Title: Evaluation of the SureX HPV Genotyping Test for the Detection of High-Risk HPV in Cervical Cancer Screening

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Abstract

Background: The SureX HPV genotyping test (SureX HPV test), which targets the human papillomavirus (HPV) E6/E7 genes was compared with the Cobas 4800 and Venus HPV tests for detecting 14 high-risk HPV (HR-HPV) types in clinical referral and follow-up patients to evaluate its value for cervical cancer screening.

Methods: Two different populations were enrolled in the study. The first population comprised 185 cases and was used for comparing the SureX HPV test (Health, China) with the Cobas 4800 test (Roche, USA). The second population comprised 290 cases and was used for comparing the SureX HPV test (Health, China) with the Venus HPV test (Zhijiang, China). Polymerase chain reaction (PCR) sequencing was performed for further confirmation of discordant results.

Results: In the first population, the overall agreement rate was 95.3% for 14 High-Risk HPV types. Eight discordant cases were confirmed by PCR sequencing, which showed that the agreement rates were 75.0% between the SureX HPV test and PCR sequencing and 25.0% between the Cobas 4800 test and PCR sequencing (P<0.01). In the second population, the overall agreement rate was 94.5%. Thirteen discordant cases were confirmed by PCR sequencing, which showed that the agreement rates were 76.9% between the SureX HPV test and PCR sequencing and 23.1% between the Venus HPV test and PCR sequencing (P<0.01). With cervical intraepithelial neoplasia grade 2+ (CIN2+) as the reference standard, the sensitivity values of the SureX HPV test and the Venus HPV test were 93.5% and 92.0%, (P>0.05), while the specificity values were 43.3% and 46.7%, respectively (P>0.05).

Conclusion: The SureX HPV test had good consistency with both the Cobas 4800 and Venus HPV tests for 14 HR-HPV types. In addition, it avoided some false negatives and false positives. Therefore, the SureX HPV test can be used for cervical cancer screening.

Key words: High-risk human papillomavirus; HPV DNA test; cervical cancer screening
Background

Cervical cancer is one of the most common malignant tumors of the reproductive system in women. There were approximately 57,0000 new cases of cervical cancer and 311,000 deaths worldwide in 2018[1].Persistent infection with high-risk human papillomavirus (HR-HPV) is recognized as the main cause of cervical cancer and precancerous lesions [2, 3]. Because of the clear relationship between the occurrence of cervical cancer and HPV infection, cervical cancer has become a preventable cancer. The methods for preventing cervical cancer mainly include HPV vaccination or cervical cancer screening. However, because the HPV vaccine has not yet been included in the planned immunization program in China, full population coverage of the HPV vaccine is difficult to achieve. Thus, the main method for preventing cervical cancer in China is still cervical cancer screening primarily by HPV DNA detection [4]. However, this detection method still needs improvement because of the overtreatment and missed diagnoses caused by false positives and false negatives, respectively [5, 6]. Some studies have found that the detection of HPV E6/E7 DNA may be more accurate than the current DNA detection methods [6]. The SureX HPV genotyping test (SureX HPV test) is a novel HPV DNA detection method using capillary electrophoresis fragment analysis technology to target the HPV E6/E7 genes. In the present study, the SureX HPV test was compared with the Cobas 4800 test[7] and Venus HPV test for detecting 14 types of HR-HPV [8, 9] in clinical referral and follow-up patients to evaluate its value for cervical cancer screening.

Materials and methods

Study population

Two different populations were enrolled in this study. The first population comprised 185 cases with cervical lesions, which contained detectable HPV DNA and underwent cervical cytopathological evaluation in the Department of Pathology of Guangdong Provincial People’s Hospital between November 2017 and March 2018. The second population comprised 290 cases with cervical lesions, which contained detectable HPV DNA and underwent cervical histopathological evaluation in the Department of Clinical Laboratory of the National Cancer Center/Cancer Hospital between March 2018 and October 2018. The inclusion criteria included an
age between 21 and 80 years, the absence of pregnancy, an intact cervix, no history of cervical lesions, and no history of chemotherapy, radiotherapy or surgical treatment.

**DNA extraction from cervical cells**

In this study, 2 ml of cervical cells was collected from the patients in the study population and used for DNA extraction. For the SureX HPV test, total cellular DNA was extracted from cervical specimens using the HPV genotyping kit for 25 types (Health Gene Technologies, Ningbo, China) according to the manufacturer's instructions. Negative and positive controls provided in the kits were included in each PCR test. For the Cobas 4800 test, HPV DNA was extracted from cervical specimens using the Cobas4800 instrument (Roche Molecular Systems, Inc., USA). For the Venus HPV test, HPV DNA was extracted from cervical specimens using the automatic nucleic acid extractor Autrax workstation (Shanghai ZJ Bio-Tech Co., Shanghai, China) for the detection of 14 HR-HPV types, in accordance with the manufacturer's instructions.

