

The feasibilities of TruScreen for primary cervical cancer screening: a self-controlled study

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Abstract

Objective Screening programs based on cytology testing led to the incidence reduction of cervical cancer mortality of about 70–80 % in industrialized countries. However, these favorable results have not been replicated in developing areas. Thus, we aim to evaluate the efficacy of TruScreen (Polartech, Sydney, Australia) in detecting of precancerous lesions in comparison with cervical cytology test.

Methods A total of 181 outpatients were screened by TruScreen using the pathological results as the gold standard. The medical records of cytological smear within 6 weeks were obtained from 169 of these participants. The reliability and yield of TruScreen and cytological smear were assessed. The screening results of TruScreen were compared with those obtained from the conventional smear.

Results The sensitivities for histologically confirmed cervical intraepithelial neoplasia (CIN) lesions by TruScreen and Pap, were 67.4 % (95 % CI 53.4–81.5) and 87.9 % (95 % CI 76.7–99.0), respectively. The specificities for histologically confirmed CIN lesions by TruScreen and Pap, were 68.1 % (95 % CI 60.3–75.9) and 74.3 % (95 % CI 70.0–81.4), respectively. In contrast to Pap smear, TruScreen was comparatively efficacious in screening of cervical cancer ($\chi^2 = 0.0133$, $P = 0.9081$).

Conclusion TruScreen is a potential test for initial cervical screening in developing world regions.

Keywords Cervical screening · TruScreen · Real-time device · Pap smear

Introduction

Cervical cancer is the second most common cancer in women worldwide, with approximately 440,000 cases reported annually [1]. But 80 % of those cancers are encountered in low-resource settings [2]. In many parts of the developing world, age-standardized incidence rates of invasive cervical cancer (ICC) are fourfold higher than in North America and Western Europe, reaching values in excess of 30-to-50 per 100,000 women in large areas of sub-Saharan Africa, Latin America, the Caribbean, South Asia and Oceania [3]. Cervical cancer is considered a preventable disease because of its relatively long period of precancerous lesions, including cervical intraepithelial neoplasia (CIN). It takes about 10 years for precancerous lesion to develop into infiltrating carcinoma. And with early detection, the survival rate for women with pre-invasive lesions is nearly 100 % [4].

The standard of care for cervical cancer screening is the conventional cytology smear (Pap smear) [5–7]. Whereas cervical cancer burden in industrialized countries decreased sharply after the widespread introduction of effective cytological screening programs, these favorable results have not been replicated in the developing world. With less experienced cytologists, cytology nurses or gynecologists, cytology tests run a high risk for false-negative or false-positive results in these countries [8]. In addition, inadequate information systems and delays with transporting specimens and reports also pose challenges [9]. Furthermore, evidence suggesting that substantial reductions in cervical disease can be anticipated by human

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papillomavirus (HPV) vaccination, but most of the benefit will not be apparent for at least another decade [10]. Hence, novel, simple, reliable and cheap tests for effective large-scale screening tests are therefore required, particularly in developing areas that do not have effective screening programs, and which have the highest rates of cervical cancer.

TruScreen (Polarprobe; Polartechnics, Sydney, Australia) is a real-time device for cervical cancer screening. This probe is currently approved for clinical use in Europe, Australia, and several Asian countries [11]. The TruScreen probe uses a combination of impedance measurements and fluorescence optical imaging to automatically detect abnormal epithelial changes. A clinical report suggested that TruScreen operates as a viable adjunctive test when used together with cervical cytology for cervical screening [12]. However, the performance of TruScreen for cervical cancer screening in low-resource settings has not been adequately measured. So we conducted this study to evaluate the possibilities of TruScreen in detecting of the precancerous lesions. Aiming to assess the sensitivity and specificity of TruScreen, we compared the results with that obtained using the Pap smear alone.

Methods

Participants

The self-controlled study recruited 183 subjects during January 2011 to December 2011 in West China Second University Hospital, Sichuan University, Chengdu, China. Those scheduled to undergo loop electrosurgical excision procedure (LEEP) treatment for CIN or other gynecological condition unrelated to cervical smear status were offered participation. The eligible criteria that must be met before LEEP was performed were: CIN confirmed by cervical biopsy, when possible; no evidence of invasive cancer or glandular dysplasia; no evidence of pelvic inflammatory disease (PID), cervicitis, vaginal trichomoniasis, bacterial vaginosis, anogenital ulcer or bleeding disorder. Written informed consent was obtained from all women enrolled into the study and Institutional Review Board approval was provided by ethics committee of West China Second University Hospital, Sichuan University. All subjects were over 20 years of age and were willing and able to sign the informed consent. Exclusion criteria for the study were current menstrual period, current or recent pregnancy (<4 months post delivery), previous total hysterectomy, and surgical treatment to the cervix within the previous 3 months.

