

Research Article

Human Papilloma Virus Self-testing as an Alternative Method for Cervical Cancer Screening

Uji Pemeriksaan Mandiri Human Papilloma Virus sebagai Metode Alternatif untuk Skrining Kanker Serviks

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Abstract

Objective: To determine the level of acceptance of self Human Papilloma Virus (HPV) examination and to compare the level of sensitivity and specificity of self HPV examination with Fluid Based Cytology on precancerous cervical lesion and cervical cancer.

Methods: The analytical method used in this research was cross sectional with purposive sampling. This study is conducted at Wahidin Sudirohusodo Hospital and its affiliation from October 2014 to May 2015 with 101 subjects. The data measurement used self HPV examination tool and fluid based cytology kit. The data collected through questionnaires before and after the examination. The laboratory examination was carried out using the way of HPV Genotyping primary system (MY09/11) method WI LTS-06, which is able to detect 35 types of HPV viruses.

Results: A total of 101 subjects were involved in this study. The subjects were divided into two groups: the abnormal and normal group (n = 50/51). The acceptance level of self HPV examination was 62.37% (n = 63/101). Majority of subjects (88.21%) were ready to repeat the same examination in the future. The level of sensitivity and specificity for self HPV were (56% (95%CI (41.25 - 70.01%)) vs 98% (95%CI (89.55 - 99.95%))), $p < 0.000001$, while the level of sensitivity and specificity for fluid based cytology were (40% (95%CI (26.41 - 54.82%)) vs 98% (95%CI (89.35 - 99.95%))), $p = 0.000002$.

Conclusion: HPV self-testing is very potential to be used as an alternative method for cervical cancer screening.

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Keywords: cervical cancer, cervical cancer screening, human papilloma virus, sensitivity, specificity

Abstrak

Tujuan: Mengetahui tingkat penerimaan pemeriksaan HPV Mandiri dan membandingkan tingkat sensitivitas dan spesifisitas pemeriksaan mandiri HPV dengan sitologi berbasis cairan, pada lesi pre kanker derajat tinggi dan kanker serviks.

Metode: Penelitian merupakan analitik cross sectional secara purposive sampling, single center di RS Wahidin Sudirohusodo dan Afiliasinya pada Bulan Oktober 2014-Mei 2015 berjumlah 101 responden. Pengukuran data menggunakan alat pemeriksaan HPV mandiri serta kit sitologi berbasis cairan. Pengumpulan data menggunakan kuesioner sebelum dan setelah melakukan pemeriksaan. Pemeriksaan laboratorium dilakukan dengan menggunakan cara HPV Genotyping sistem primer (MY09/11) metode WI LTS-06, mampu mendeteksi 35 tipe virus HPV.

Hasil: Keseluruhan responden berjumlah 101 orang, terbagi menjadi kelompok abnormal/normal (n=50/51). Tingkat penerimaan pemeriksaan HPV mandiri sebesar 62,37% (n=63/101). Sebagian besar responden (88,21%) bersedia mengulangi pemeriksaan serupa di masa mendatang. Tingkat sensitivitas dan spesifisitas yang didapatkan untuk HPV Mandiri (56% (95%CI (41,26 - 70,01%)) vs 98% (95%CI (89,55 - 99,95%))), $p < 0,000001$, sedangkan tingkat sensitivitas dan spesifisitas untuk sitologi berbasis cairan (40% (95%CI (26,41 - 54,82%)) vs 98% (95%CI (89,35 - 99,95%))), $p = 0,000002$.

Kesimpulan: Pemeriksaan HPV mandiri ini sangat potensial untuk dijadikan metode pemeriksaan alternatif untuk pemeriksaan skrining kanker serviks.

