Research Article

# Sensitivity and Specificity of the Self-Administered HPV Testing in Detecting Precancerous Conditions of the Cervix and Cervical Cancer

## Sensitivitas dan Spesifisitas Pemeriksaan Mandiri dalam Mendeteksi Lesi Prakanker dan Kanker Serviks

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## Abstract

**Objective**: To determine the sensitivity and specificity of self-administered Human Papilloma virus (HPV) test in detecting pre-cancerous lesions and high degree cervical cancer.

**Methods**: A case control study design was used in this study. This study was conducted at Dr. Wahidin Sudirohusodo Hospital and its affiliate hospitals during the period of October 2014 to May 2015. Measurement data using HPV self test grant from the Dutch School Netherlands, Evalyn Brush. Collecting data used questionnaires before and after doing HPV self test. Laboratory tests are carried out in Kalbe Genomic using HPV Genotyping capable detect 35 types of the HPV virus.

**Results**: A total of 101 subjects were involved in this study. The subjects were divided into two groups, the case and the controls (n = 50/51). Level of sensitivity and specificity were obtained for HPV self test (56% vs 98%). The level of acceptance of new tests by 62.37% (63 out of 101 respondents) of them admitted that the new test is simple / easy enough to do. The acuracy rate of diagnostic test of this examination is 79%.

**Conclusion**: Self-administered HPV test could be used as an alternative or primary screening for cervical cancer.

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**Keywords**: HPV, self, specificity, the sensitivity

## Abstrak

**Tujuan**: Mengetahui nilai sensitivitas dan spesifisitas pemeriksaan mandiri human papilloma virus (HPV) dalam mendeteksi lesi pre kanker derajat tinggi dan kanker serviks.

**Metode**: Merupakan penelitian analitik case control, single center di RS Dr. Wahidin Sudirohusodo dan Afiliasinya pada bulan Oktober 2014-Mei 2015. Pengumpulan data menggunakan kuesioner sebelum dan setelah melakukan pemeriksaan HPV mandiri. Pemeriksaan laboratorium dilakukan di Kalbe Genomic dengan menggunakan cara HPV Genotyping yang mampu mendeteksi 35 tipe virus HPV.

**Hasil**: Penelitian menunjukkan keseluruhan responden berjumlah 101 orang, terbagi menjadi kelompok sakit dan sehat (n=50/51). Tingkat sensitivitas dan spesifisitas yang didapatkan untuk HPV Mandiri (56% vs 98%). Tingkat penerimaan pemeriksaan baru sebesar 62,37% (63 dari 101 responden) di antaranya mengakui bahwa pemeriksaan baru ini mudah/cukup mudah untuk dilakukan. Tingkat akurasi uji diagnosis pemeriksaan ini didapatkan sebesar 79%.

**Kesimpulan**: Pemeriksaan HPV mandiri dapat digunakan sebagai alat pemeriksaan alternatif atau skrining primer pada kanker serviks.

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**Kata kunci**: HPV, mandiri, sensitivitas, spesifisitas

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## INTRODUCTION

Cervical cancer is the third largest cancer in the world, and fortunately, it is the only cancer that could be detected early. Thus, we can prevent this cancer from progressing. It is the third most frequent type of cancer and declared as the fourth most common cause of deaths from cancer in women world wide. In 2008, it is estimated that approximately 530,232 women were diagnosed with cancer, and 275,008 of them died.[1] The majority of cervical cancers (85%) occur in developing countries, including Indonesia. The prevalence of women with cervical cancer in Indonesia is quite high. Every day, 40-45 new cases are identified, with the number of deaths reached 20-25 people. In addition, the number of women at the highest risk states is 48 million people.[2] The Department of Health in South Sulawesi reported that the highest incidence of breast cancer and cervical cancer patients were observed in Makassar, Gowa, Wajo, Bone and Luwu Utara. In 2009, 97 cases of cervical cancer were detected in hospitals and 177 in primary health care centers in South Sulawesi.