Measures

Once ethics committee approval was obtained with all subjects providing signed informed consent, relevant

demographics together with history of a recent (<6 weeks) Pap smear results and related treatment history were obtained from the medical records by two investigators. Then the dual-test TruScreen screening procedure was performed by two trained interns according to manual prior to LEEP treatment performed in the same location. The patients were placed in the lithotomy position and the operator placed the tip of the instrument with its single-use biosensor in direct contact with different points of the cervix using a pre-determined protocol and topographical scanning path. After the operator had signaled completion of the examination by pressing a button on the handpiece, the screening result was calculated and printed from the console. It returned out one of two possible final patient's screening results: "normal" (normal squamous epithelium, columnar epithelium, physiologic metaplasia, or latent HPV-related changes) or "abnormal" (CIN 1, CIN2, CIN3 or ICC) [13].

Then as in our routine practice, the cervix was evaluated by colposcopy after application of 5 % acetic acid to identify the lesion, the transformation zone and the endocervical limits. Loop electrosurgical excision procedure (LEEP) was performed by experienced gynecologist after local anesthesia was administered. The electrosurgical generator (Surgitron Ellman International, New York, USA) was operated using the cutting mode recommended by the manufacturer. Size of the loop used in each patient varied to ensure complete removal of the lesion. Subjects who underwent excision therapy were followed through completion of scheduled visits. All LEEP specimens were measured and fixed in formalin and processed in a standard fashion. Then the specimens were submitted for histopathologic examination including maximal neoplastic severity and extension to margins. All histological slides were reviewed by two experienced pathologists at the Department of Pathology, West China Second Hospital, Sichuan University. The LEEP histological results were classified into five groups: absence of CIN, CIN1, CIN2, CIN3 and ICC.

Data processing and statistical analysis

Patients were mainly subjected to Pap smear, TruScreen, LEEP treatment and histopathologic diagnoses subsequently, and the tests records classified as negative (normal or no neoplastic abnormalities) or positive [CIN 1, CIN2, CIN3 or ICC] were counted. The degree of agreement between each histological diagnosis and interpretation with TruScreen or Pap smear was compared and calculated. Subsequently, the results were listed as a table to evaluate the correlation of both primary screening approaches. To evaluate the validity and yield of TruScreen and cytological smear compared with pathological results, the

sensitivity (SEN), specificity (SPE), positive predictive value (PPV) and negative predictive value (NPV) were calculated. And to compare the screen tests, paired Chi-square (χ^2) test was carried out for statistical analysis. For all statistical tests, *P* value less than 0.05 were considered significant. Data were analyzed with SPSS 11.0 (SPSS, Chicago, IL, USA).

Results

The study population consisted of 183 patients accrued from outpatients of our hospital. The mean age of study participants was 37.4 years old, with a range of 20–58 years old. Patients were eliminated from analysis if they did not complete the TruScreen testing (1 patient) or if the device malfunctioned (1 patient). The analysis was limited to the 181 patients for whom all tests were currently completed: TruScreen test and histopathologic report. The analysis was limited to the 169 patients for 12 patients did not have conventional cytological smear within 6 weeks. Within the outpatient population, the prevalence of CIN was 23.8 % (43/181), including CIN1 7.7 % (14/181), CIN2 8.3 % (15/181), CIN3 7.7 % (14/181). It reflected the relatively high risk at inner city referral zones for the clinical treatment participating in the study.

The results of the TruScreen tests compared with that from pathological test are showed in Table 1. The characteristics of the TruScreen test were as the following: SEN, 67.4 % (29/43) (95 % CI 53.4–81.5); SPE 68.1 % (94/138) (95 % CI 60.3–75.9); PPV, 39.7 % (29/73) (95 % CI 28.5–51.0); NPV, 87.0 % (94/108) (95 % CI 80.7–93.4).

The results of the conventional cytological smear compared with that from pathological test are showed in Table 2. The characteristics of the conventional cytological smear were as the following: SEN, 87.9 % (29/33)

(95 % CI 76.7–99.0); SPE, 74.3 % (101/136) (95 % CI 70.0–81.4); PPV, 45.3 % (29/64) (95 % CI 33.1–57.5); NPV, 96.2 % (101/105) (95 % CI 92.5–99.9).

