Efficacy of a real time optoelectronic device (TruScreen™) in detecting cervical intraepithelial pathologies: a prospective observational study

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Abstract

Objective: To assess the effect of TruScreen™ (an objective optoelectronic cervical screening device) in improving the sensitivity of cervical screening programs either alone or in combination with Papanicolaou (PAP) smear or human papilloma virus (HPV) DNA screening.

Material and Methods: Our study was performed in 285 patients with abnormal Pap test results. TruScreen™ and HPV screening methods were performed in all participants. Consistency and differences between the tests were compared with cervical biopsy results.

Results: TruScreen™ was found to be an approach method in the determination of cervical pathologies (ROC curve area underlined=0.606) and with an 89.5% negative predictive value. HPV screening remains a counterpart to TruScreen™ with a 0.620 area underlined in the ROC curve and an 83% negative predictive value.

Conclusion: As determined in our study, TruScreen™ with a sensitivity of 86.1% can be used as a screening test with instant and not professional dependent results for cervical cancer screening. Avoiding from subjectivity in interpretation of Pap smears and requirement for pathologists, TruScreen™ can be a used for cervical cancer screening especially in countries with a low socio-economic status. The combination of TruScreen™ and HPV screening was not able to demonstrate a significant rise of effectiveness in screening. (J Turk Ger Gynecol Assoc 2015; 16: 41-4)

Keywords: Cervical screening, optoelectronic device, CIN

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Introduction

Cervical cancer is one of the most common gynecological cancers. It is the fourth most common cancer in women. GLOBOCAN data revealed 528,000 new cases in 2012 (1). Cervical cancer is considered as a preventable malignancy because of its close relation with the causative agent human papillomavirus (HPV) and the long period of precancerous lesions. HPV DNA was detected in 95%-100% cervical cancer patients (2). Moreover, it takes 58 months for the development of cervical intraepithelial neoplasia (CIN) 1 to carcinoma in situ and 38 and 12 months for CIN 2 and CIN 3, respectively (3).

The incidence of cervical cancer has decreased in developed countries with the aid of cervical cancer screening policies. However, in developing and under-developed countries, cervical cancer is still considered as an important public health problem. Inadequate screening programs, absence of experienced pathologists, and financial difficulties in organizing community-based screening programs seem to be the main reasons for the high incidence of cervical cancer in developing and under-developed countries. Therefore, screening programs are crucial for decreasing morbidity/mortality and for increasing the cure rate of the cervical cancer treatment. Moreover, adjunctive complementary test methods can be helpful for the improvement of detection rates of CINs and cervical cancer.

Nowadays, many methods are available for evaluating the various physical properties of human tissue. Radiation, magnetic and electrical fields, sound waves, and light can be used for the evaluation of human tissue. Optical and dielectrical impedance of human tissue is one of the potentially promising methods for the evaluation of human tissue. Because of the optical and dielectrical properties of different tissue components, human tissue has a specific intrinsic resistance and capacitance (4). Because normal or HPV infected tissues have differences in fundamental structure, it can also be assumed that optical and dielectrical impedance differences can exist between these tissues. TruScreen™ (Polarprobe; Polartechnics, Sydney, Australia) is a new real-time opto-electric screening method for cervical cancer (5). The working mechanism of this method is based on the frequency-dependent impedance spectrum. The system injects a current in different frequencies into the tissue and measures the voltage response of the tissue. There is no specification of the degree of abnormality as in a Papanicolaou (Pap) smear in the design of TruScreen™. The test detects an abnormality of the cervical tissue if present and gives results as normal or abnormal.

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Table 1. Comparison of Cervical biopsy and TruScreen results

		Cervical Biopsy		
		Positive[a]	**Negative[b]**	**Total**
TruScreen	Abnormal[c]	56 (%19.6)	143 (%50.2)	199
	Normal[d]	9 (%3.2)	77 (%27.0)	86
	Total	65	220	285

[a]Includes LSIL, HSIL, or ICC
[b]Includes normal or non-neoplastic changes
[c]Includes CIN 1, CIN 2, CIN 3, or ICC
[d]Includes normal squamous epithelium, columnar epithelium, physiologic metaplasia, or latent HPV-related changes

This real-time optoelectronic device offers the advantage of instant diagnosis, decreases the need for pathologists, and allows clinicians to counsel and manage the patient with abnormal test results in the first screening visit. These advantages can be a solution for difficulties in appropriate cervical screening programs in developing countries. We aimed to evaluate differences and consistencies between TruScreen™, Pap smear, HPV DNA screening, and pathological biopsy results in patients with cervical abnormalities in a separate manner. We also tried to determine the possible predictivity of combined methods in the early diagnosis of CINs.