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Kata kunci: human papilloma virus, kanker serviks, sensitivitas, skrining kanker serviks, spesifisitas

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INTRODUCTION

Cervical cancer is the third most common cancer in the world. It is the only cancer that can be identified early thus making it able to be prevented. Cervical cancer is the fourth cause of death due to cancer in the world. In 2008, it estimated that 530,232 women were diagnosed with cervical cancer worldwide and 275,000 of them died.¹ The

majority of cervical cancer (85%) occurred in developing countries, including Indonesia. The prevalence of women with cervical cancer in Indonesia is fairly high; 40-45 new cases were found daily with number of deaths reached 20-25 people while women at risk of cervical cancer was 48 millions.² Data from health department demonstrated that regions with the highest

number of cervical and breast cancer were Makassar, district of Gowa, Wajo, Bone, and North Luwu. In 2009, it was found that 97 cervical cancer cases was in hospital and 177 cases was in primary health care.³

Human Papilloma Virus (HPV) infection is a significant event for the occurrence of cervical cancer. It is estimated that 50-80% of sexually active women will be infected by HPV in their life and approximately 80% will be infection-free in 2 years and will not cause cancer. Persistent HPV infection is one of the predispositions of dysplasia and cervical cancer. The course of HPV infection developing into cervical cancer may take up to 10-20 years. HPV infection process which later becomes precancerous is mostly asymptomatic.⁴⁻⁶

Cytology examination has become cervical cancer screening standard for more than 50 years. This examination evaluates cell morphology abnormalities from cervical epithelial specimen.⁷ This examination often results in false negative due to inadequate sample and poor procedure standard. Liquid-based examination may improve this disadvantage. The high false negative result of this examination leads to reevaluation in the interval period of time.⁸⁻¹⁰

HPV DNA examination has the advantage of very high negative predictive value, even towards adenocarcinoma precursor.¹¹ Human papilloma virus has a high sensitivity in detecting high degree precancer lesion and has high positive predictive value.¹² The effectiveness of this cervical cancer screening programme may be increased by the use of HPV self examination. According to a study in Netherlands, an HPV self examination tool, Evalyn brush, has a sensitivity and specificity of 81.5% and 66.4%, respectively.¹³ Efforts on early detection in high risk women are organized into a screening programme or an opportunistic screening. Management and early detection of precancer lesions are 'see and treat' programme and histopathology-based-diagnosis.

A good screening examination should be accurate, highly reproducible, cheap, easy to use, easy to monitor, highly accepted, and safe.¹⁴

Examination to be used should have been through long period of evaluation and tested in real life. Clinical application of the proposed HPV DNA examination may be as single primary screening

instrument or combination with cytology and monitoring women with precancer lesion who has received treatment in order to predict the success of therapy.

High sensitivity means that HPV examination also has high negative predictive value. Negative result of examination may prolong the need to repeat the cervical cancer screening up to 5-8 years.¹³ Cytologic examination is often constrained by the lack of infrastructure, particularly in developing countries. Alliance for cervical cancer prevention seeks for alternatives other than cytologic examination, such as acetic acid visual inspection and HPV DNA test. According to a study conducted by Qiao et al, HPV DNA examination and liquid based cytology had higher sensitivities than acetic acid visual inspection.¹²

Self examination of vaginal or cervical specimen sampling has developed in recent years. Self examination derived from vaginal specimen has the inability of the specimen for cytologic examination. However, vaginal specimens are very suitable for HPV examination sample because the result do not significantly differ from those of liquid based cytology or cervical specimen. In self examination, women would collected their own specimen sample using several tools including brush, tampon, and vagina rinse instrument. Some research showed that self vaginal specimen sampling was sufficient for laboratory analysis, both delivered through liquid or dry media.¹⁵

The ability to detect high risk HPV from self HPV examination or liquid based cytology examination shows no significant differences. This explains that there is no difference in the ability to detect HPV between self examination and examination by paramedics. One advantage of self examination is it does not need paramedics to be performed and ensure privacy. Based on user experiences, this examination is considered easy to use. As cervical cancer screening tool, this tool will improve the outreach of screening on women who has not or rarely checked. Most cervical cancer are found in women who never or rarely check.¹⁶⁻¹⁸ We aimed to know the level of acceptance of HPV self examination and compare the sensitivity and specificity of HPV self examination and liquid based examination on high degree pre cancer lesion and cervical cancer.

METHODS

A cross sectional study design was used. This study was conducted at several teaching hospitals affiliated with the department of Obstetrics and Gynecology, Faculty of Medicine, Hasanuddin University, Makassar from October 2014 until May 2015.

The subjects were women who experienced spontaneous abortion and normal term delivery in several teaching hospitals of Obstetric and Gynecology Department Universitas Hasanuddin Faculty of Medicine in Makassar. Samples were obtained from blood samples of the mothers who met the inclusion criteria.

