons for non-existent cervix; women treated with cervical surgery within 3 months; women with acute gynecological inflammation. After signing informed consent, the participants will have their HPV testing taken by the corresponding outpatient clinician(Figure 1).

A total of 891 participants with a positive hrHPV went to the OCT clinic. Two gynecologists were present in the OCT room, one asked and recorded the patient's basic information, and the other performed OCT without knowing the patient's HPV and TCT results. After that, the former referred all patients to the colposcopy room for colposcopy (except for patients with syphilis and human immunodeficiency virus). A total of 813 patients had credible OCT results and underwent colposcopy, of which 813 patients had reliable colposcopic findings(Figure 1). We performed a cytology test on the patient in the OCT room.

Clinical Routine HPV Testing

HPV tests were collected using the Hybribio Female Sample Collection Kit (Hybribio Co., Guangdong, China). The kit consists of an intracervical collection brush and a tube with a specimen transfer medium. All specimens were tested for HPV DNA and stored at -20. HrHPV genotyping was performed using the HBRT-H14, which is a 14 hrHPV genotyping real-time PCR kit (Hybribio Co., Guangdong, China). HPV subtype 16, HPV subtype 18, and 12 other hrHPV subtypes were tested separately for each specimen. HBRT-H14 showed high compliance with the WHO HPV DNA proficiency panel report as reported by the International HPV Genotyping Proficiency Study of the WHO Global HPV Laboratory Network (LabNet).

OCT examination

The OCT system was the UL-C110 ultra-LUT cervical scanning system(Zhengzhou Ultra Lucia Medical Technology Co)in the study. The device was equipped with a broadband light source with a central wavelength of 850 nm, a full-width half-height bandwidth of >155 nm, an axial resolution of <5 μm, and a lateral resolution of <10 μm in the tissue. A handheld probe was used to deliver the imaging beam to the cervical surface. The output beam of the probe had an optical power of <5 mW. The outer diameter of the probe was about 10 mm and easily passed through the speculum. The maximum scanning speed is 80,000 A-scans/s and the imaging depth is approximately 1 mm.

The image acquisition was performed in a cyclic scanning mode. The scanning diameter can be adjusted in the range of 0-2 mm depending on the setting, taking into account the beam size and the focus-scatter effect. Compared with the conventional linear scanning mode, the circular scanning mode allowed a wider scanning range, so that more tissue information can be captured in each frame of the OCT image. In this study, the number of A-scans per frame was set to 1200 to maintain adequate pixel density and image resolution. Scanning diameters ranged from 0.9 mm (the inner circle) to 1.1 mm (the outer circle). Ten circular scans were performed within the annular region with equal intervals between adjacent circles

The OCT examination was performed by gynecologists who were blinded to the hrHPV and gynecological results. The participant lay down in the lithotomy position. The operator disinfected the OCT probe with

75% alcohol and put it on a protective sleeve, squeezing out the air between the sleeve and the probe with a cotton swab. After inserting a speculum, the participant's cervical surface was wiped clean with a large gynecological swab. 12 images of the cervical os were taken clockwise with the OCT probe for 2-3 seconds at each point, followed by 12 images of the mid-circle of the cervix. The OCT images were transmitted online to Zhengzhou Light Ultrasound for reading by a special reader (the reader knew nothing about the patient except that the 24 images of a patient were from the same patient). Two skilled readers will give separate readings and conflicting results will be decided by a third skilled reader.

OCT results were classified according to the 2-class criteria described previously. The results can be divided into high-risk and low-risk groups. OCT high-risk refers to high-grade squamous intraepithelial lesions (HSIL) and invasive lesions. OCT low-risk refers to normal/mild inflammation, ectropion, and low-grade squamous intraepithelial lesion (LSIL) [10]. The positive result was given if at least one location was marked as high-risk for each patient. Otherwise, a negative result was given.

Cytologic Screening

Cytology was performed using a kit from Hologic. Cervical sample cells were collected with a special brush, then stored in PreservCyt solution for the NewPherson cytology test. The participant was in the recumbent position and the sampling brush was rotated clockwise 6 to 8 turns at her cervical orifice. The brush head was then placed in the Thinprep fixative solution. Cytologic findings were classified by the Bethesda System: negative for intraepithelial lesions or malignant neoplasm (NILM); atypical squamous cells of unknown significance(ASC-US); LSIL; atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion(ASC-H); and HSIL.[11]

Colposcopy & histology

All selected participants underwent a colposcopy performed by the investigator in the hospital. Standardized colposcopy of the cervix was performed by a qualified gynecologist who knew the patient's HPV, TCT results, and basic information but not the patient's OCT results. Each examination is performed with 3-5% acetic acid and a Schiller test. Lesions were described as characterized by color, margins, vascularity, and diiodine staining. Colposcopy revealed NILM, LSIL, HSIL, and cancer. Colposcopy-guided biopsy specimens were obtained in a target area with acetylated albinism degeneration or higher abnormalities from an acetylated albino lesion evident on the Schiller test. When no abnormal findings were found on colposcopy, the patient will undergo cervical scratching if it is a transformation zone type III, and if it is a transformation zone type I or II, a 3, 6, 9, or 12 o'clock point biopsy will be selected when the physician has a high suspicion that the patient has a lesion based on previous HPV and TCT results. The biopsy specimens were reviewed and interpreted by two pathologists according to standard hospital procedures.