Material and Methods

This prospective observational study was conducted in Zekai Tahir Burak Women's Health Education and Research Hospital in Ankara, Turkey, which is a reference center for gynecological oncology cases for the entire country. Academic approval of the study was obtained from our hospital's ethic committee. Informed written consents were obtained from all participants. The study was performed on patients who had been admitted to our hospital with abnormal cervical cytology defined by the Bethesda Classification of Cervical Cytology.

Inclusion criteria that must be met for this study were confirmed conventional Pap smear abnormality with at least atypical squamous cells uncertain significance (ASCUS), not having undergone hysterectomy before, not pregnant or not been pregnant for the last 3 months, not having undergone any cervical intervention or treatment for any diseases, and not having undergone pelvic radiotherapy treatment. Demographic features such as age, gravity, parity, abortion, and pregnancy history of all the participants were recorded. A total of 285 of 305 patients were recruited for the study.

Polartechnics' TruScreen™ device was used to perform TruScreen™ screening for the patients who were chosen according to the inclusion criteria. The TruScreen™ screening procedure was performed by a single trained physician with the method defined by Copellson et al. previously. The operator placed the tip of the probe (TruScreen™) with its single-use sensor. The operator targeted different points of the cervix using a predetermined protocol and topographical scanning path, which is defined in the manual of the device. After the completion of the examination, the result was calculated by the device and printed out from the console. The results are defined as "normal" for normal squamous epithelium, columnar epithelium, physiological metaplasia, or latent HPV-related changes or "abnormal" for CIN 1, 2, and 3 and invasive cervical carcinoma (6).

After TruScreen™ screening, specimens were also taken for HPV screening test from all participants. HPV DNA tests were evaluated via NucleoSpin® Blood kit (manufactured by Pharmatech©, New Jersey, USA).

Colposcopic investigations of all participants were performed by a single gynecologist with Allyn Videopath Colposcope (Medical Device Depot©, Ellicot City, MD, USA) after the application of 3% acetic acid to the cervix. After the colposcopic investigation, cervical biopsies were obtained from suspected areas, and pathological investigations were performed in our hospital's pathology laboratory. In order to avoid variability issues in the interpretation of pathological specimens, the specimens were investigated by a single expert pathologist.

Statistical analysis was performed with SPSS version 19.0 (SPSS, IBM, Chicago, USA). To evaluate the efficacy of TruScreen™, HPV DNA testing, and conventional Pap smear with the cervical biopsies, the sensitivity, specificity, and positive and negative predictive values were calculated. Because of the values identified as nominal, Chi-square test was used to evaluate differences between screening tests; kappa test was used to evaluate the consistency of tests. ROC curve analysis was used to evaluate the adequacy of tests in screening the cervical cytopathologies.

Results

This prospective observational study was performed in 285 patients who had abnormal Pap smear results. From a total of 285 participants, Pap smear results included 175 (61.4%) cases with ASCUS, 66 (23.4%) with low-grade squamous intraepithelial lesions (LGSIL), 13 (4.6%) with high-grade squamous intraepithelial lesions (HGSIL), 20 (7.0%) with atypical glandular cells of undetermined significance, 6 (2.1%) with malignant squamous carcinoma, and 5 (1.8%) with atypical squamous cells cannot exclude HSIL.

The colposcopic biopsy results showed 65 (22.3%) patients with abnormal results (LSIL, HSIL or Carcinoma). Among these pathological results, 42 (14.7%) cases had LGSIL, 15 (5.3%) had HGSIL, and 8 (2.8%) had squamous carcinoma. There were 56 cases with positive results for both biopsy and TruScreen™, including 33 cases with LGSIL, 15 with HGSIL, and 8 with invasive carcinoma. TruScreen™ did not miss any case of HGSIL or invasive carcinoma (Table 1). Nine patients with LSIL in the pathological investigation were reported as normal by TruScreen™.

The positivity rate of TruScreen™ was 69.8% (199/285). The sensitivity and specificity of the TruScreen™ test were found as 86.1% (56/65) and 35% (77/220), respectively. Additionally, positive and negative predictive values were 28.1% (56/199) and 89.5% (77/86), respectively. In the ROC curve analysis, the area underlined value was 0.606, and there was a consistency between the TruScreen™ and pathological biopsy results (Figure 1).

