THE EVALUATION OF A REAL-TIME OPTOELECTRONIC METHOD FOR THE DETECTION OF CERVICAL INTRAEPITHELIAL NEOPLASIA ('CIN')

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Key words: real-time optoelectronic method, cervical screening, cervical intraepithelial neoplasia, CIN.

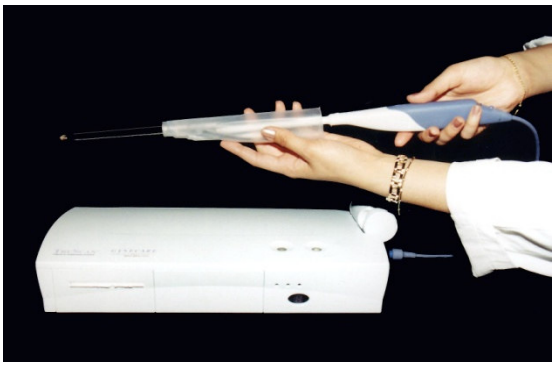
Objectives: Biotechnology is becoming an important tool in the prevention of cervical cancer. One of the most promising primary screening technologies for cervical cancer is TruScreen, an optoelectronic medical device that provides an immediate result. This study was conducted to determine the effectiveness of TruScreen in the detection of CIN.

Methods: A study was conducted on 234 women with normal or abnormal cytology results during the period August 2006 to August 2008 by the Laboratory of Pathophysiology of Uterine Cervix in Gynaecology & Obstetrics Clinical Hospital of Poznan University of Medical Sciences. In the blinded study, a real-time optoelectronic device ('TruScreen') was used for primary cervical cancer screening followed by HPV DNA test (Amplicor-Roche PCR), colposcopy examination and histopathological biopsy. The histopathological material was evaluated by two independents pathomorphologists. Results: The specificity for TruScreen was 82%. The sensitivity was 63% for CIN 1 and 85% for severe grades (CIN 2/3, carcinoma planoepitheliale). The opto-electronic method did not detect the two cases of adenocarcinoma.

Conclusions: The advantage of the opto-electronic device over cytology and colposcopy is its ability to generate an immediate and objective result automatically at the end of the examination and its ease of use. TruScreen is an effective tool for the detection of cervical neoplastic changes and is potentially an important improvement to the traditional cervical screening process.

Introduction

Cervical cancer is a significant health issue for women worldwide. In many developing countries it is the most common malignancy amongst women [1]. Over 3000 Polish women were diagnosed with cervical cancer in 2005 accounting for 5% of all oncologic diagnoses in the female population. The morbidity and mortality rates for cervical cancer in Poland are estimated to be 11.5% and 5.7% respectively [2].



The etiology of this cancer follows HPV infection, particularly high oncogenic types such as HPV 16 and 18 [3]. Type 16 is related to the pathogenesis of squamous cervical cancer, whilst type 18 is associated with glandular cervical cancer.

The pre-cancerous stage of cervical cancer is typically referred to as cervical intraepithelial neoplasia ('CIN'). There are three grades of neoplasia: mild, moderate and severe (CIN 1, CIN 2, and CIN 3 respectively). Cervical cancer neoplasia of severe grade CIN 3 includes pre-invasive cervical cancer, carcinoma-in-situ ('CIS').

It may take 3-10 years before CIN develops into cervical cancer. Mild grade CIN is often the result of a temporary HPV infection and 80% of these

tissue change events do not require treatment as they naturally clear themselves within a few months. However, persistent HPV infection, caused by oncogenic viral types are associated with unfavourable prognoses and may develop into CIN 2 /3 and then into cervical cancer.

In 1942, the first classification system of cytological smear evaluation was suggested by Papanicolaou [4]. The implementation of these 'pap tests' reduced the morbidity rate of cervical cancer by 50% and mortality by 70% [5]. In 1988, a new system of cytological smear evaluation was introduced – The Bethesda System ('TBS'). Its improved categorisation of neoplasia states resulted in reduced false negative and false positive results. However, despite introducing TBS, sensitivity and specificity of the Pap test, used to diagnose cervical intraepithelial neoplasia, has still not exceeded 70% and 80% respectively. The introduction of molecular methods to identify oncogenic HPV types has simplified the qualification of women into the cervical intraepithelial neoplasia high risk group. The only diagnostic method and 'gold standard' is histopathology where the specimen is obtained from the suspected lesion during colposcopy.