Statistical Analysis

Although we did not biopsy every patient, our colposcopists were well trained and knew the HPV and cytology results and take a biopsy if possible, so we treat those who do not take a cervical biopsy as negative. Although OCT results do not allow exploration of the cervical canal, we consider the highest pathological grade between surface biopsies, cervical canal scrapings, and cervical redundancies as the final pathological result to allow a fair comparison with cytology results.

Differences in positivity, sensitivity, and specificity were evaluated using an exact McNemar $\chi 2$. The differences in predictive values were evaluated using the method developed by Leisenring, using the R package and DTComPair (R Foundation for Statistical Computing) [12]. Population baseline information was analyzed by R package and tableone (R Foundation for Statistical Computing) for data analysis. Fisher's exact test was used for categorical variables, and ANOVA was used for continuous variables.

Results

Patient characteristics and colposcopy biopsy results

Of 813 women included in this study, 10 had cancer, 60 had CIN3 or adenocarcinoma in situ, 81 had CIN2, 267 had CIN1, 325 had negative histological results, and 70 did not indicate a biopsy(Figure 1).

Of the total HPV positive patients, 423 (52.0%) had negative cytology results, 235 (28.9%) with ASC-US, 119 (14.6%) with LSIL, 19 (2.3%) with ASC-H, and 17 (2.1%) with HSIL. (Table S1).

Of 20.9% (170/813) women with HPV16/18 positive results, 48.2% (82/170) had positive cytological results, and 34.1% (58/170) had OCT High-risk results; 79.1% (643/813) were women who had positive hrHPV12 results, of which 47.9% (308/643) were women with positive cytological results, OCT High-risk women accounted for 27.1% (174/813). A total of 10 cancers were detected in our study, and cytology detected all with OCT detected 8. The 2 cases not detected by OCT were from cervical scratching results. (Table 1).

The mean age of all patients was 44.68 years, with 169 under 35 years, 226 35-44 years, 253 45-54 years, and 165 greater than or equal to 55 years. There was a significant difference between the different age groups in terms of education level, current residence, pathological findings, OCT findings, cervical transformation zone, cervical size, nascent gland cyst, and prevalence of atrophic vaginitis ($p<0.01$)(Table S2).

The above results were judged by two investigators separately (Kappa=0.87) and the disputed results by a third investigator (Table S3).

Cytologic and OCT triage for detecting precancerous lesions

For all HPV-positive patients, OCT had a higher specificity than cytology in its ability to detect CIN2+ (529/662 [79.9%; 95% CI, 76.9%-83.0%] vs. 386/662 [58.3%; 95% CI, 54.6%-62.1%]; $P < 0.01$), while OCT testing had a higher positive predictive value (109/242 [45.0%; 95% CI, 38.8%-51.3%] vs. 114/390 [29.2%; 95% CI,24.7%-33.7%]; $P < 0.01$).OCT testing found a similarly higher specificity for CIN3+ than cytology (556/743 [74.8%; 95% CI, 71.7%-78.0%] vs 411/743 [55.3%; 95% CI, 51.7%- 58.9]%];$P < 0.01$), although OCT examinations had higher positive predictive values compared to cytology but were not statistically significant. The sensitivity of the ability of OCT assays to detect CIN2+,CIN3+, and negative predictive values were both lower than cytology, but not statistically significant(Table 2).

Compared with the combination of HPV16/18 genotyping or cytological findings, the combination of HPV16/18 genotyping or OCT had higher specificity in the ability to detect CIN2+ and CIN3+(311/662 [47.0%; 95% CI, 43.2%-50.8%] vs 437/663 [66.0%; 95% CI, 62.4%-69.6%]; $P < 0.01$) and (327/743 [44.0%; 95% CI, 40.4%-47.6%] vs 454/743 [61.1%; 95% CI, 57.6%-64.6%]; $P < 0.01$). While a combination of OCT or HPV16/18 genotyping had a higher positive predictive value, which was not statistically significant. Although the combination of OCT or HPV16/18 genotyping had a lower sensitivity and negative predictive value than the combination of cytology and HPV16/18 genotyping screening, it was not weaker than cytology alone in both CIN2+ and CIN3+ (Table 2).

Cervical precancerous lesion risk of primary HPV screening with OCT

Table 4 demonstrates the risk stratification of HPV-positive patients. According to the 2019 ASCCP guidelines, patients with an immediate CIN3+ risk of 4% or more should undergo a colposcopy, and patients with an immediate CIN3+ risk of 0.55%-4% will be reviewed after one year. We designed three triage strategies combining HPV and OCT (Figure S1).

For the FDA-approved HPV screening and partial genotyping with cytologic triage, our trial's immediate CIN3+ risk stratification was consistent with expectations. The FDA-approved cytology with HPV genotyping protocol requires 58.8% to be referred for colposcopy, detects one case of CIN3+ for every 8.0 colposcopies performed and one case of CIN2+ for every four 3.8 people. For HPV screening with cytology triage, 48.0% were referred for colposcopy. This strategy required 6.7 colposcopies to detect CIN3+ findings and 3.4 to detect CIN2+ at immediate referral (Table 2).

