

Cervicouterine Cancer Screening – TruScreen™ vs. Conventional Cytology: Pilot Study

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Abstract

Introduction: Cervicouterine cancer (CC) is a health problem worldwide and is the fourth most common cancer in women, with a greater proportion of individuals affected by advanced stages of the disease in developing countries. **Objective:** To determine the sensitivity and specificity of the TruScreen™ opto-electronic device vs. conventional cytology in CC screenings. **Methodology:** This is a prospective observational study that included individuals who presented for the first time at the Dysplasia Clinic of the Instituto Nacional de Cancerología from March 1 through April 30, 2016, and those referred due to abnormal conventional cytology. The patients were evaluated with the TruScreen™ device, conventional cytology, colposcopy and, if necessary, cervical biopsy. The results were analyzed by descriptive statistics as well as the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the TruScreen™, using conventional cytology as the standard. **Results:** Thirty-two patients were included who met the inclusion criteria. The average age of the patients was 40 years (range, 23–61 years). For the diagnosis of high-grade intraepithelial lesions, the TruScreen™ device showed a 43% sensitivity, a 92% specificity, a PPV of 60%, and a NPV of 85%, whereas evaluation via cervical biopsy exhibited a 33% sensitivity, an 86% specificity, a 33% PPV, and an 86% NPV. The Kappa agreement index of the TruScreen™ with the colposcopies was 0.70. **Conclusions:** TruScreen™ demonstrated low sensitivity and high specificity compared with conventional cytology, which had a high NPV.

Keywords: Cervicouterine cancer, conventional cytology, opto-electronic device, screening, TruScreen™

INTRODUCTION

In 2012, according to GLOBOCAN reports, cervicouterine cancer (CC) was the fourth most common cancer in women, with 528,000 new cases and 266,000 deaths.^[1] It predominantly affects women with economic, social, and cultural disadvantages; thus, it is much more common in developing countries, where 85% of new cases occur, in contrast to developed countries, in which only 3.6% of such cases are registered.^[2]

Cervical cancer (CC) is preceded by intraepithelial lesions, which are characterized by alterations in the cells of the cervical epithelium, without involving the stroma. These alterations are related to infections with the human papilloma virus (HPV). The presence of HPV does not necessarily cause cancer, but it does cause the persistence of the cancer. The presence of HPV has been demonstrated in up to 99.7% of CC cases.^[3]

Cervical intraepithelial neoplasms (CIN) develop in the transformation zone of the cervix and produce changes in the cytoplasm, a loss of polarity in the cell nucleus, pleomorphism, and mitosis. Currently, CIN1 lesions and infection by HPV correspond to low-grade squamous intraepithelial lesions (LSILs), whereas CIN2 and CIN3 correspond to high-grade squamous intraepithelial lesions (HSILs) according to the Bethesda reporting system, which is the most accepted one.^[4] The process of developing a CIN can take many years; on average, it is estimated that 8–10 years pass from the initial HPV infection until the development of CIN3 or HSIL. However, this period has been demonstrated to be much shorter in young patients, as shown by Winer *et al.* in a study

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that included 603 university students with an average age of 19 years. These authors observed that prior to the presence of HPV16 or HPV18, the average time for developing a low-grade epithelial lesion was 4 months, whereas that for a high-grade lesion was 14 months.^[5]

Populational screening with the Papanicolaou (PAP) examination (conventional cytology) was introduced in Latin America at the beginning of the 1960s; however, mortality rates due to CC have shown only a slight reduction in countries such as Mexico, Costa Rica, and Chile.^[6] This was demonstrated by Lazcano-Ponce *et al.*, who, in 2008, published the results of a study evaluating the effectiveness of the Programa Nacional de Escrutinio para Cáncer Cervicouterino en México (National Screening Program for Cervical Cancer in México); they found a correlation between the decrease in mortality by CC and the increased utilization of the PAP test as well as a decrease in the birth rate. These authors also demonstrated that this test can result in false negatives for up to 53% of uses, particularly in the southern part of the country.^[7]