The ever increasing financial constraints on the health systems in most countries drives the demand for cheaper and more efficient cervical screening & treatment programs. The World Health Organisation has defined a need for *"prevention programs that are viable in low-resource settings and achieve high screening coverage, offer effective and acceptable test & ensure appropriate treatment of test-positive women"*. This suggests that the ideal solution for many countries is a non-invasive, screening tool that provides an accurate & objective result, which is available immediately and does not require laboratory work and follow-up. It should allow the clinician to diagnose pathology as well as define the diagnostic process within one controlled visit.

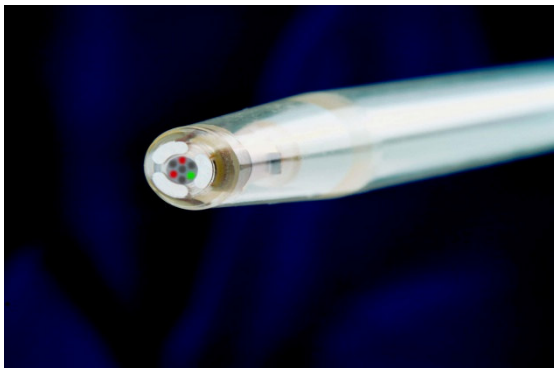
Biophysics is becoming an important field in the area of cervical cancer prevention and diagnosis. These technologies can have an advantage over cytology in terms of a lower percentage of false positive and negative results. One of the most promising technologies for use in cervical cancer prevention programs is TruScreen.

TruScreen is a primary cervical screening tool for the detection of pre-cancerous and cancerous tissue. TruScreen is a novel opto-electronic device, which uses low-level electrical and optical signals to scan the cervix [6]. The response is measured, and computer-based expert system software is then used to classify the tissue response, by comparing the signals with those stored in a computer database representative of the range of cervical tissue types [7].

If the tissue is abnormal, the TruScreen technology will allow the clinician to immediately make management decisions and communicate these decisions to the patient. Therefore it may minimise the labour intensive follow-up and lessen the chance of a patient being lost to recall.

TruScreen comprises a hand piece connected to a compact processing and interpretation console with disposable single use only sheath. The tip of the probe, which is in contact with the cervix, scans the tissue by repetitively pulsing it with low levels of optical and electrical energy. Real-time interpretation of the cervix tissue response is achieved by automatic comparison with a digitally stored catalogue of tissue signatures [8].

The hand piece of is a long, thin, pen-shaped instrument approximately 310 mm in length, which is hand-held by the operator. The section of the probe that enters the vagina is less than 150 mm in length with a tip diameter less than 7mm. The tip is used by the operator to scan the cervix during the TruScreen examination.



The TruScreen delivers multiple electrical pulses of 0.8V for a duration of 100 microseconds. The resulting electrical decay curves are measured and salient features used as an input for the expert system.

The optical measurements operate within the visible and near infrared spectrum. The light emitting diodes (LEDs) have a power output range of 7-130 microwatts. The light intensity is far below that of the colposcope. Four LEDs are used

to emit light at three discrete wavelengths. The reflected and backscattered light is measured and this tissue response forms an additional input for the expert system. The electrical and optical measurement cycles is completed 14 times per second.

A disposable sheath or Single Use Sensor ('SUS') covers the hand piece, and this sheath is discarded after use. This hand piece is part of the TruScreen device.

TruScreen was granted regulatory approval (CE Marking) by the European regulatory authorities in 2002, as a screening instrument for the detection of cervical pre-cancer and cancer.

A confirmation of the value of TruScreen in detecting CIN could have a significant impact on the current cervical cancer rate in Poland by facilitating the wider implementation of prevention programs as well as the earlier detection of cervical intraepithelial neoplasia.

Objective

To evaluate the sensitivity and specificity of TruScreen, a non-invasive device that uses opto-electronic technology to detect cervical intraepithelial neoplasia.