For HPV16/18 with OCT triage, 43.1% were referred for colposcopy, 1 CIN3+ case per 5.7 colposcopies performed, 1 CIN2 case per 2.8 colposcopies (Table 2). For HPV screening with OCT triage, 29.8% were referred for colposcopy. This strategy required 4.4 colposcopies to detect CIN3+ findings and 2.2 to detect

CIN2+ at immediate referral (Table 2). Both two new OCT strategies reduced the number of colposcopy referrals compared to the FDA strategy while expanding the ability to detect CIN3+/CIN2+ per unit of colposcopy.

The risk of CIN3+ of OCT low-risk triage with HPV+ and non-16,18 high-risk HPV-positive were 2.63% (5%CI, 1.32%-3.94%) and 1.94% (95%CI, 0.69%-3.20%), respectively. Their risk of intermediate CIN3+ was below 4%, and slightly lower than the FDA-approved strategy (2.84% (95%CI,1.25%-4.42%) and 2.39% (95% CI, 0.75%-4.02%)). However, there was no statistical difference between them (Figure 2, Table S4).

Effect of age on OCT detection ability

We evaluated the ability of OCT to detect CIN2+, CIN3+ in HPV-positive patients by age. We found that the sensitivity of OCT for CIN2+ and CIN3+ decreased with increasing age, and the specificity and positive predictive value increased and were statistically different ($P<0.05$) (Table S5). We believe that the cervical transformation zone might be responsible for the difference in the ability to detect cervical lesions by OCT at different ages. We analyzed the ability of OCT in different transformation zones to detect cervical CIN2+, CIN3+. The type II and type III transformation zones possessed lower sensitivity and higher specificity compared to the type I transformation zone (Table S6) ($p<0.05$).

Discussion

Main findings

HPV combined with OCT triage is feasible and has a similar immediate CIN3+ risk stratification compared to cytology triage. OCT has a significant specificity and positive predictive value advantage over cytology. The OCT triage approach reduces the number of colposcopic triages and increases the ability to detect CIN3+, CIN2+ per patient with little loss of ability to detect cervical lesions in the patient. OCT results are influenced by age, a possible reason for the difference in recognition of inverted pictures influenced by the transformation zone or other cervical factors. However, we could not prove this because we implemented OCT in the outpatient clinic and could not correspond specific images to the biopsy tissue.

Strengths and limitations

The strength of our study is its prospective design, with a large number of women undergoing the same HPV, cytology, and OCT examinations. We collected more images per patient (24 images) than in previous OCT studies, and we collected complete information about the women, including age, education, address, past medical history, and cervical condition.

A limitation of our study is that we collected patients from a single source, which limits the generalizability of our conclusions. Another limitation is that we did not perform follow-up to know the patients' risk of prevalence of subsequent cervical intraepithelial lesions.

Interpretation

We collected OCT and cytology data from 813 hrHPV-positive patients to compare their advantages and disadvantages and to propose a feasible strategy for OCT application for cervical cancer prevention screening based on immediate CIN3+ risk. We collected clinical and personal information of patients and grouped them according to age and found that OCT test results correlated with patients' age.

The main inferiority of OCT over cytology tests are they both influenced by subjective raters and the stability of the results is difficult to guarantee. The main advantages of OCT are that no biological specimens need to be taken and the data are images based which may facilitate remote interpretation and automatic interpretation. The disadvantage is that even though OCT gets a major improvement over the previous one, the small probe area requires multiple probes increasing the examination time and the probe must be perpendicular to the surface of the cervical surface, making it difficult to detect the intracervical canal.

Compared with the inclusion of hrHPV-positive patients in ATHENA and 5250 hrHPV-positive patients in IMPACT. The proportion of non-biopsy was 8.6% (70/813) for us, 21.6% (697/3225), and 20.6%

(1016/4927)for the remaining two. The percentage of CIN2+ lesions we found was 18.6 %(151/813), and the remaining two were 14.6%(472/3225) and 10.9%(536/4927). The percentage of CIN3+ lesions we found was 8.6% (70/813), and the remaining two were 7.3% (236/3225) and 4.5% (222/4927). Our biopsy rate and percentage of cervical intraepithelial neoplasia findings were higher than the two large clinical studies. The main reason for this may be that our clinical outpatient population may include some patients who are self-referred to our gynecology clinic from other hospitals with abnormal findings, and it is clear that the likelihood of finding cervical intraepithelial lesions is higher among them than in the general outpatient population.

The sensitivity of our cytology test was 75.5% (114/151) and specificity 58.3% (386/662) in the CIN2+ population. The immediate sensitivities of ATHENA and IMPACT were 81.3% and 65.9%, specificity 44.6%, and 66.8%. The sensitivity and specificity of our cytological assay for CIN2+ lesions were in between, and the same conclusion still holds in CIN3+ lesions.

A multicenter clinical trial in 2021 found a sensitivity of 87% (82.2%-90.7%) and a specificity of 84.1% (80.3-87.2%) for CIN2+ lesions on OCT in 733 patients. We found a sensitivity of 72.2% (65.0%-79.3%) and a specificity of 79.9% (76.9-83.0%) for CIN2+ lesions in 813 patients. There was a significant decrease in the sensitivity of our assay, even though we detected 24 point images for one patient, while they only had 12 point images for one. The reason for this result may be due to the difference in the testing environment, and the population tested. The inclusion criteria for their trial population were hrHPV positive or cytology ASC-US+, and the testing site was in the colposcopy room facilitating the correspondence of the OCT images to the location of the pathological biopsy.