The parameters above mentioned and their corresponding 95 % confidence intervals (CIs) were used to estimate the validity and yield difference between the TruScreen test and cytological smear of cervical screening. Overall, more efficacious screening results were found with pap smear but the differences were not significantly different with each other, including sensitivity (SEN), specificity (SPE), positive predictive value (PPV) and negative predictive value (NPV) ($P > 0.05$) (Fig. 1). Moreover, there was also no significant difference between the TruScreen results and cytological smear results ($\chi^2 = 0.2162$, $P = 0.6419$). The results of TruScreen test compared with that from the Cytological test are showed in Table 3.

Discussion

As we all know, there is no consensus on the best screening tests to use for less-developed countries because adherence to appropriate intervals and requisite quality control cannot be adequately assured under such conditions. TruScreen is an automated portable device that measures the response to optical and electrical stimulation of the cervix and returns a screening result in real time. The present study focused on the role of TruScreen for cervical cancer screening. We evaluated the novel device for its validity and yield to detect CIN or ICC, compared with conventional cytological smear completed by gynecologists. The sensitivities for histologically confirmed CIN lesions by TruScreen and Pap, were 67.4 % (95 % CI 53.4–81.5) and 87.9 % (95 % CI 76.7–99.0), respectively. The specificities for histologically confirmed CIN lesions by TruScreen and Pap, were 68.1 % (95 % CI 60.3–75.9) and 74.3 % (95 % CI 70.0–81.4), respectively. Our results indicated that in

Table 1 Result of consistency rate between TruScreen and pathological test

TruScreen result	Pathological result		Total
	Positive ^a	Negative ^b	
Positive ^c	29	44	73
Negative ^d	14	94	108
Total	43	138	181

^a Include CIN1, CIN2, CIN3 or ICC

^b Include normal or no neoplastic abnormalities

^c Include CIN 1, CIN2, CIN3 or ICC

^d Include normal squamous epithelium, columnar epithelium, physiologic metaplasia, or latent HPV-related changes

Table 2 Result of consistency rate between cytological and pathological test

Cytological result	Pathological result		Total
	Positive ^a	Negative ^b	
Positive ^c	29	35	64
Negative ^d	4	101	105
Total	33	136	169

^a Include CIN1, CIN2, CIN3 or ICC

^b Include normal or no neoplastic abnormalities

^c Include atypical squamous cells uncertain significance (ASCUS), low-grade squamous intraepithelial lesions (LISL), high-grade squamous intraepithelial lesions (HISL) or invasive cervical cancer (ICC)

^d Include normal, inflammation or no neoplastic abnormalities

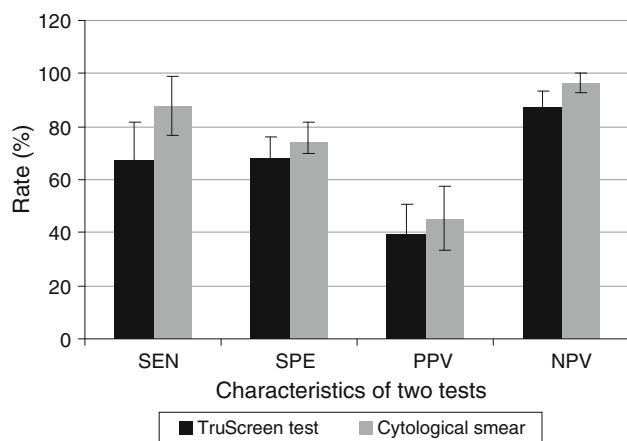


Fig. 1 Consistency rate between TruScreen and cytology test results of histologically confirmed lesions. Characteristics of TruScreen (black) and cytological smear (gray) results are shown in figure. *SEN* sensitivity, *SPE* specificity, *PPV* positive predictive value, *NPV* negative predictive value. Point estimates and 95 % confidence interval bar for the TruScreen and cytological smear characteristic results are shown for the validity and yield comparison. No significant difference were found between the four parameters of the two screening tests ($P > 0.05$)

Table 3 Results of the TruScreen are compared with those from the cytological test

Cytological result	TruScreen result		
	Positive ^a	Negative ^b	Total
Positive ^c	25	38	63
Negative ^d	37	69	106
Total	62	107	169

^a Include CIN 1, CIN2, CIN3 or ICC

^b Include normal squamous epithelium, columnar epithelium, physiologic metaplasia, or latent HPV-related changes

^c Include atypical squamous cells uncertain significance (ASCUS), low-grade squamous intraepithelial lesions (LISL), high-grade squamous intraepithelial lesions (HISL) or invasive cervical cancer (ICC)

^d Include normal, inflammation or no neoplastic abnormalities

contrast with pap smear, TruScreen was comparatively efficacious in primary screening of cervical cancer ($\chi^2 = 0.0133$, $P = 0.9081$).