Methods & Materials

A study was conducted on 234 women with normal or abnormal cytology results during the period August 2006 to August 2008 by the Laboratory of Pathophysiology of Uterine Cervix in the Gynaecology & Obstetrics Clinical Hospital of Poznan University of Medical Sciences. A real-time opto-electronic device ('TruScreen') was used to screen for cervical cancer with the results encrypted until the final histopathological diagnosis. The study was approved by the Bioethics Committee of the University and each patient provided a written consent. The patients underwent the following examinations: TruScreen, repeat of cytological examination, HPV DNA test, colposcopy and biopsy/histology.

TruScreen examination

The examination was performed with the use of TruScreen. The device was developed and manufactured by Polartechnics Ltd. Obtaining the result is straightforward, takes only 1-2 minutes and is painless for the patient. A new disposable cover is placed over the biosensor probe and then its tip is moved around the cervix in a pre-defined pattern with guidance from the 'stop-go traffic light' LEDs located on the hand piece. To ensure trial validity the TruScreen device was pre-set to 'encryption mode' whereby the operator was unable to see whether the result was 'normal' or 'abnormal' but the data could be extracted at a later date.

Viral examinations

The material for the presence of oncogenic types of human papilloma virus (DNA HPV HR) was collected with the Cervex Brush from the ectocervix, endocervical canal and the cervical fornicibus. It was then processed using PCR method (Amplicor – Roche).

Colposcopic examination

The examination was performed with the use of a stereoscopic colposcope (Olympus OCS – 500). Each examination was performed with 3-5% acetic acid and Schiller test. For the colposcopic view evaluation, the eight points Reid's scale was used to evaluate the border, whiteness, iodo-negative and vessels of changes. Three points or greater indicated an incorrect result.

Biopsy of suspected lesions

A biopsy was taken from suspected lesions of the cervix with endocervical abrasion. In the case of an unsatisfactory colposcopy, four biopsies and abrasions were performed.

If the results from colposcopy, cytology and TruScreen were all negative then the histopathological examination was not performed. If any of the results were positive then a full histopathological examination was performed, which included biopsy and endocervical curettage. All histopathological examinations were blinded and evaluated by two independent pathologists.

Results

The percentage of abnormal histopathology results in the examined group 63/234 was 27%.

The examined group was divided according to histopathologic results into the following groups as shown below and in Figure 1:

- 27 patients with CIN 1 diagnosis

- 15 patients with CIN 2 diagnosis

- 12 patients with CIN 3 diagnosis

- 6 patients with carcinoma planoepitheliale – CA diagnosis

- 3 patients with adenocarcinoma – ACA diagnosis

- 171 patients with diagnosis lacking neoplasia features.

The sensitivity of the opto-electronic method in the case of histopathologic diagnosis for cervical intraepithelial neoplasia of low grade (CIN 1) was 63%. The method allowed us to identify 17 pathological cases out of the group of 27 women as shown by the final diagnosis in Table 1.

In the case of CIN 2 changes, the sensitivity was higher at 80%. In the population of 15 women with confirmed pathology, we obtained three false negative results as shown in Table 1.

For CIN 3 changes the sensitivity of the opto-electronic method was higher again at 83%. The sensitivity increased to 100% for cases of carcinoma planoepitheliale. The method did not detect the two cases of adenocarcinoma change (Table 1).

Specificity for normal results came to 82%. Sensitivity for intraepithelial changes of low grade (CIN 1) in the area of squamous epithelium was 63%, and for high grade (CIN 2, CIN3, Carcinoma planoepitheliale) it increased to 85% (Table 2).

The test for the presence of oncogenic types of human papilloma virus, DNA HPV HR, detected all three cases of adenocarcinoma in the area of the mucous membrane of cervix.

The specificity of colposcopy for the normal results came to 54%. Sensitivity of colposcopy for intraepithelial changes of low grade (CIN 1) in the area of squamous epithelium was 85% and for high grade (CIN 2, CIN3, Carcinoma planoepitheliale) it increased to 97% (Table 3).

Table 1. Sensitivity of opto-electronic method when compared against histopathologic diagnoses CIN 1, CIN 2, CIN 3, carcinoma planoepitheliale('CA') and adenocarcinoma ('ACA').