Method of collecting data

Samples were selected based on an assessment of researchers that met the eligible inclusion criteria with purposive sampling method between 2 group. Data were obtained by self HPV examination tool, liquid based cytology kit, and before and after examination questionnaire. Laboratory test was done by QI LTS-06 method of primary system (MY09/11) HPV Genotyping which was able to detect 35 types of HPV.

Data analysis

Data were analyzed using SPSS. Diagnostic 2x2 table test is used to determine the capability of each tool.

RESULTS

A total of 101 subjects were involved in this study. The subjects were divided into abnormal/normal group (n=50/51). The most age group percentage was the age group of 40-49 year, 40.58% (n=41/101). The respondent was mostly at the education level of high school/on the equal degree, 54.45% (n=50/101). Majority of the subjects were housewives, 73.26% (n=74/101). There were 23 subjects who work as private or civil employees. Most of the subjects was multiparous, 88.12% (n=89/101), did not use contraception, 57.42% (n=27/101). Majority of respondents complained of leucorrhoea, 45.54% (n=46/101), 56.5% was abnormal and 43.5% was normal. Majority of the normal population had no complain (n=24/51.47%) before the examination, whereas majority of the abnormal group complained of leucorrhoea

(26/50.52%). Majority of the respondents did not know about cervical cancer screening, 79.2% (n=80/101). The major result of Pap smear test of the normal and abnormal group were follicular cervicitis [(n=34/51, 66.67%) and (23/50, 46%), respectively].

Acceptance rate of self HPV examination was 62.37% (n=63/101). As many as 37.62% (n=38/101) of the respondent suggested the examination was difficult/could not do the examination by her-self because it was difficult to recognize or to insert the instrument (n=27/38, 71.05%). 92 subjects (92/101, 91.01%) did not find difficulties to perform the examination, 54.3% of which was abnormal and 45.7% was normal. However there was 5 subjects who reported pain, 1 subject reported bleeding, 2 subjects failed to used the tool. Of 89 subjects (n = 89/101), 88.12% would repeat HPV testing self-sampling and 12 subjects (n = 12/101) 11.8% would not repeat this test. From those who were willing to repeat the examination in the future because it was easy to use (n = 75/101) 84.23%.

Half of our subjects were highly educated. 64% stated that this tool were ease to use. 84 subjects did not know anything about cancer screening, 66.2% managed to use this tool easily.

The sensitivity and specificity were obtained for HPV Self sample collection test is 56% (95% CI (41.25 to 70.01%)) vs 98% (95% CI (89.55 to 99.95%)), with positive predictive value of 68, 25%, 95% CI (22.75 to 96.43%); 96.73% negative predictive value, 95% CI (20.9 to 99.28%); Accuracy of 0.78, 95% CI (0.68 to 0.85); Compliance Test Kappa 0.543, 95% CI (0.365 to 0.72); $p < 0.000001$.

While the sensitivity and specificity for liquid-based cytology is 40% (95% CI (26.41 to 54.82%)) vs 98% (95% CI (89.35 to 99.95%)); Positive predictive value of 60%, 95% CI (13.54 to 93.35%); 95.6% negative predictive value, 95% CI (89.32 to 98.74%); Accuracy 0.69, 95% CI (0.59 to 0.78); test the suitability of Kappa = 0.38, 95% CI (0.22 to 0.54); $p = 0.000002$.

The results of diagnostic test liquid-based cytology (LBC) in cervical cancer and precancerous lesions of the 16 samples were defined as abnormal by 76.19% who tested positive on HPV testing independently (HPV-SSC) and 23.8% expressed negative. While 79 normal results showed that

83.54% had negative on HPV testing independently (HPV-SSC) and 16.45% tested positive. The results of the suitability test results of both tests Kappa value = 0.524 95% CI (0.28 to .768).

All HPV virus detected in the abnormal group were the high-risk HPV types, such as type 16, 18, 31, 33, 45, 51, 53. In the normal group, we obtained one sample who was detected as low risk HPV type.

DISCUSSION

This study evaluated the use of HPV self sample collection test in Makassar as a new diagnostic tool. Our evaluation was done by comparing the histopathology, thus we may determine the ability of each new diagnostic screening tool. The Acceptance rate was fairly, good (62.37%). This finding is consistent with several studies (73%¹⁷; 87%¹⁸; 77.1%¹⁹).