Although cervical cancer is frequently found in women above 50 years, it is more often found in reproductive aged women in developing countries. In several countries where good screening program do not exist, cervical cancer patients often come lately with an advanced stage, and most of the patients can not be cured.[3] HPV (Human Papillomavirus) infection of the cervix is an important event for the occurrence of cervical cancer. It is estimated that 50-80% of sexually active women will become infected with HPV in their lives. The existence of persistent HPV infection is one of the predisposing factors of dysplasia and cervical cancer. HPV 16 and 18 are the main causes of this cancer and found in 70% of cases of cervical cancer in the world. The sequential plot from being infected with HPV to having cervical cancer takes a long time, which is approximately 10 to 20 years. However, HPV infection is often asymptomatic that the majority of the patients do not realize that they are being infected. The infection they may progress to pre-cancerous stage, which is also frequently asymptomatic. It begin with the change of normal cells into pre-cancerous cells and then into cancer cells (dysplasia).[4]

Visual inspection with acetate (VIA) or with Lugol's iodine (VILI) is an alternative of the cytology and HPV laboratory tests. These examinations use visual observation without magnification to detect pre-cancerous lesions on the cervical columnar squamous junction. According to various studies, both test had a sensitivity of 55-85%, and the specificity for each test was 49-86% for VIA and 73-93% for VILI. These tests are suitable for developing countries, since both of these test do not require complex laboratory equipments. Moreover, the time needed to train health workers to conduct these tests is relatively short. This examination is used as an initial screening method for cervical cancer due to its low cost. A cervical cancer prevention program named 'see and treat', a one day sevice where a woman would undergo VIA or VILI test followed with cryotherapy, has been proven to effectively reduce the incidence of high-grade precancerous lesions and cervical cancer in developing countries.[5]

Cytology is often constrained by the powerlessness of sufficient infrastructure, especially in developing countries. Thus, there are only few women who can get access to screening or initial treatment programs. Alliance for Cervical Cancer Prevention has seeked some alternatives such as cytology, VIA, and HPV DNA test.[3]

The high level of sensitivity of HPV DNA tests may lead to high negative predictive value, even against the precursor of adenocarcinoma, which is often not detected by cytology.[6] HPV test has a higher level of sensitivity in detecting high-grade precancerous lesions, and the positive predictive value is higher due to high incidence of cervical cancer in developing countries. The effectiveness of cervical cancer screening programs can be increased by using self-administered HPV test. Self-administered HPV test is globally acceptable and has been shown to increase patients' obedience and rate of screening coverage despite existence of overcoming sociocultural barriers in developing countries.[7] This study is aimed to determine the sensitivity and specificity of self-administered HPV test indetecting the high degree precancerous lesions and cervical cancer, as well as the acceptance of self-administered HPV test on high degree precancerous lesions and cervical cancer. We hope this test could an alternative screening tool for detecting high degree precancerous lesions and cervical cancer.

## METHODS

A case control study design was used. Samples were taken from October 2014 until May 2015 at several teaching hospitals where were connected to Department of Obstetrics and Gynecology, Faculty of Medicine Universitas Hasanuddin, Makassar, such as RSUP Dr. Wahidin Sudirohusodo and other network hospitals.

Subjects were sexually active women aged 20-55 years who had undergone Pap smear tests at the laboratory of Anatomic Pathology and several teaching hospitals in Makassar. The inclusion criteria were sexually women aged 20-55 years, sexually active, normal Pap smear results in the last 3 months, the abnormal results of Pap smear and or biopsy in the last 3 months. While the exclusion criteria are recently menstruation within 1 week, were using drugs in the form of ovules, are pregnant, have undergone radiation to the pelvic area, had undergone surgical removal of the uterus. This study was approved by the Ethics Committee for Biomedical Research In Humans at the Faculty of Medicine Universitas Hasanuddin, Makassar.