Conclusions

HPV combined with OCT screening is effective in outpatient settings. The specificity of OCT in detecting CIN2+/CIN3+ in hrHPV-positive patients is higher than that of cytology. Based on immediate CIN3+ risk stratification, compared with HPV combined with cytology triage strategy, the three OCT strategies reduce the number of colposcopy referrals.

Disclosure of interests

None declared. Completed disclosure of interests forms is available to view online as supporting information.

Contribution to authorship

All the authors have made substantial contributions to the conception, design of the work, the acquisition, analysis, or interpretation of data for the work. They have participated in drafting the manuscript and approved the version to be published. Conception and design: Xiao X, Chun F . Acquisition of data: Xiao X, Lei Y, Liyan S. Analysis of the samples: Xiao X, Lei Y, Xue Y. Statistical analysis: Xiao X . Data interpretation: Xiao X, Zhixian Z, Chun F. Manuscript writing: Xiao X, Chun F. Final approval of manuscript: Xiao X, Lei Y, Liye S, Zhixian Z, Xue Y, Chun F. Accountable for all aspects of the work: Xiao X, Lei Y, Liye S, Zhixian Z, Xue Y, Chun F.

Details of ethics approval

All the authors report adherence to ethical standards in the conception of the work, data collection, and writing of the manuscript.

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IRB status

The study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University (ethics number LYF2021026).

Submission declaration and verification

This manuscript has not been published previously, is not under consideration for publication elsewhere, and this publication is approved by all authors and the responsible authorities where the work has been carried out. This manuscript will not be published elsewhere in the same form.

Transparency statement

This manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted. Any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing statement

Data used in this study are available from the corresponding author on reasonable request.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Table 1. OCT Results and Cytologic Test Results Among 813 HPV-Positive Women

HPV Test Result No. (%)	Total (n=813)	Benign (n=325)	CIN1 (n=267)	CIN2 (n=81)	CIN3 or AIS (n=60)
Positive HPV16/18 result	**170 (20.9)**	**71 (21.8)**	**34 (12.7)**	**26 (32.1)**	**22 (36.7)**
TCT[?]ASC-US	81 (47.6)	21 (29.6)	15 (44.1)	17 (65.4)	17 (77.3)
OCT High-risk	58 (34.1)	13 (18.3)	8 (23.5)	15 (57.7)	14 (63.6)
Positive HR HPV12 result	**643 (79.1)**	**254 (78.2)**	**233 (87.3)**	**55 (67.9)**	**38 (63.3)**
TCT[?]ASC-US	308 (47.9)	99 (39.0)	127 (54.5)	39 (70.9)	30 (78.9)
OCT High-risk	174 (27.1)	50 (19.7)	48 (20.6)	37 (67.3)	25 (65.8)
TOTAL	**813(100)**	**325 (40.0)**	**267 (32.8)**	**81 (10.0)**	**60 (7.4)**
TCT[?]ASC-US	390 (48.0)	120 (36.9)	142 (53.2)	56 (69.1)	48 (80.0)
OCT High-risk	232 (28.5)	63 (19.4)	56 (21.0)	52 (64.2)	39 (65.0)

Abbreviations: AIS, adenocarcinoma in situ; ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia (grades 1-3); HSIL, high-grade squamous intraepithelial lesions; HPV, human papillomavirus; HPV16/18+, positive for either HPV16 or HPV18; HR HPV12+, positive for at least 1 of the other high-risk HPV types; LSIL, low-grade squamous intraepithelial lesions; No Biopsy, No indication for colposcopy/biopsy. The percentage in the first row in each cytology category gives the total across all cytology groups; the other percentages are within the cytology category.

Table 2. Performance of Cytologic Testing, OCT, HPV16/18 Testing, and Combinations Among 813 HPV-Positive Women to Detect CIN3+ and CIN2+

	Women, No./Total No. (%) [95% CI]	Women, No./Total No. (%) [95% CI]	Women, No./Total No. (%) [95% CI]	Women, No./Total No. (%) [95% CI]
Characteristic	Cytologic Findings	OCT Results	HPV16/18 or Cytologic Findings	HPV16/18 or OCT
Threshold	ASC-US+	High-risk	Either ASC-US+ or positive results for HPV16 or HPV18	Either OCT High-risk or positive results for HPV16 or HPV18
Positivity	390/813(48.0)[44.5-51.5]	242/813(29.8)[26.6-33.0]	478/813(58.8)[55.3-62.2]	350/813(43.1)[39.6-46.5]
Detection of CIN2+:(n=151)				