**SureX HPV genotyping test**

The SureX HPV test (Health Gene Technologies, Ningbo, China) utilizes amplification of target HPV DNA by multiplex polymerase chain reaction (PCR) and capillary electrophoresis to detect and genotype 25 HPV types according to the length of specific amplification fragments in a single analysis. For detection, the plasmid pcDNA 3.1(+) (pcDNA) and human β-globin gene were used to monitor the PCR amplification and sample processing, respectively. The peak height of pcDNA should be ≥500 relative fluorescence units (RFU). For PCR amplification products (1µl) subjected to capillary electrophoresis in an ABI 3500 Dx/3500xL Dx genetic analyzer, the peak heights of the specific HPV types were ≥300 RFU, and the HPV type was positive.

**Cobas 4800 HPV test**

The Cobas 4800 test (Roche Molecular Systems, Inc., USA) uses PCR and nucleic acid hybridization technology to specifically detect HPV16, HPV18 and 12 other HR-HPV types. In addition, β-globin was used as an internal control (IC) to ensure a sufficient sample quantity for HPV DNA detection. If the cycle threshold (Ct) cutoff value for HPV16 was ≤40.5, a sample was
considered HPV-positive; if the Ct cutoff value was >40.5 and β-globin was effective, it was considered negative; otherwise, it was considered invalid. If the Ct cutoff value for HPV18 or any of the 12 other high-risk types was ≤40, a positive result was determined; and if the Ct cutoff value was >40 and β-globin was effective, a negative result was determined; otherwise, the result was considered invalid.

**Venus HPV genotyping test**

The Venus HPV genotyping test (Zhijiang Bio-Tech Co., Shanghai, China) is based on real-time fluorescence PCR technology. Detection of amplified HPV DNA fragments was performed in the fluorimetric channels FAM, HEX/VIC/JOE, TEXAS RED/Cal Red 610 and CY5 with the fluorescent quencher BHQ1. Human minibrain homolog (MNBH) was amplified as an internal control (IC) to indicate the presence of sufficient nucleic acid from the human MNBH gene. The Ct value was calculated. If the Ct value was ≤38.0, a sample was considered HPV-positive. If the Ct value of the IC was ≤32.0, and "undetermined" or "no CT" was displayed in the other channels, the sample was determined to be HPV-negative. If the Ct value was 38.0~40.0, the reaction was repeated. If the Ct value remained in this range and the amplification curve was a typical S-shape, the sample was considered HPV-positive; if the amplification curve was not a typical S-type, as the sample was considered HPV-negative.

**Sequencing**

PCR sequencing was performed for further confirmation of discordant results. Sequencing reactions were performed using the ABI PRISM BigDye Terminator V3.0 kit (Applied Biosystems) and analyzed in an ABI 3730 genetic analyzer (Applied Biosystems) at Sangon Biotech Co. (Shanghai). DNA sequences were then compared with the sequences of known HPV types using the Basic Local Alignment Search Tool from the National Center for Biotechnology Information website (http://www.ncbi.nlm.nih.gov/BLAST).

**Histological diagnosis**

The cytopathological diagnosis was based on the nomenclature of the Bethesda system of cervical
cytology. The histopathological diagnosis was classified according to the WHO histological criteria for cervical tumors and was used as the gold standard, with cervical intraepithelial neoplasia grade 2 (CIN2) and higher (CIN2+) considered positive. Cytological diagnosis was performed by the Department of Pathology, Guangdong Provincial People’s Hospital; pathological diagnosis, by the Cancer Hospital, Chinese Academy of Medical Sciences.

**Statistical analysis**

All statistical analyses were conducted using SPSS 23.0. The consistency checks were evaluated by the Kappa (k) values. Using CIN2+ as a reference, the sensitivity, specificity, and area under the receiver operating characteristic (ROC) curve (AUC) were calculated. All differences with P values of < 0.05 (two-tailed) were considered statistically significant.

**Results**

**Population 1**

**HR-HPV infection**

The overall positive rates of the 185 cases for the SureX HPV test and the Cobas 4800 test were 72.4% (134/185) and 70.3% (130/185), respectively. In the different cervical cytopathological categories, no significant difference was observed in the positive rates of the 14 HR-HPV types between the SureX HPV test and the Cobas 4800 test (P >0.05) (Table 1).

**Agreement rate**

The results of the SureX HPV test and the Cobas 4800 test are shown in Table 2. The validation showed good agreement between the two different methods for the 14 HR-HPV types. The overall agreement rate was 95.3% (162/170, Kappa=0.894) (95% confidence interval [CI]: 0.812- 0.961).