The good representation of the TruScreen for screening is especially interesting in the light of some recent studies [14–16]. The sensitivities for histologically confirmed CIN 2 and 3 lesions by TruScreen, Pap, and TruScreen and Pap combined were 70, 69, and 93 %, respectively [13]. The improvement in sensitivity for the combined test compared with the Pap smear alone was significant. In another report, the sensitivity of TruScreen and Pap was 32.2 and 42.2 %, with specificity of 96.7 and 93.7 % in detecting cervical cancer, respectively [17]. We had a higher sensitivity at the cost of specificity because of the participation of treatment

clinic subjects. This “enriched” population had a higher underlying CIN prevalence rate and thus increased the test sensitivities. However, the overall detecting consistency for precancerous lesions when the TruScreen was used as a single screening test was shown to be equivalent to that of a high-quality screening Pap smear. These consistent findings suggested that TruScreen also had cervical screening potentiality in developing world regions without organized cytological screening programs.

Because women’s participation in screening, test accuracy and reproducibility, rapidity with which results are available, and test acceptability and affordability to women may influence the effectiveness of a cervical cancer prevention program [9], acetic acid (VIA) and HPV-DNA test were suggested for developing countries [18]. Such as Sankaranarayanan et al. [19] and others have demonstrated impressive results using visual inspection with acetic acid (VIA) in single-armed and in a randomized controlled trial. These methods were in real time, but in many parts of the world trained personnel for VIA screening were not available. Meanwhile, VIA and cytology both rely on considerable quality-control mechanisms for optimal performance, and in expert hands, the reproducibility of VIA was similar to cytology [20]. The interpretation of VIA was subjective and its performance cannot be readily evaluated against objective standards [21]. Therefore, we did not believe that it was appropriate to perform a VIA test without adequate equipment and supplies, or trained providers. In contrast, the use of TruScreen screening test would minimize training requirements and assist in the standardization of results. The result of automated test was more reproducible and immediately available making it theoretically possible to provide treatment, if necessary or to plan further management at the same visit.

The identification of specific papillomavirus types as causative agents for cancer of the cervix and its precursor lesions allowed the development of a new method for cancer screening and early diagnosis—HPV-DNA test. A meta-analysis by Cuzick and colleagues et al. [22] showed the sensitivity of cytology to be 53.0 % (95 % CI 48.6–57.4) versus a sensitivity of 96.1 % (94.2–97.4) for cervical HPV-DNA testing (HC2, QIAGEN Inc, Gaithersburg, MD, USA; formerly Digene Corporation) for the detection of moderate or severe cervical intraepithelial neoplasia (CIN). However, HPV infections were very common and usually clear spontaneous, especially in younger women that it would be impractical to follow-up [23]. Thus, detection of HPV-DNA carries a risk of unnecessary colposcopies, psychological distress and possibility of over diagnosis [5]. Also, current technical and infrastructural requirements can make HPV testing difficult to implement in low-resource areas. Furthermore, they are relatively expensive and therefore prohibitive for a large part of the world where cervical cancer is

still a principal cause of death. Therefore, HPV-DNA test was inappropriate for application in low-resource settings in developing countries so far.

There were several strengths to this study: participants included various diseases, such as CIN, cervical polyp, serious cervical erosion and high-risk HPV infection. The enrichment population allowed a more precise determination of test efficacy since presence of a reliable reference standard, calculations of sensitivity and specificity were independent of the prevalence of disease in the population, except insofar as prevalence affected the calculation of sample size. Because specimens were obtained from the LEEP treatment of all the subjects, histologically confirmed CIN was used as the gold standard for evaluation of screening programs, without the potentiality for missed lesions. There are also some limitations to this study: only outpatients were included in our study, this may affect the reproducibility of TruScreen in normal population screening; cytological smears were not performed at the same period of TruScreen. However, the impact on the results of the study is likely to be mitigated by the use of a recent (<6 weeks) Pap smear results. Also, sample size involved was relatively small in our study, which for any single study may be underpowered to detect the precise effects. Therefore, as with any public health intervention, quality assurance of TruScreen for cervical cancer prevention needs further evaluation for test effectiveness and especially cost-effectiveness in the future. The potential importance of a population-based approach and screen monitoring and coordination to achieve and maintain high coverage should not be overlooked.

In conclusion, TruScreen is an effective screening test in areas where Pap screening is nonexistent or unreliable. It is similar to cytological smear test for the initial cervical cancer screening. The low-cost, minimal training requirements, speed of analysis, automated features and effective screening of TruScreen make it ideal for primary cervical screening in low-resource settings where the impact would be the highest. However, because of the limited sample size in our study, the large-scale randomized clinical trials are needed for further exploration of the screening potentiality of TruScreen.

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Conflict of interest The authors declare that they have no conflict of interest.

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