HPV DNA positivity was determined in 85 participants. Subtypes of HPV infection were also exhibited, and the most common sub-types that were examined in all participants (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) were included the study. The positivity rate of HPV screening was 29.8% for all participants. The sensitivity and specificity of the HPV screening test

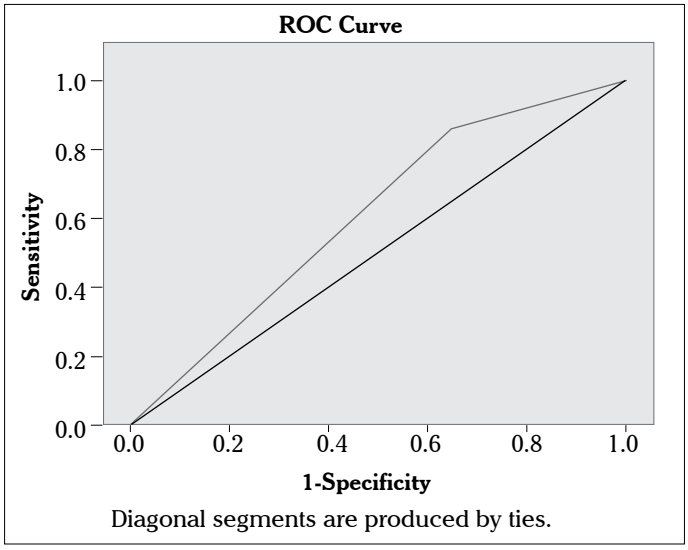

Figure 1. ROC curve analysis of TruScreen™ with pathological results in patients with cervical histological abnormalities

Table 2. Comparison of Cervical biopsy and HPV DNA results

		Cervical Biopsy		
		Positive[a]	Negative[b]	Total
HPV DNA	Positive[c]	31 (10.9%)	54 (18.9%)	85
	Normal[d]	34 (11.9%)	166 (58.2%)	200
	Total	65	220	285

[a]Includes LSIL, HSIL, or ICC
[b]Includes normal or non-neoplastic changes
[c]Includes positive for High Risk HPV DNA Type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
[d]Includes negative result for High Risk HPV DNA DNA Type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68

Table 3. Sensitivity, specificity, false positive, and false negative results for each screening regime

	TruScreen™	HPV DNA
Sensitivity for abnormal cervical biopsy results[a]	86.1%	47.7%
Corresponding false negative rate for abnormal cervical biopsy results	89.5%	83%
Specificity for abnormal cervical biopsy results	35%	75.4%
Corresponding false positive rate for abnormal cervical biopsy results	28.1%	36.4%

[a]Include CIN 1, CIN 2, CIN 3 or ICC

were found as 47.7% (31/65) and 75.4% (166/220), respectively, in our study. The positive and negative predictive values were 36.4% (31/85) and 83% (166/200), respectively (Table 2). In the ROC curve analysis, the area underlined value was 0.616, and it demonstrated a consistency between HPV screening and pathological biopsy results (Figure 2). The sensitivity, specificity, and negative and positive predictive values of both tests are mentioned in Table 3.

Because the combination of TruScreen™ and HPV screening did not demonstrate better results in the ROC curve analysis

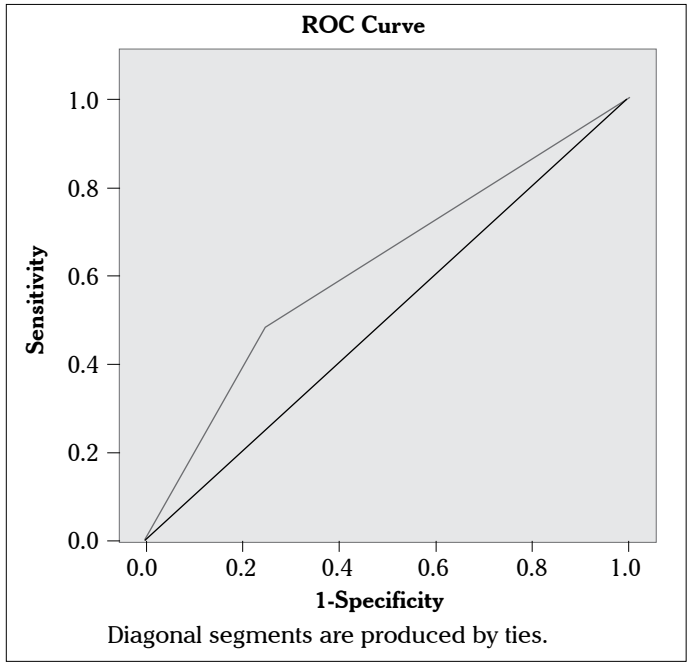

Figure 2. ROC curve analysis of HPV screening with pathological results in patients with cervical histological abnormalities

(area underlined value=0.614) and negative predictive value evaluation (negative predictive value 86%), we concluded that the combination of HPV DNA test and TruScreen™ cannot provide significant enhancement in the screening program. For this reason, we did not consider the combination as an efficient screening regime.