There were 8 discordant results between the SureX HPV test and the Cobas 4800 tests; these results were confirmed by PCR sequencing, as shown in Table 3. Of the discordant results, 6 were positive by the SureX HPV test and PCR sequencing but negative by the Cobas 4800 test. The agreement rate was 75.0% (6/8) between SureX HPV test and PCR sequencing. Two cases were positive by the Cobas 4800 test and PCR sequencing but negative by the SureX HPV test. The
The agreement rate was 25.0% (2/8) between the Cobas 4800 test and PCR sequencing. The agreement rates were significantly different (P<0.01).

**Population 2**

**HR-HPV infection**

The overall positive rates of the 290 cases for the SureX HPV test and Venus HPV test were the same (78.3%, 227/290), as shown in Table 4. The positive rates of the 14 HR-HPV types did not differ significantly between the two methods in the different histopathological categories (P>0.05).

**Agreement**

The results of the SureX HPV test and the Venus HPV test are shown in Table 5. For both methods, HPV16 was the most frequently detected type, followed by HPV18 and HPV58 and HPV52. The concordance of the two methods for HPV 16, 18, 58, 52, 33, 51, 66, 35, 59, 56, and 39 was good, but was poor for HPV 45, 31, and 68. The overall agreement rate was 94.5% (274/290, Kappa=0.838, 95% CI: 0.750~0.906, P<0.01).

Thirteen results were discordant between the SureX HPV test and Venus HPV test; these results were confirmed by PCR sequencing, as shown in Table 6. Of the discordant results, 7 were positive by the SureX HPV test and PCR sequencing but negative by the Venus HPV test, and 3 were negative by the SureX HPV test and PCR sequencing but positive by the Venus HPV test. Thus, the agreement rate was 76.9% (10/13) between the SureX HPV test and PCR sequencing.

Three cases were positive by the Venus HPV test and PCR sequencing but negative by the SureX HPV test. The agreement rate between the Venus HPV test and PCR sequencing was 23.1% (3/13). The agreement rates differed significantly (P<0.01).

**Sensitivity and specificity**

With CIN2+ as the reference standard, the sensitivity values of the SureX HPV test and Venus HPV test were 93.5% and 92.0%, (P>0.05), and the specificity values were 43.3% and 46.7%, respectively (P>0.05). The AUCs for the SureX HPV test and Venus HPV test were 0.751 (95% CI:
Discussion

In the detection of HPV DNA PCR amplification, the selection of the target region and the design of the primers are particularly important for maximizing the amplification efficiency [10, 11]. Because of the high conservation of HPV L1 DNA across genotypes, universal primers can be designed to amplify DNA from multiple genotypes; L1 DNA from different genotypes presents sufficient sequence differences to allow further analysis of specific genotypes by other methods[12]. Therefore, most HPV DNA tests currently on the market detect HPV L1 DNA [13]. The Cobas 4800 HR-HPV test uses HPV L1 DNA as an amplification target and can detect HPV16, HPV18, and 12 other HR-HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). The Venus HPV genotyping test also uses HPV L1 DNA as the detection target and can detect 15 HR-HPV subtypes, including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 82. The Venus HPV test is widely used in China because of its specificity and sensitivity, which are better than those of similar products, and because it is easy to perform and inexpensive.

However, HPV L1 may be lost during the integration of HPV DNA into the host genome, and HPV tests based on L1 may lead to missed diagnoses of cervical cancer, which may affect the clinical sensitivity and positive predictive value of such tests [14, 15]. Research has shown that 0.3% of CIN2 and 3.94% of CIN3 lesions among HPV16-positive women were L1-negative[16]. Some research has shown that the HPV E6/E7 genes are more closely related to cervical cancer than the L1 gene. Moreover, as cervical lesions developing, E6/E7 is not lost. Therefore, some researchers think that detection methods based on the E6/E7 gene are better than those based on the L1 gene [17, 18]. The SureX HPV test uses specifically designed primers targeting the HPV E6/E7 genes and uses capillary electrophoresis to detect and genotype 25 HPV types, including HPV 6, 11, 16, 18, 26, 31, 33, 35, 39, 42, 43, 44, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 81, 82, and 83, according to the length of specific amplification fragments in a single analysis.

In this study, we compared the SureX HPV test with the Cobas 4800 and Venus HPV tests, which are widely used at home and abroad. The overall agreement rates were 95.3% (162/170, Kappa=0.894) between the SureX HPV and the Cobas 4800 tests, and were 94.5% (274/290, Kappa= 0.838) between the SureX HPV and the Venus HPV tests. Therefore, good concordance
was shown for detecting the 14 HR-HPV types between the SureX HPV and the Cobas 4800 tests and between the SureX HPV and the Venus HPV tests.