Despite the development of molecular techniques for detecting the DNA of high-risk HPV and the messenger RNA of high-risk HPV, there is a constant demand to increase the sensitivity and specificity of various diagnostic tools for detecting cervical lesions because it has been demonstrated that the detection of HPV16 and HPV18 has the greatest efficiency in terms of screening for CC. Ten colposcopies are required to detect a high-grade epithelial lesion in patients submitted to this type of screening, which leads to a considerable number of unnecessary colposcopies and high institutional and public costs.^[8]

In addition to being sensitive and specific, it is also desirable for a detection test to be cost-effective, reproducible, and noninvasive such that a physician can carry out a simultaneous detection of pathologies during only one appointment. Such solutions are necessary in all countries, such as ours, where there is no access always to cytodagnostic laboratories or adequately trained medical and paramedical personnel.

The biophysical methods (specifically those based on the changes of impedance of the tissues) are emerging as options that nearly match this ideal. These methods have an advantage over cytology in terms of giving fewer false positive and false negative results, which are frequently due to human error.

In 1980, at the University of Sydney, an automated opto-electronic reading device was developed for the instantaneous detection of low- and high-grade cervical intraepithelial lesions, and its commercialization began at the end of the 1990s.^[9] The mechanism of action of this instrument is based on frequency-dependent spectral impedance, which measures the voltage response of the tissue without specifying the degree of abnormality; that is, it detects only whether some abnormality is present or not in the cervical tissue, and the results are reported as normal or abnormal.^[10] The first to report on the usefulness and reach

of this opto-electronic device was Coppleson in 1994.^[11,12] Currently, this device is commercialized under the name of TruScreen™ [Polarprobe] (Polartechnics Ltd., Sydney, Australia), and it permits an immediate evaluation of the basal membrane of the cervical epithelium.

The objective of the present work was to determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the TruScreen™ opto-electronic device, using conventional cytology as the standard, in the screening of CC.

PATIENTS AND METHODS

We conducted a prospective, transversal, and observational study that included patients who presented for the first time at the Dysplasia Clinic of the Instituto Nacional de Cancerología de México (INCan) in Mexico City from March 1 through April 30, 2016, who were referred due to abnormal conventional cytology and who complied with the following criteria: did not have cervico-vaginal lesions at the time of the study, have not received vaginal treatment in the past 3 months, have not received radiotherapy in the pelvic region, not being pregnant, not had a delivery in the last 4 months, and not had any cervical cytology studies in the last 6 weeks.

The patients who were included in the study were submitted to a speculoscopy and later to an evaluation with an opto-electronic TruScreen™ device, conventional cytology (PAP), colposcopy, and, if necessary, a cervical biopsy [Figure 1].

Evaluation with the TruScreen™ was initiated with the placement of the vaginal speculum and complete exposure of the cervix. In cases in which mucus or flux was observed, the speculum was removed to allow adequate reading by the device; a carefully placed piece of cotton was used to avoid trauma to the cervix. In some cases, the use of saline solution was necessary. We proceeded to calibrate the instrument as per the manufacturer's instructions. A detachable catheter was set in place and introduced into the vagina until the cervix was localized, taking a reading at 22 distinct points of the cervix from outside to inside, clockwise. Finally, the sequence of opto-electric readings was processed with the impression of the results, which were not read or seen by the operator.

The conventional cytology was performed after the speculoscopy and the reading by the opto-electronic device, with a visualization of the complete cervix. The sample was collected using an Ayre's spatula, with a rotation of at least 360°, for both the exocervix and endocervix samples. Each sample was applied to previously identified slides which were fixed with 96% ethanol. The cytology was reviewed at the Laboratory of the INCan Cytopathology Department following standardized procedures and according to the quality control protocols of the laboratory.