Discussion

In a recent study including 176 women, a difference between impedance spectrum of cancerous and normal cervical tissue was demonstrated. The results indicated screening with this method could detect CIN II/III with a sensitivity of 74% and a specificity of 53% (7).

Pap smear is the standard screening test for cervical cancer and premalignant cervical lesions. It was determined that approximately 50% of women who have cervical cancer have no history of regular cervical screening (8). According to the report from Agency for Health Care Policy and Research, the conventional Pap smear has a sensitivity of 51% and a negative predictive value of 47% (9). On the other hand, according to a study in 2000, 47% of women who develop cervical cancer may report an adequate screening history (10). They indicated that the complementary tests can improve detection rates for high grade CINs and can also increase the overall sensitivity for cervical cancer screening. These data reveal that new screening methods should be developed for patients who cannot be determined by conventional screening methods. The objective of the study was to assess the efficacy of TruScreen™ in improving the sensitivity of cervical screening programs either alone or in combination with another test.

Including our country, most countries have difficulties in cervical cancer screening that covers the entire population. Despite

the presence of a large number of people to be screened, a lack of experienced cytopathologists makes a proper population-based screening program challenging. Moreover, subjectivity in the interpretation of Pap smear tests and need for consecutive doctor visits in case of abnormal results reveal an urgent need for additional, cost-effective methods for better results in the early diagnosis of cervical carcinoma. A multicenter trial by Singer et al. that was performed in 671 patients in 10 centers showed sensitivities for histologically confirmed CIN 2/3 lesions by TruScreen™, Pap, and a combination of these two techniques as 70%, 69%, and 93%, respectively (11). In the same study, the sensitivities of the TruScreen™, Pap, and the combined test for CIN 1 positive (+) patients were 67%, 45%, and 87%, respectively. Two recent studies also describe TruScreen™ as a good and objective method for cervical screening with high sensitivity results (12, 13). In our study, the sensitivity of TruScreen™ was 86.1% and the negative predictive value was 89.5%, which is similar to Singer et al. (11) results.

Screening with HPV DNA seems to be more reliable for screening cervical pathologies in our study. The negative predictivity rate and specificity of HPV DNA testing were found to be 83% and 75.4%, respectively, in our study. In a meta-analysis, the specificity HPV DNA testing was calculated as 71% for ASCUS and LSIL and as 77% for HSIL lesions on screening, which is similar to our results (14). As an objective, standardized test HPV DNA test is a promising screening modality; however, in daily circumstances, there are some doubts about the test's cost-effectivity especially for larger populations. Morin et al. (15) suggested that even HPV should be tested first; the repetitive cytological tests should be performed in the management of cervical screening. An increase in the effectiveness of a cervical cancer prevention program is related to women's participation, test's acceptability, affordability, accuracy, and rapidity (16). Conventional cytology needs not only special equipment and supplies but also trained specialists for interpretation. The obligation of second doctor visit for results can be defined as another factor that decreases the acceptability and increases the affordability of the screening program with the Pap smear. In contrast, TruScreen™ would minimize training requirements and assist in the standardization of results (13).

In conclusion, with a sensitivity of 86.1% and advantages such as being and objective and real-time test, makes TruScreen™ an accepted valuable screening test for detecting preinvasive cervical lesions especially in areas where Pap screening cannot be effectively performed. TruScreen™ can be an alternative way for cervical screening, especially in under-developed and developing countries that have a lack of experienced pathologists and have difficulties in patient follow-up. The combination of TruScreen™ and HPV screening was not able to demonstrate a significant rise of effectiveness in screening, although only HPV screening was able to demonstrate an acceptable efficacy. However, the combination of TruScreen™ with Pap smear can be effective in enhancing the sensitivity of cervical cancer screening. Because of limited cases and deficiency in cervical biopsy results of patients with normal Pap smear, the significance of TruScreen™ needs further investigation with larger cases.

Ethics Committee Approval: *Ethics committee approval was received for this study from the ethics committee of Zekai Tahir Burak Women's Health Education and Research Hospital, Educational Planning and Coordination Decision 09/2009- 17.*

Informed Consent: *Written informed consent was obtained from patients who participated in this study.*

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