	BIOPSY RESULT	TRUSCREEN TRUE POSITIVE	TRUSCREEN FALSE NEGATIVE	SENSITIVITY
CIN1	27	17	10	**63%**
CIN2	15	12	3	**80%**
CIN3	12	10	2	**83%**
CA	6	6	0	**100%**
ACA	3	0	3	**0%**

Table 2. Sensitivity for intraepithelial changes of low grade in the area of squamous epithelium (CIN 1) and for high grade (CIN 2, CIN3, Carcinoma planoepitheliale).

	BIOPSY RESULT	TRUSCREEN TRUE POSITIVE	TRUSCREEN FALSE NEGATIVE	SENSITIVITY
LOW GRADE	27	17	10	**63%**
HIGH GRADE	33	28	5	**85%**

Table 3. Comparison of sensitivity and specificity of opto-electronic method and colposcopy

	OPTOELECTRONIC METHOD	COLPOSCOPY
HIGH GRADE	85%	97%
LOW GRADE	65%	85%
NORMAL	82%	54%

Figure 1. The percentage of normal and abnormal histopathology results in the examined group

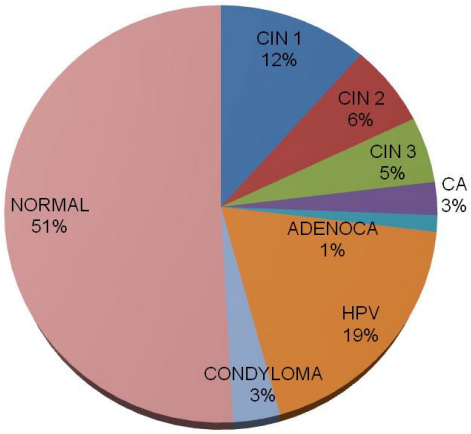


Figure 2. The percentage of normal (n=159) and abnormal (n=75) results of opto-electronic method in the examined group

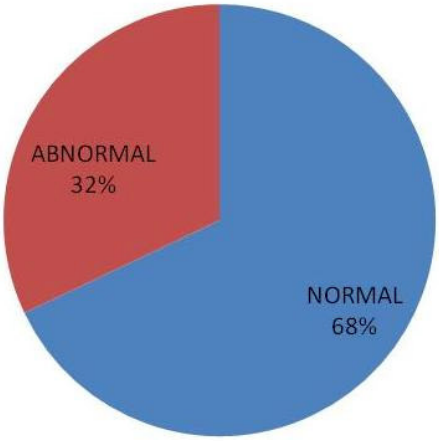
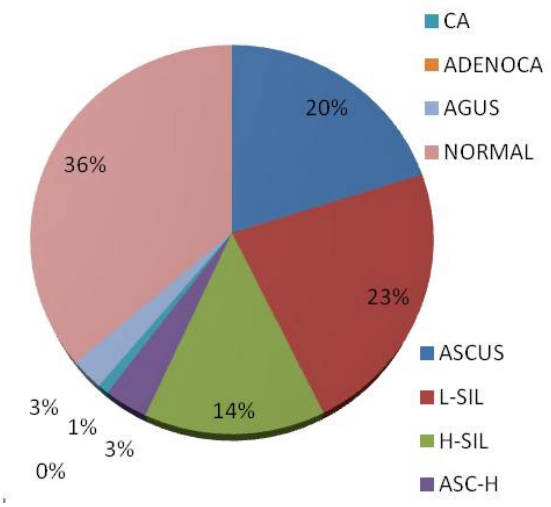


Figure 3. The percentage of normal (n=149) and abnormal (n=85) Pap test in the examined group



Discussion

There is an opportunity with new cervical screening methods to improve sensitivity and specificity rates and identify patients with neoplasia more effectively by using automated processes which eliminate the risk of human error. TruScreen offers the advantage of providing an immediate result thereby reducing the number of patient visits, shortening the screening-treatment timeline and ultimately reducing the cost of cervical cancer prevention programs.