Colposcopies were carried out using Carl Zeiss 1170 equipment. This procedure involved evaluating the general characteristics of the cervix. This procedure comprised an

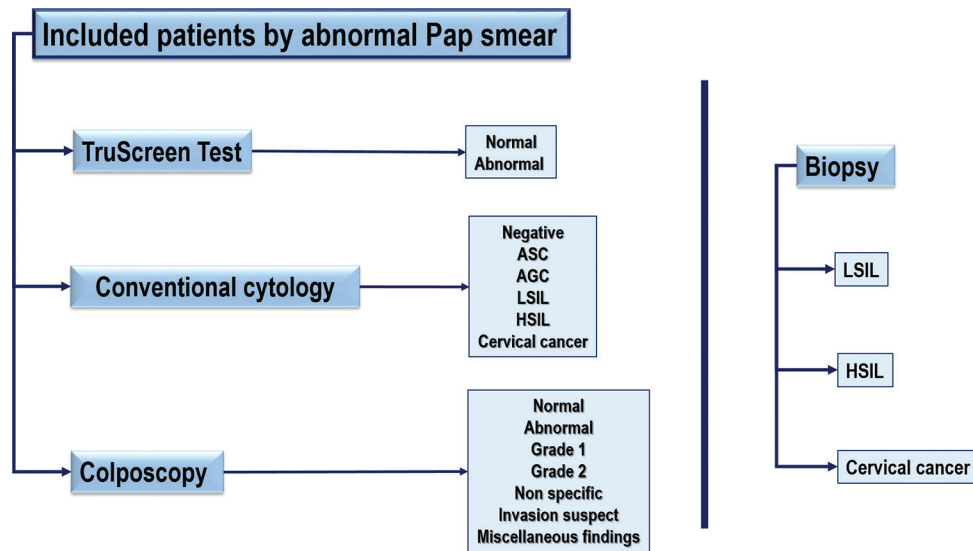


Figure 1: Algorithm used to treat the patients in this study. When cervical biopsy was taken and reported as normal, LSIL, HSIL, or carcinoma. ASC, Atypical squamous cells; AGC, Atypical glandular cells; LSIL, Low-grade squamous intraepithelial lesion; HSIL, High-grade squamous intraepithelial lesion

evaluation of the general characteristics of the cervix, with the subsequent application of a solution of acetic acid at 5% on the entire surface of the cervix, for at least 1 min. For the report of the colposcopic finding, the current nomenclature certified by the International Federation of Cervical Pathology and Colposcopy (IFCPC, 2011) was used.^[13]

A cervical biopsy was undertaken with the colposcopy in the case of abnormal findings in the cervical epithelium. We proceeded to procure an incisional biopsy by obtaining a punch specimen of the lesion or lesions that had been found. The samples were placed in a flask with the previously identified buffered formalin and sent to the Institute's Pathology Department for their analysis. Histological analysis of the specimen pieces was performed following standardized procedures and according to the quality control protocols of the laboratory.

We utilized descriptive statistics with central trend and dispersion measurements for the demographic data. We calculated the values of sensitivity, specificity, PPV, and NPV as well as the probability coefficients (likelihood ratio [LR]) for the TruScreen™, using conventional cytology as the standard. We calculated the kappa agreement index for the TruScreen™ results and for the colposcopy. We used the Statistical Package for the Social Sciences (SPSS) v22 software (SPSS, Inc., Chicago, IL, USA).

RESULTS

During the study period, 32 patients were included who met the inclusion criteria. The demographic characteristics of the population are presented in Table 1. The average age of the patients was 40 years (range, 23–61 years), the average age at which they became sexually active was 17 years (range, 12–30 years), 15% (five cases) reported being smokers, and the median number of sexual partners was 2 (range, 1–7 partners). The abnormality of conventional

cytology for which the patients were referred to our institution is depicted in Table 2. In this table, it can be observed that 20 patients were referred for LSIL, six for HSIL, three for atypical squamous cells, and the remainder for atypical lymph gland cells (one patient), *in situ* carcinoma (one patient), and invasive carcinoma (one patient).