	Women, No./Total No. (%) [95% CI]	Women, No./Total No. (%) [95% CI]	Women, No./Total No. (%) [95% CI]	Women, No./Total No. (%) [95% CI]
Sensitivity	114/151(75.5)[68.6-82.4]	109/151(72.2)[65.0-79.3]	127/151(84.1)[78.3-89.9]	125/151(82.8)[76.8-88.8]
Specificity	386/662(58.3)[54.6-62.1]	529/662(79.9)[76.9-83.0]	311/662(47.0)[43.2-50.8]	437/463(66.0)[62.4-69.6]
PPV	114/390(29.2)[24.7-33.7]	109/242(45.0)[38.8-51.3]	127/478(34.6)[29.6-39.6]	125/350(35.7)[30.7-40.7]
NPV	386/423(91.3)[88.6-93.9]	529/571(92.6)[90.5-94.8]	311/335(93.2)[90.9-95.5]	437/469(94.4)[92.3-96.5]
Detection of CIN3+:(n=67)				
Sensitivity	58/70(82.9)[74.0-91.7]	55/70(78.6)[69.0-88.2]	62/70(88.6)[81.1-96.0]	61/70(87.1)[79.3-95.0]
Specificity	411/743(55.3)[51.7-58.9]	556/743(74.8)[71.7-78.0]	327/743(44.0)[40.4-47.6]	454/743(61.1)[57.6-64.6]
PPV	58/390(14.9)[11.3-18.4]	55/242(22.7)[17.4-28.0]	62/478(13.0)[10.0-16.0]	61/350(17.4)[13.5-21.4]
NPV	411/423(97.2)[95.6-98.7]	556/571(97.4)[96.1-98.7]	327/335(97.6)[96.0-99.2]	454/463(98.1)[96.8-99.3]

Abbreviations: ASC-US+, Atypical Squamous Cells of Undetermined Significance or more severe cytologic diagnosis; CIN2+, cervical intraepithelial neoplasia grade 2 or worse; CIN3+, cervical intraepithelial neoplasia grade 3 or worse; HPV, human papillomavirus; NPV, negative predictive value; PPV, positive predictive value.

Table S1. HPV16/18 and OCT Positivity by Histologic Test Results and Cytologic Test Results Among 813 HPV-Positive Women

Cytologic Test Result		Total (n=813)	Benign (n=325)	CIN1 (n=267)	CIN2 (n=81)	CIN3 or AIS (n=60)	Cancer (n=10)	No Biop (n=70)
NILM No. (%)		**423 (52.0)**	**205 (63.1)**	**125 (46.8)**	**25 (30.9)**	**12 (20.0)**	**0 (0.0)**	**56 (80.0)**
Positive HPV16/18	Positive HPV16/18	88 (20.8)	50 (24.4)	19 (15.2)	9 (36.0)	4 (33.3)	0 (NaN)	6 (10.7)
Positive HR HPV12	Positive HR HPV12	335 (79.2)	155 (75.6)	106 (84.8)	16 (64.0)	8 (66.7)	0 (NaN)	50 (89.3)
Positive OCT	Positive OCT	106 (25.1)	41 (20.0)	28 (22.4)	17 (68.0)	8 (66.7)	0 (NaN)	12 (21.4)
ASC-US No. (%)		**235 (28.9)**	**79 (24.3)**	**83 (31.1)**	**37 (45.7)**	**18 (30.0)**	**4 (40.0)**	**14 (20.0)**
Positive HPV16/18	Positive HPV16/18	43 (18.3)	13 (16.5)	5 (6.0)	11 (29.7)	8 (44.4)	3 (75.0)	3 (21.4)
Positive HR HPV12	Positive HR HPV12	192 (81.7)	66 (83.5)	78 (94.0)	26 (70.3)	10 (55.6)	1 (25.0)	11 (78.6)
Positive OCT	Positive OCT	63 (26.8)	14 (17.7)	14 (16.9)	22 (59.5)	9 (50.0)	2 (50.0)	2 (14.3)

Cytologic Test Result		Total (n=813)	Benign (n=325)	CIN1 (n=267)	CIN2 (n=81)	CIN3 or AIS (n=60)	Cancer (n=10)	No Biop (n=70)
LSIL		**119**	**38**	**52**	**15**	**13**	**1**	**0 (0.0)**
No. (%)		**(14.6)**	**(11.7)**	**(19.5)**	**(18.5)**	**(21.7)**	**(10.0)**	
Positive HPV16/18	Positive HPV16/18	26 (21.8)	7 (18.4)	7 (13.5)	6 (40.0)	5 (38.5)	1 (100.0)	0 (NaN
Positive HR HPV12	Positive HR HPV12	93 (78.2)	31 (81.6)	45 (86.5)	9 (60.0)	8 (61.5)	0 (0.0)	0 (NaN
Positive OCT	Positive OCT	39 (32.8)	7 (18.4)	11 (21.2)	10 (66.7)	10 (76.9)	1 (100.0)	0 (NaN
ASC-H		**19**	**1 (0.3)**	**6 (2.2)**	**3 (3.7)**	**7**	**2**	**0 (0.0)**
No. (%)		**(2.3)**				**(11.7)**	**(20.0)**	
Positive HPV16/18	Positive HPV16/18	4 (21.1)	0 (0.0)	3 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (NaN
Positive HR HPV12	Positive HR HPV12	15 (78.9)	1 (100.0)	3 (50.0)	3 (100.0)	7 (100.0)	1 (50.0)	0 (NaN
Positive OCT	Positive OCT	11 (57.9)	0 (0.0)	3 (50.0)	2 (66.7)	4 (57.1)	2 (100.0)	0 (NaN
HSIL OR AGC	**HSIL OR AGC**	**17**	**2 (0.6)**	**1 (0.4)**	**1 (1.2)**	**10**	**3**	**0 (0.0)**
No. (%)	No. (%)	**(2.1)**				**(16.7)**	**(30.0)**	
Positive HPV16/18	Positive HPV16/18	9 (52.9)	1 (50.0)	0 (0.0)	0 (0.0)	5 (50.0)	3 (100.0)	0 (NaN
Positive HR HPV12	Positive HR HPV12	8 (47.1)	1 (50.0)	1 (100.0)	1 (100.0)	5 (50.0)	0 (0.0)	0 (NaN
Positive OCT	Positive OCT	13 (76.5)	1 (50.0)	0 (0.0)	1 (100.0)	8 (80.0)	3 (100.0)	0 (NaN
Total		**813(100)**	**325**	**267**	**81**	**60**	**10**	**70**
No. (%)			**(40.0)**	**(32.8)**	**(10.0)**	**(7.4)**	**(1.2)**	**(8.6)**
Positive HPV16/18	Positive HPV16/18	170 (20.9)	71 (21.8)	34 (12.7)	26 (32.1)	22 (36.7)	8 (80.0)	9 (12.9)
Positive HR HPV12	Positive HR HPV12	643 (79.1)	254 (78.2)	233 (87.3)	55 (67.9)	38 (63.3)	2 (20.0)	61 (87.1)
Positive OCT	Positive OCT	232 (28.5)	63 (19.4)	56 (21.0)	52 (64.2)	39 (65.0)	8 (80.0)	14 (20.0)