The data were collected by means of a questionnaire. Subjects were asked to fill out a questionnaire. They were accompanied by a research assistant. Subjects were asked regarding his willingness to participate in the study. If they agreed to be participants, we would give them explanations both by verbal and written through leaflets about the self-administered HPV test. After giving a brief explanation and informed consent, we asked the subjects to wash their hands and go to the cubicles. Subsequently, the subjects would perform the self-administerd HPV test. Specimens derived from the tests were incorporated into a sterile tube containing solution of 1 ml Phosphate Buffered Saline (PBS) and vortexed during 3x15 seconds. Consequently, 0.5ml of each sample was used for the extraction of nucleic acids and the remaining would be stored in a freezer at a freezing rate of -20° C. Extraction, detection and genotyping of HPV were performed using MY09/11 PCRat the Kalbe Genomic laboratory and conducted according to the standard protocol. The assay was done by using automated DNA extraction, DNA amplification using PCR, and detection of high risk HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, and 68) and low risk HPV genotypes (6, 11, 42, 43, 44, and 81). The entire negative results that were found rid of the presence of types of HPV above at a level of 50 IU.[8]

The total subjects in this study were 91 patients. Of these, 50 were categorized as abnormal, while the others were categorized as normal. Data analysis using SPSS 18, 2x2 tables can be used to assess the sensitivity and specificity of HPV Self test and then we concluded the hypothesis test using 2 times trial for the interpretation of diagnostic test results. P value < 0.05 was considered significantly available.

## RESULTS

The majority of the subjects were in the 40-49 age group, had graduated from high school, worked as housewives, were multiparous, did not use contraceptive methods, complained of vaginal discharge, did not know about cancer screening. (Table 1). According to biopsy results, the majority of the abnormal group had perform CIN II in the amount of 85.7%. In addition, based on pap smear result, the majority of the normal group has perform Follicular servisitis as many as 24 respondents (100%).

**Table 1.**  Characteristics of the Subjects

| Characteristics | Abnormal (n=50) | | Normal (n=51) | | TOTAL (n=101) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| **Age (year)** | | | | | | |
| 20-29 | 3 | 17.6 | 14 | 82.4 | 17 | 100 |
| 30-39 | 15 | 45.5 | 18 | 54.5 | 33 | 100 |
| 40-49 | 22 | 53.7 | 19 | 46.3 | 41 | 100 |
| > 50 | 10 | 100 | 0 | 0 | 10 | 100 |
| **Educational status** | | | | | | |
| No educational/primary | 2 | 50.0 | 2 | 50.0 | 4 | 100 |
| Primary school graduates | 2 | 33.3 | 4 | 66.7 | 6 | 100 |
| Junior high school graduates | 6 | 46.2 | 7 | 53.8 | 13 | 100 |
| Senior high school graduates | 20 | 40.0 | 30 | 60.0 | 50 | 100 |
| Scholars | 20 | 71.4 | 8 | 28.6 | 28 | 100 |
| **Occupation** | | | | | | |
| Company employees/civil servants | 18 | 78.3 | 5 | 21.7 | 23 | 100 |
| Self employer | 2 | 50.0 | 2 | 50.0 | 4 | 100 |
| Housewife | 30 | 40.5 | 44 | 59.9 | 74 | 100 |
| **Parity** | | | | | | |
| Nulliparous | 9 | 75.0 | 3 | 25.0 | 12 | 100 |
| Multiparous | 41 | 46.1 | 48 | 53.9 | 89 | 100 |