The results obtained by our team confirm the advantage of TruScreen over traditional cytology. In trials previously performed in Australia and the United Kingdom, sensitivity in the area of squamous epithelium was 67% (70% for high grade lesions) whereas the sensitivity using cytology was 43% (69% for high grade lesions)[9].

In 1997 Mould and fellow workers designed a questionnaire to evaluate patient comfort when having Pap and TruScreen tests performed. The questionnaire was completed by 152 patients. Most of the examined population regarded TruScreen as the most comfortable and painless of the two methods. Approximately 98% of patients claimed that the major advantage of the method was the immediate result. None of the women reported any pain during the examination with TruScreen [10].

A key advantage of the TruScreen examination is the possibility of finally eliminating the human error during cervical screening, which historically has often been an issue caused by the

inexperience of the doctor or colposcopist. The technology is objective, inexpensive, offers an immediate result and, most importantly, does not rely on the clinical experience of the person performing the examination. This simplification of the screening programme together with the performance improvement may facilitate the adoption of such innovative technologies to combat cervical cancer [11].

The device is suitable for general screening, however it is not recommended for use if the patient has had a recent cervical procedure, radiotherapy, has excessive bleeding or is currently pregnant.

Similar to cytology and colposcopy the opto-electronic method is unable to identify neoplasia located in the endocervix as demonstrated by the two cases of adenocarcinoma. TruScreen may be able to detect such cases where the disease is also present on the ectocervix, however further data is required to draw reliable conclusions.

Conclusion

The advantage of TruScreen over cytology and colposcopy is its ability to generate an immediate and objective result automatically at the end of the examination and its ease of use.

TruScreen is an effective tool for the detection of cervical neoplastic changes and is potentially an important improvement to the traditional cervical screening process.

References

1. Parkin D, Pisani P, Frelay J. Estimates of the worldwide frequency of 18 major cancers in 1985. Int J Cancer 1993; 54: 594–606.

2. Oncological Centre – Maria Skłodowska-Curie Cancer Centre & Institute of Oncology. *Polish National Cancer Registry:* 2008-02-18. http://epid.coi.waw.pl/krn/.

3. Kędzia W, Schmidt M, Poręba, [et al.]. Diagnosis of papilloma viruses in cervical cancer in 414 women from Wielkopolska region by the immunohistochemical assessment. Ginekol Pol. 2005 Jul;76(7):548-54.

4. Papanicolau GN: A new procedure for the staining of vaginal smears. Science 1942; 95: 438 – 439.

5. Gene S, Mc Neeley Jr. New cervical cancer screening techniques. Am J Obstet Gynecol 2003; Vol 189 No 4.

6. Coppleson M, Reid BL, Skladnev VN, Dalrymple JC. An electronic approach to the detection of pre-cancer and cancer of the uterine cervix: a preliminary evaluation of Polarprobe. Int J Gynecol Cancer 1994; 4: 79—83.

7. S C Quek,*MRCOG, T Mould,*MRCOG, K Canfell,**BE (Hons), A Singer,***PhD, FRCOG, V Skladnev,†BSc, ME, M Coppleson,‡MD, The Polarprobe—Emerging Technology for Cervical Cancer Screening FRACOG,FRCOG Cervical Screening: September 1998, Vol. 27 No. 5.

8. Coppleson M, Canfell K, Skladnev V. The Polarprobe — An instantaneous optoelectronic approach to cervical screening. CME J Gynecol Oncol 2000; 5: 31—8.

9. Singer A, Coppleson M, Canfell K *et al.* A real time optoelectronic device as an adjunct to the Pap smear for cervical screening: a multicenter evaluation. *International Journal of Gynecological Cancer 2003;* 13: 804–811.

10. Mould TAJ, Quek SC, Lovegrove J, Gallivan S, Singer A. The acceptability of cytological screening for cervical cancer compared to a new electronic screening device - the Polarprobe, Proceedings of the EUROGIN Third International Congress; 1997 March 24-27; Paris. Paris: European Research Organization on Genital Infection and Neoplasia, 1997.

11. Pruski D, Kedzia W, Przybylski M, [et al.]. Assesment of real optoelectronic method in the detection of cervical intraepithelial neoplasia. Ginekol Pol. 2008 May; 79(5):342-346.