Table S2. Baseline information of the patient

Variable	level	level	Age stage (%)
			Overall
n	n		813
AGE (mean (SD))	AGE (mean (SD))		44.68 (11.34)
Education level n.(%)	Education level n.(%)	Elementary school and below	110 (13.5)
		Middle and High School	403 (49.6)
		University degree and above	300 (36.9)

Variable	level	level	Age stage (%)
Region n.(%)	Region n.(%)	Rural	199 (24.5)
		Town	257 (31.6)
		City	357 (43.9)
Last hr-HPV result positive n.(%)	Last hr-HPV result positive n.(%)		167 (44.2)
Last TCT results[?]ASC-US n. (%)	Last TCT results[?]ASC-US n. (%)		38 (10.1)
Abnormal previous biopsy n. (%)	Abnormal previous biopsy n. (%)		84 (22.2)
Pathology n .(%)	Pathology n .(%)	Benign	325 (40.0)
		CIN1	267 (32.8)
		CIN2	81 (10.0)
		CIN3	57 (7.0)
		AIS	3 (0.4)
		Cancer	10 (1.2)
		No Biopsy	70 (8.6)
OCT High-risk n.(%)	OCT High-risk n.(%)		232 (28.5)
TCT n.(%)	TCT n.(%)	NILM	423 (52.0)
		ASC-US	235 (28.9)
		LSIL	119 (14.6)
		ASC-H	19 (2.3)
		HSIL	16 (2.0)
		CA	1 (0.1)
HPV 16 18 n. (%)	HPV 16 18 n. (%)		170 (20.9)
transformation zone n.(%)	transformation zone n.(%)	Type 1 transformation zone	141 (17.3)
		Type 2 transformation zone	226 (27.8)
		Type 3 transformation zone	440 (54.1)
		Tumour-like appearance	6 (0.7)
Cervical size n.(%)	Cervical size n.(%)	Contraction	109 (13.5)
		Normal size	419 (51.9)
		Hypertrophy	279 (34.6)
Nascent gland cyst n. (%)	Nascent gland cyst n. (%)		188 (23.3)
Atrophic vaginitis n. (%)	Atrophic vaginitis n. (%)		55 (6.8)
Surgical n.(%)	Surgical n.(%)		107 (13.2)

Table S3. Results from blinded diagnosis of OCT images from two independent investigators.

Parameter	Investigator 1	Investigator 2	Final Results
Positvity No./Total No. (%) [95% CI]	228/813(28.0)[25.0-31.3]	238/813(29.3)[26.2-32.5]	242/813(29.8)[26.6-33.0]
Sensitivity No./Total No. (%) [95% CI]	94/151(62.3)[54.5-70.0]	108/151(71.5)[64.3-78.7]	109/151(72.2)[65.0-79.3]
Specificity No./Total No. (%) [95% CI]	528/662(79.8)[76.7-82.8]	532/662(80.4)[77.3-83.4]	529/662(79.9)[76.9-83.0]
PPV No./Total No. (%) [95% CI]	94/228(41.2)[34.8-47.6]	108/238(45.4)[39.1-51.7]	109/242(45.0)[38.8-51.3]
NPV No./Total No. (%) [95% CI]	528/585(90.3)[87.9-92.7]	532/575(92.5)[90.4-94.7]	529/571(92.6)[90.5-94.8]
Kappa	0.87		