Persistent HR-HPV infection is the key factor for cervical cancer. The most common HPV genotypes causing cervical cancer are HPV 16 and 18[19, 20]. The results of a large-scale multicenter epidemiological study in China showed that the most common types of HPV causing infection were HPV16 and HPV18, followed by HPV52 and HPV58[21]. In this study, the results in the second population were consistent with those of that large-scale study.

To determine the actual HPV infection, PCR sequencing was performed to further confirm discordant results. In our study, 6 cases were positive by the SureX HPV test and PCR sequencing but negative by the Cobas 4800 test, and 7 were positive by the SureX HPV test and PCR sequencing but negative by the Venus HPV test. As both the Cobas 4800 and the Venus HPV tests target HPV L1 DNA, these 13 results may be false negatives due to missed detection of HPV L1 DNA. In addition, 2 cases were positive by the Cobas 4800 test and PCR sequencing, while 3 cases were negative by the SureX HPV test, and 3 cases were positive by the Venus HPV test and PCR sequencing but negative by the SureX HPV test. The reason for this discrepancy may be that the results of capillary electrophoresis in the SureX HPV test showed a peak height of pcDNA in the five samples of approximately 500 RFU, which may have resulted in low amplification efficiency because of low levels of HPV DNA in the cervical cell specimens. Additionally, studies have shown that although the HR-HPV DNA test had high sensitivity, the potential hazard of this method was that it could detect a large number of women with false-positive results, who were likely to have transient infections. After a few months, HPV is cleared naturally by the body without causing cervical cancer or precancerous lesions[22]. Three patients in our study were positive by the Venus HPV test but negative by the SureX HPV test and sequencing; these results may be false positives. The results of this study indicated that the agreement rate between the SureX HPV test and PCR sequencing was were 75.0% (6/8) in the first population and 76.9% (10/13) in the second population; therefore, the SureX HPV test could be used for HR-HPV detection.

The method of screening cervical cancer and precancerous lesions by detecting HPV DNA was characterized by high sensitivity, while specificity was related to the positive rate of HPV. The
specificity differed greatly among different populations[23]. The sensitivity and specificity of different HPV DNA tests for screening CIN2+ patients in the general population were greater than 90% and approximately 80%, respectively; however, for the population referred by colposcopy, the sensitivity did not change greatly, while the specificity was only 40%[24]. The cases in our study came mainly from the population with cervical lesions, and most cases were referred for colposcopy. In our study, the sensitivity and specificity of the SureX HPV test were 93.5% and 92.0%, and those of the Venus HPV test were 43.3% and 46.7%, consistent with the reported results.

**Conclusion**

In summary, in this study, we compared a novel HPV genotyping test, the SureX HPV test, with the Cobas 4800 and the Venus HPV tests. The SureX HPV test had good consistency with the Cobas 4800 and the Venus HPV tests for detecting 14 HR-HPV types. In addition, the SureX HPV test could avoid some false-negative and false-positive results, and its sensitivity and specificity for pathological grade CIN2+ lesions was equivalent to that of the Venus HPV test. Therefore, the SureX HPV test can be used for cervical cancer screening. However, as the population selected for this study was the primary screening-positive population rather than the general population, further comparative analysis of these three methods through large-sample studies in the general population to provide a basis for the development of a large-scale cervical cancer screening strategy.

**Abbreviations**

HR-HPV: High-risk human papillomavirus; PCR: Polymerase chain reaction; SureX HPV test: SureX HPV genotyping test; RFU: Relative fluorescence units; IC: Internal control; Ct: Cycle threshold; ROC: Receiver operating characteristic curve (AUC); MNBH: Human minibrain homolog; CI: confidence interval; CI: Confidence interval; CIN: Cervical intraepithelial neoplasia; HSIL: High-grade squamous intraepithelial lesion; LSIL: Low-grade squamous intraepithelial lesion; ASCUS: Atypical squamous cells of undetermined significance; CA: Cancer; SCC: Squamous cell carcinoma;
NILM: Negative for intraepithelial lesion or malignancy; AGC: Atypical glandular cell; AIS: adenocarcinoma in situ; Neg: negative.

**Ethical approval**

The study was approved by the Ethics Committee at National Cancer Center/Cancer Hospital.

**Consent for publication**

Not applicable.

**Availability of data and materials**

Not applicable. All relevant data are within the paper.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

Baojun Wei carried out the experiments and prepared the manuscript; Ping Mei and Xueting Yu collected the samples and carried out the experiments; Shengkai Huang and supported the manuscript writing; Tong Zhi and Guojing Wang carried out the control experiments; Xiaotian Xu, Lin Xiao and XinDong analysed data; Wei Cui provided the original ideas and experimental structure and supported the experiments and manuscript writing.

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Figure Legends

Fig. 1 ROC curves for the SureX HPV test and Venus HPV test in CIN2+ lesions