| Characteristics | Abnormal (n=50) | | Normal (n=51) | | TOTAL (n=101) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| **History of contraception** | | | | | | |
| Never use | 31 | 53.4 | 27 | 46.6 | 58 | 100 |
| Condom | 2 | 50.0 | 2 | 50.0 | 4 | 100 |
| Pil | 6 | 60.0 | 4 | 40.0 | 10 | 100 |
| Injection | 10 | 37.0 | 17 | 63.0 | 27 | 100 |
| IUD | 0 | 0 | 1 | 100 | 1 | 100 |
| Tubectomy | 1 | 100 | 0 | 0 | 1 | 100 |
| **Symptoms** | | | | | | |
| No symptoms | 0 | 0 | 24 | 100 | 24 | 100 |
| Vaginal discharge | 26 | 56.5 | 20 | 43.5 | 46 | 100 |
| Abnormal bleeding | 14 | 93.3 | 2 | 6.7 | 15 | 100 |
| Postcoital bleeding | 9 | 75.0 | 3 | 25.0 | 12 | 100 |
| Lower abdominal pain | 1 | 50.0 | 1 | 50.0 | 2 | 100 |
| Pruritus | 0 | 0 | 2 | 100 | 2 | 100 |
| **Knowledge about Screening** | | | | | | |
| Do not know | 43 | 53.8 | 37 | 46.2 | 80 | 100 |
| Conventional Pap Smear | 7 | 33.3 | 14 | 66.7 | 21 | 100 |
| **Histopathological results** | | | | | | |
| **Biopsy** | | | | | | |
| CIN II | 12 | 85.7 | 2 | 14.3 | 14 | 100 |
| CIN III | 7 | 100 | 0 | 0 | 7 | 100 |
| Adenocarcinoma | 8 | 100 | 0 | 0 | 8 | 100 |
| Squamous Cell Carcinoma | 23 | 1000 | 0 | 0 | 23 | 100 |
| **Pap Smear** | | | | | | |
| Normal | 0 | 0 | 10 | 100 | 10 | 100 |
| Follicular cervicitis | 0 | 0 | 24 | 100 | 24 | 100 |
| Bacterial Vaginosis | 0 | 0 | 1 | 100 | 1 | 100 |
| Candidiasis | 0 | 0 | 6 | 100 | 6 | 100 |
| Gardanella infection | 0 | 0 | 7 | 100 | 7 | 100 |

## Distribution of the Subjects

63 subjects felt easy to perform self-administered HPV test (60.3% in abnormal group and 39.7% of normal group). 92 subject did not experience any problems or symptoms during or following the self-administered HPV test (54.3% in abnormal group and 45.7% in normal), however, there were 5 subject who experienced pain. One subject reported bleeding and 2 subejcts' devices were put off spontaneously. Approximately 89 subjects still wanted to repeat self-administered HPV test due to the ease of test (56% of abnormal group and 44% of normal). 12 subjects did not want to repeat self-administered HPV test due to pain and no specific reason (100% of the normal group). There were 63 subjects that liked the self-administered HPV test ( 60.3% of abnormal group and 39.7% of normal), and there were 10 subjects prefer the Pap smear test (20% of abnormal group and 80% of normal).

**Table 2.**  Distribution of Subject Regarding Self-administered HPV Test Acceptability Based On Patients' Characteristic.

| Subjects'acceptability of the self-administered HPV test | Easy (n=63) | | Difficult (n=38) | | TOTAL (n=101) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| **Age (years)** | | | | | | |
| 20-29 | 7 | 41.2 | 10 | 58.8 | 17 | 100 |
| 30-39 | 22 | 66.7 | 11 | 33.3 | 33 | 100 |
| 40-49 | 27 | 65.9 | 14 | 34.1 | 41 | 100 |
| > 50 | 7 | 70.0 | 3 | 30.0 | 10 | 100 |
| **Educational status** | | | | | | |
| No educational/primary | 0 | 0 | 4 | 100 | 4 | 100 |
| Primary school graduates | 2 | 33.3 | 4 | 66.7 | 6 | 100 |
| Junior high school graduates | 11 | 84.6 | 2 | 15.4 | 13 | 100 |
| Senior high school graduates | 32 | 64.0 | 18 | 36.0 | 50 | 100 |
| Scholars | 18 | 64.3 | 10 | 35.7 | 28 | 100 |
| **Occupation** | | | | | | |
| Company employees/civil servants | 17 | 73.9 | 6 | 26.1 | 23 | 100 |
| Self employer | 3 | 75.0 | 1 | 25.0 | 3 | 100 |
| Housewife | 43 | 58.2 | 31 | 41.9 | 74 | 100 |
| **Parity** | | | | | | |
| Nulliparous | 5 | 41.7 | 7 | 58.3 | 12 | 100 |
| Multiparous | 58 | 65.2 | 31 | 34.8 | 89 | 100 |
| **History of contraception** | | | | | | |
| No use | 33 | 56.9 | 25 | 43.1 | 58 | 100 |
| Condom | 3 | 75.0 | 1 | 25.0 | 4 | 100 |
| Pil | 8 | 80.0 | 2 | 20.0 | 10 | 100 |
| Injection | 17 | 63.0 | 10 | 37.0 | 27 | 100 |
| IUD | 1 | 100 | 0 | 0 | 1 | 100 |
| Tubectomy | 1 | 100 | 0 | 0 | 1 | 100 |
| **Symptoms** | | | | | | |
| No symptoms | 17 | 70.8 | 7 | 29.2 | 24 | 100 |
| Vaginal discharge/Fluor albus | 23 | 50.0 | 23 | 50.0 | 46 | 100 |
| Abnormal bleeding | 15 | 100 | 0 | 0 | 15 | 100 |
| Postcoital bleeding | 6 | 50.0 | 6 | 50.0 | 12 | 100 |
| Lower abdominal pain | 1 | 50.0 | 1 | 50.0 | 2 | 100 |
| Pruritus | 1 | 50.0 | 2 | 50.0 | 2 | 100 |
| **Knowledge about Screening** | | | | | | |
| Do not know | 53 | 66.2 | 27 | 33.8 | 80 | 100 |
| Conventional Pap Smear | 10 | 47.6 | 11 | 52.4 | 21 | 100 |