Table S4. Cervical Precancerous Lesion Risk of Cytologic Testing, OCT, HPV16/18 Testing, and Combina-

tions Among 813 HPV-Positive Women to Detect CIN3+ and CIN2+

Stratum	All women in stratum(n)	CIN2+ in Stratum(n)	Risk	95% Confidence Interval	CIN3+ in Stratum(n)	Risk	95% Confidence Interval
HPV+;OCT High-risk	242	109	45.04%	38.77%-51.31%	55	22.73%	17.45%-28.01%
HPV+;OCT Low-risk	571	42	7.36%	5.21%-9.50%	15	2.63%	1.32%-3.94%
HPV16/18+; OCT High-risk	62	40	64.52%	52.61%-76.43%	24	38.71%	26.59%-50.83%
HPV16/18+; OCT Low-risk	108	16	14.81%	8.11%-21.51%	6	5.56%	1.24%-9.88%
HPV16/18-; OCT High-risk	180	69	38.33%	31.23%-45.44%	31	17.22%	11.71%-22.74%
HPV16/18-; OCT Low-risk	463	26	5.62%	3.52%-7.71%	9	1.94%	0.69%-3.20%
HPV+; ASC-US+ cytology	390	114	29.23%	24.72%-33.74%	58	14.87%	11.34%-18.40%
HPV+; NILM cytology	423	37	8.75%	6.05%-11.44%	12	2.84%	1.25%-4.42%
HPV16/18+; ASC-US+ cytology	82	43	52.44%	41.63%-63.25%	26	31.71%	21.64%-41.78%
HPV16/18+; NILM cytology	88	13	14.77%	7.36%-22.19%	4	4.55%	0.19%-8.90%
HPV16/18-; ASC-US+ cytology	308	71	23.05%	18.35%-27.76%	32	10.39%	6.98%-13.80%
HPV16/18-; NILM cytology	335	24	7.16%	4.40%-9.93%	8	2.39%	0.75%-4.02%
HPV16/18+	170	56	32.94%	25.88%-40.01%	30	17.65%	11.92%-23.38%
HPV16/18-	643	95	14.77%	12.03% -17.52%	40	6.22%	4.35%-8.09%

Table S5. Comparison of OCT and cytology tests by age

Threshold	Cytology ASC-US+	95% CI	OCT High-risk	95% CI
[?]34 years (169 women,25 CIN2+)	**[?]34 years (169 women,25 CIN2+)**	**[?]34 years (169 women,25 CIN2+)**	**[?]34 years (169 women,25 CIN2+)**	**[?]34 years (169 women,25 CIN2+)**
sensivity	72.00%	54.40%-89.60%	88.00%	75.30%-100.00%
specifity	65.30%	57.50%-73.10%	68.80%	61.20%-76.30%
PPV	26.50%	16.00%-37.00%	32.80%	21.60%-44.10%
NPV	93.10%	88.10%-98.00%	97.10%	93.80%-100.00%
35-44 years (226 women,45 CIN2+)	**35-44 years (226 women,45 CIN2+)**	**35-44 years (226 women,45 CIN2+)**	**35-44 years (226 women,45 CIN2+)**	**35-44 years (226 women,45 CIN2+)**
sensivity	68.90%	55.40%-82.40%	80.00%	68.31%-91.69%
specifity	59.10%	52.00%-66.30%	76.24%	70.04%-82.44%
PPV	29.50%	20.80%-38.20%	45.57%	34.59%-56.55%
NPV	88.40%	82.70%-94.10%	93.88%	90.00%-97.75%
45-54 years (253 women,54 CIN2+)	**45-54 years (253 women,54 CIN2+)**	**45-54 years (253 women,54 CIN2+)**	**45-54 years (253 women,54 CIN2+)**	**45-54 years (253 women,54 CIN2+)**
sensivity	75.93%	64.52%-87.33%	62.96%	50.08%-75.84%
specifity	54.77%	47.86%-61.69%	83.92%	78.82%-89.02%
PPV	31.30%	23.36%-39.24%	51.52%	39.46%-63.57%
NPV	89.34%	83.87%-94.82%	89.30%	84.88%-93.73%
55+ years (165 women,27 CIN2+)	**55+ years (165 women,27 CIN2+)**	**55+ years (165 women,27 CIN2+)**	**55+ years (165 women,27 CIN2+)**	**55+ years (165 women,27 CIN2+)**
sensivity	88.89%	77.03%-100.00%	62.96%	44.75%-81.18%
specifity	55.07%	46.77%-63.37%	90.58%	85.71%-95.45%
PPV	27.91%	18.43%-37.39%	56.67%	38.93%-74.40%
NPV	96.20%	91.99%-100.00%	92.59%	88.17%-97.01%
[?]34 years (169 women,7 CIN3+)	**[?]34 years (169 women,7 CIN3+)**	**[?]34 years (169 women,7 CIN3+)**	**[?]34 years (169 women,7 CIN3+)**	**[?]34 years (169 women,7 CIN3+)**
sensivity	85.70%	59.80%-100.00%	100.00%	100.00%-100.00%
specifity	61.70%	54.20%-69.20%	63.00%	55.50%-70.40%
PPV	8.80%	2.10%-15.60%	10.40%	3.10%-17.80%
NPV	99.00%	97.10%-100.00%	100.00%	100.00%-100.00%
35-44 years (226 women,17 CIN3+)	**35-44 years (226 women,17 CIN3+)**	**35-44 years (226 women,17 CIN3+)**	**35-44 years (226 women,17 CIN3+)**	**35-44 years (226 women,17 CIN3+)**
sensivity	70.60%	48.90%-92.20%	88.24%	72.92%-100.00%
specifity	55.50%	48.80%-62.20%	69.38%	63.13%-75.63%
PPV	11.40%	5.30%-17.50%	18.99%	10.34%-27.64%
NPV	95.90%	92.30%-99.40%	98.64%	96.77%-100.00%
45-54 years (253 women,29 CIN3+)	**45-54 years (253 women,29 CIN3+)**	**45-54 years (253 women,29 CIN3+)**	**45-54 years (253 women,29 CIN3+)**	**45-54 years (253 women,29 CIN3+)**
sensivity	82.76%	69.01%-96.51%	68.97%	52.13%-85.80%
specifity	52.23%	45.69%-58.77%	79.46%	74.17%-84.75%
PPV	18.32%	11.70%-24.94%	30.30%	19.22%-41.39%
NPV	95.90%	92.38%-99.42%	95.19%	92.12%-98.25%