When carrying out the analysis, using abnormal cytology with high-grade intraepithelial lesions as the standard, the TruScreen™ demonstrated a 43% sensitivity, a 92% specificity, a 60% PPV, and an 85% NPV, with a positive log likelihood ratio (LR+) of 5.38 and a negative log likelihood ratio (LR–) of 0.62 [Table 3]. When the analysis was performed using cervical biopsy as the standard, it revealed a 33% sensitivity, an 86% specificity, a PPV of 33%, and a NPV of 86%, with a LR+ of 2.36 and a LR– of 0.78 [Table 4]. An evaluation that we consider to be of great importance is the level of agreement that the TruScreen™ device has with abnormal colposcopic findings, which was 0.7 [Table 5].

DISCUSSION

Because the test-under-study was designed to be utilized in a physician's office when a macroscopic lesion did not exist, our results showed low sensitivity with high specificity compared with conventional cytology; that is, CC screening did not improve with respect to the sensitivity and specificity values of conventional cytology. However, it did allow an immediate decision to be made to perform a colposcopic evaluation. With respect to the colposcopy procedures used in our study, we observed an agreement of up to 70% for normal grade 1 and grade 2 findings [Table 5].

In 1999, the Agency for Healthcare Research and Quality (AHRQ) (U.S.) reported that the sensitivity of conventional cytology is much less than that which we considered, with only a 51% sensitivity and a NPV of 47%, and

Table 1: Demographic characteristics of the study participants (n=32)

Variable	N
Age*	40±12.53 years
Age became sexually active	17±3.26 years
Sexual partners**	2
Pregnancies**	4
Occupation	
Housewife	20
Employee	6
Entrepreneur	4
Stylist	1
Secretary	1
Civil status	
Single	10
Domestic partnership	5
Married	13
Divorced	1
Widowed	3
Education	
None	2
Elementary school	13
Junior school	8
High school	7
Bachelor	2
Comorbidities	
Diabetes	3
Hypertension	2
Metabolic syndrome	1
Contraceptive methods	
None	17
Preservatives	4
Hormonal pills	1
Hormonal device	2
Intrauterine device	1
BTO	7
Sexual life	
Active	18
Inactive	14
Smoking	
Active	5
Inactive	27
Alcoholism	
Active	1
Inactive	31

*Mean±standard deviation. **Average

Table 2: Abnormalities in the conventional cytology (Pap smear) found in the referred patients

Abnormality	n
Atypical squamous cells (ASC-US)	3 (9.37%)
Atypical glandular cells (AGC)	1 (3.1%)
LSIL	20 (62.5%)
HSIL	6 (18.75%)
Carcinoma <i>in situ</i>	1 (3.1%)
Invasive cancer	1 (3.1%)

Table 3: Comparison between TruScreen and cervical cytology

	Negative/LSIL	HSIL
TruScreen		
Normal	23	4
Abnormal	2	3

LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion

Table 4: Comparison between TruScreen and cervical biopsy

	Biopsy	
	Negative	NIC 2+
TruScreen		
Normal	12	2
Abnormal	2	1

that it is more accurate when it is utilized for high-grade lesions but has very poor discrimination for low-grade lesions.^[14]

The opto-electronic method is one of the most promising concepts of the biophysical program in terms of diagnosing premalignant lesions and CC. In their study, Pruski *et al.* examined 293 patients and found a sensitivity for low-grade intraepithelial lesions of 65.7%, and 90.38% for high-grade intraepithelial lesions and carcinomas. They also obtained a 78.89% specificity for the absence of cervical pathology.^[11]

In 2003, Singer *et al.* conducted one of the first multicenter assays to evaluate the usefulness of this technology. A total of 671 patients from 10 hospital centers were included, and their results showed a sensitivity of CIN2 and CIN3 of 70% for this opto-electronic device, 69% for conventional cytology, and 93% for the combination of the two techniques.^[15]