Approximately 91.01% of the subjects did not have difficulties in doing the examination and 88.12% of the subjects were willing to repeat a similar examination in the future. Some parts of the tools fell apart and left in the vagina were the short comings of the tool integrity and expected to have an impact on the design and improvement of educational plan using the tool. Subjects who admitted to have difficulties to perform self-HPV testing said that there was no denial of the usage of these tools which we were considered suitable with our society culture or religion. HPV testing self-denial rate was found relatively high in all age groups (30 to 58.8%), and employment (25 to 41.9%). This result is understandable because HPV testing is a new independent examination. We may increase the acceptance rate by considering on education and make this as a routine examination.

Cytology has become gold standard examination for cervical cancer screening more than last 50 years. This examination evaluates the presence of morphological abnormalities from epithelial cervical specimens. Conventional cytological examination has a sensitivity of 30-87% and specificity of 86-100% for detecting high-grade precancerous lesions. Smear results are often unsatisfactory with high false negative value. Later, liquid-based cytology was developed. Its sensitivity and specificity are 80% and 98%. The number of samples found unsatisfactory on LBC decreased 11.45%.²⁰ Several studies found the level of

sensitivity of liquid-based cytology 13% higher than the conventional Pap smear test. These results suggested that liquid-based cytology had a higher level of sensitivity and specificity levels lower than Pap smear test.²⁰ On the use of routine screening cytological examination only have a level of sensitivity ranged from 47-62% and a specificity ranged from 60-95%. A meta-analysis of the results revealed similar results to those obtained in this study, the rate reaches 97-100% specificity and sensitivity is only 29-56%.²¹ However, these results still show a sensitivity level much lower than the results of research in general. The new technology for cervical cancer (NTCC) and Netherland Thin Prep versus Conventional Cytology (NETHCON) indicates that there is no difference in the detection capability CIN2 / 3 on both methods.²²

The level of sensitivity of HPV DNA tests for the detection of CIN2 + was better than cytology (94% vs 65%).^{21,23} In this study, the sensitivity of self-HPV testing is higher than liquid-based cytology with a difference of 16%, the specificity found similar on both tests. A study in China demonstrated that self-HPV testing had a sensitivity of 86.2% and a specificity of 80.7% while liquid-based cytology had lower sensitivity in detecting CIN2.²⁴ High risk HPV DNA can be identified 99.7% of cervical cancers and 95% of high-grade precancerous lesions.^{25,26} The results of this study showed different results that only high risk HPV types identified (n = 16/32) 50% of cervical cancers and (n = 6/19) 31.57% of high-grade precancerous lesions. All types of HPV detected in the abnormal group were high risk HPV types. HPV DNA PCR method used in this study was GMP09 / 11. The use of PCR method has been shown to have higher sensitivity for detecting high-risk HPV compared to HC2. According to the results of one RCT, amplification method GPM09 / 11 had very low sensitivity level, which accounted for 49%.²⁶ Therefore, our decision to use similar method could potentially cause low levels of sensitivity.

The usage of certain fixation media and specimen processing of cells contained in the media might influence our results. This might be due to the lack of uniformity filtration process and the possibility of not drawing a specimen of cells in the remaining media.²⁰ Methods of sample collection for HPV testing can be done through swab, brush, tampon or lavage. The various methods mentioned

showed 78-81% sensitivity rate for the swab or brush, 67-94% for tampons, and <81% for lavage.²⁷ The collection method used in this study is brush, and it's likely affect the validity of the test. The prevalence of high-risk HPV 62.3% (95% CI: 53.7 to 70.2) was detected in the examination without media fixation and 56.2% (95% CI: 47.6 to 64.4) in the use of media fixation.²⁸ Sample collection without using fixation was likely to affect the results of our study.

Population and national study which evaluate the level of acceptance, economic impact, the accuracy and precision tools, awareness, adherence screening and suitability level of HPV examination results need to be conducted before using this HPV testing as a screening method in institutions.²⁷ This study has not been able to ascertain with certainty the validity of the examination, however, the examination is potential to be used as an alternative method of screening.

CONCLUSIONS

Cervical cancer has a long course of the disease, yet it can be prevented. Self-testing of HPV the latest potential modality for cervical cancer screening that corresponds to the cultural, economic, human resources and geographics in Indonesia.

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