Threshold	Cytology ASC-US+	95% CI	OCT High-risk	95% CI
55+ years (165 women,17 CIN3+)	**55+ years (165 women,17 CIN3+)**	**55+ years (165 women,17 CIN3+)**	**55+ years (165 women,17 CIN3+)**	**55+ years (165 women,17 CIN3+)**
sensivity	94.12%	82.93%-100.00%	76.47%	56.31%-96.63%
specifity	52.70%	44.66%-60.75%	88.51%	83.38%-93.65%
PPV	18.60%	10.38%-26.83%	43.33%	25.60%-61.07%
NPV	98.73%	96.27%-100.00%	97.04%	94.18%-99.90%

Table S6. Effect of transformation zone on OCT results

Threshold	Cytology ASC-US+	95% CI	OCT High-risk	95% CI
I TZ(141 women,27 CIN2+)	**I TZ(141 women,27 CIN2+)**	**I TZ(141 women,27 CIN2+)**	**I TZ(141 women,27 CIN2+)**	**I TZ(141 women,27 CIN2+)**
sensivity	70.37%	53.15%-87.59%	92.59%	82.71%-100.00%
specifity	65.79%	57.08%-74.50%	62.28%	53.38%-71.18%
PPV	32.76%	20.68%-44.84%	36.76%	25.30%-48.22%
NPV	90.36%	84.01%-96.71%	97.26%	93.52%-100.00%
II TZ (226 women,59 CIN2+)	**II TZ (226 women,59 CIN2+)**	**II TZ (226 women,59 CIN2+)**	**II TZ (226 women,59 CIN2+)**	**II TZ (226 women,59 CIN2+)**
sensivity	74.58%	63.47%-85.69%	67.80%	55.87%-79.72%
specifity	52.69%	45.12%-60.27%	73.05%	66.32%-79.78%
PPV	35.77%	27.30%-44.24%	47.06%	36.45%-57.67%
NPV	85.44%	78.62%-92.25%	86.52%	80.89%-92.16%
III TZ (440 women,59 CIN2+)	**III TZ (440 women,59 CIN2+)**	**III TZ (440 women,59 CIN2+)**	**III TZ (440 women,59 CIN2+)**	**III TZ (440 women,59 CIN2+)**
sensivity	76.27%	65.42%-87.13%	62.71%	50.37%-75.05%
specifity	58.53%	53.58%-63.48%	88.19%	84.95%-91.43%
PPV	22.17%	16.45%-27.88%	45.12%	34.35%-55.89%
NPV	94.09%	91.09%-97.09%	93.85%	91.37%-96.34%
I TZ (141 women, 9 CIN3+)	**I TZ (141 women, 9 CIN3+)**	**I TZ (141 women, 9 CIN3+)**	**I TZ (141 women, 9 CIN3+)**	**I TZ (141 women, 9 CIN3+)**
sensivity	88.89%	68.36%-100.00%	88.89%	68.36%-100.00%
specifity	62.12%	53.85%-70.40%	54.55%	46.05%-63.04%
PPV	13.79%	4.92%-22.67%	11.76%	4.11%-19.42%
NPV	98.80%	96.45%-100.00%	98.63%	95.96%-100.00%
II TZ (226 women, 24 CIN3+)	**II TZ (226 women, 24 CIN3+)**	**II TZ (226 women, 24 CIN3+)**	**II TZ (226 women, 24 CIN3+)**	**II TZ (226 women, 24 CIN3+)**
sensivity	75.00%	57.68%-92.32%	83.33%	68.42%-98.24%
specifity	48.02%	41.13%-54.91%	67.82%	61.38%-74.26%
PPV	14.63%	8.39%-20.88%	23.53%	14.51%-32.55%
NPV	94.17%	89.65%-98.70%	97.16%	94.42%-99.90%
III TZ (440 women, 31 CIN3+)	**III TZ (440 women, 31 CIN3+)**	**III TZ (440 women, 31 CIN3+)**	**III TZ (440 women, 31 CIN3+)**	**III TZ (440 women, 31 CIN3+)**

Threshold	Cytology ASC-US+	95% CI	OCT High-risk	95% CI
sensivity	83.87%	70.92%-96.82%	67.74%	51.29%-84.20%
specifity	56.72%	51.92%-61.53%	85.09%	81.63%-88.54%
PPV	12.81%	8.21%-17.40%	25.61%	16.16%-35.06%
NPV	97.89%	96.06%-99.72%	97.21%	95.50%-98.91%

Abbreviations: TZ: Cervical transformation zone.

Figure 1. CONSORT Diagram

Abbreviations: HPV, human papillomavirus; NILM, negative for intraepithelial lesions or malignant neoplasm.

Figure 2. Recommendation of a process for cervical cancer screening management in hospitals

Figure S1. Screening and Triage Algorithms