In 2006, a study of 176 patients demonstrated that the opto-electronic device reflected the detection for CIN2 and CIN3 with a 74% sensitivity and 53% specificity, thus exhibiting a difference between the spectral impedance of cancerous cervical tissue and normal tissue. Thus, the authors concluded that cervical impedance spectroscopy provides a detection tool in real time with a sensitivity and specificity similar to current studies for this screening procedure.^[16]

In 2013, Long *et al.* demonstrated a 67.4% sensitivity for TruScreen™ and an 87.9% for conventional cytology in detections with a histological confirmation of CINs.^[17] In 2014, the use of TruScreen™ as the screening procedure for detecting CC resulted in an 86.1% sensitivity and 35% specificity, demonstrating a greater sensitivity than the gold standard, which is the PAP, with instantaneous results and without the need for interpretation by cytopathology, which has the additional disadvantage of being operator-dependent.^[18]

In 2015, Özgü *et al.*, in a prospective observational study of 285 patients with abnormal results by conventional cytology,

Table 5: Comparison between TruScreen and colposcopy

	Colposcopy	
	Normal Grade 1	Grade 2
TruScreen		
Normal	27	0
Abnormal	2	3
Kappa value=0.7		

observed a sensitivity for TruScreen™ of 86.1%, with a 35% specificity, a PPV of 28.1% and a NPV of 89.5%.^[18]

CONCLUSIONS

This is, to our knowledge, the first study conducted in Mexico and Latin America in which we can observe that for the detection of high-grade intraepithelial lesions, TruScreen™ demonstrated low sensitivity and high specificity compared with conventional cytology, with a high NPV. The impact of this study lies in the possible diagnostic usefulness of the TruScreen™ in not having to wait for the result of the PAP and in the fact that the results can be similar to those obtained by conventional cytology, in which the sensitivity can be similarly low, reaching 51.5%, as shown in a study performed in the U.S. with more than 47,000 patients submitted to a conventional cytology,^[17] and the advantages of diminishing the need of a pathological report and establishing a protocol of treatment from the first clinical assessment prior to an abnormal result for the opto-electronic device. The greatest impact of the latter would be in primary care-level services, where a high percentage of patients who have a screening test, such as conventional cytology, do not return for the results or the results take a long time to be delivered. In Mexico, for most care services at this level, the patients are located when they present an abnormal PAP test result indicating a carcinoma. However, patients with a report of low-grade, or even high-grade lesions are not able to be located. Therefore, by possessing this instrument in health centers, private physicians' offices, especially at the location of primary-level care or prevention, the patient can be immediately given the result. If the result indicates that their test is abnormal and requires colposcopy and follow-up, the latter can even be provided on the same day if the center has colposcopic care.

The ability to utilize this technology would not only be advantageous for diagnosing the cancer during its early stages and providing follow-up to premalignant lesions with precise indications to the patient, but it could also diminish costs and the number of consultations and could, above all, avoid the loss of the patient due to issues involving follow-ups. This device is an instrument that is easy to use; thus, training could be provided for nurses in the prevention area, thereby diminishing to an even greater extent the number of consultations by the physician.

One of the greatest limitations in this study is the small number of individuals and that all of the patients had been referred due

to abnormal cytology. However, on carrying out a new study, it was evident that there were differences among the centers at which these studies are conducted.

A strength of our study is that we observed good agreement upon comparing the result of the opto-electronic device with the colposcopic evaluation.

Additional studies are required with larger numbers of individuals and with characteristics that are more similar to those of the population that does not come to a dysplasia clinic with an abnormal cytology, thus allowing the identification of the true value of this equipment in an environment such as ours, always bearing in mind the costs entailed in having such equipment and the necessary consumable goods.

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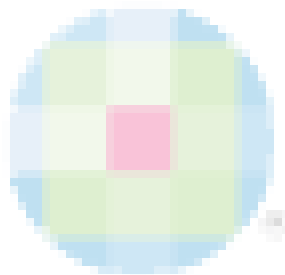
Conflicts of interest

There are no conflicts of interest.

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