**Table 3.**  The Result of Self-administered HPV Test as a Diagnostic Test in Identifying Pre-cancerous Lesion and Cervical Cancer.

| Self-administered HPV test | Histopathological Results | | | | | | p Value |
|---|---|---|---|---|---|---|---|
| | Abnormal | | Normal | | Total | | |
| | N | % | N | % | N | % | |
| Abnormal | 28 | 96.6 | 1 | 3.4 | 29 | 100 | 0.000 |
| Normal | 22 | 30.6 | 50 | 69.4 | 72 | 100 | |
| **TOTAL** | 50 | 50 | 51 | 50 | 101 | 100 | |

The self-administered HPV test for detecting high degree of precancerous lesions and cervical cancer had a sensitivity of 56% and a specificity of 98% (Table 3).

## DISCUSSION

Self-administered HPV has a sensitivity and specificity of 56% and 98%. In our study, the ability of self-administered HPV test to ensure positive results is up to 96%. However, using this test for screening is not recommended, because screening requires a high negative predictive value.

Previous researchers set an age limit of 20 years based on the pathogenesis of the disease, some women who are sexually active at a young age will give a positive HPV test results. However, approximately 70% newly infected young women with HPV would be free of infection after 12 months. Meanwhile, an age limit of 55 years was approved due to the effectiveness of VIA test known to decline in older age groups, and become 20% in women aged above 55 years.

These criteria are based on the manifestation histologically of low-grade changes (CIN1) on new infections with high risk type of HPV. These changes are usually temporary, whereas in CIN2/3 are more like a precursor to cervical cancer. High degree lesions CIN2/3, along with several risk factors would increase the incidence of persistent high-risk HPV infections. In addition, the latest pap smear test (during the last 3 months) and histopathological diagnosis using biopsy are the last enforcement and the gold standard throughout the examination. This would have a direct impact on the results of diagnostic tests performed.[9]

In this study, we found only 5.94% (6 of 101) subjects complained pain symptoms. There were no subjects that constrained shame/shy to do the test. Constraints related to the examination device feature are also found in this study, there were two respondents who had to re-examination due to the testing vaginal brush on the device is taken off and left inside the vagina. This caused discomfort among respondents, and this was one of the negative outcomes that was found in terms of the integrity of the device so that the study was expected to have an impact on the design and plan to use the device properly. Pain and shame is not a problem in the population in Italy.[10]

In our study, the self-administered HPV test had a sensitivity level of 56% and a specificity of 98% in detecting HPV in a high degree of precancerous lesions and cervical cancer. These results indicate that screening is only able to detect 56% of the abnormal group, and if the result is negative, we could ensure the absence of disease is up to 98%. The accuracy of this diagnostic test is up to 79%. These results indicate that 79% of the tests that carried out have compatibility with the gold standards from the results of the whole sample. In brief, we could say that if a person is diagnosed negatively with self-administered HPV test, the probability to get a negative result in histopathology finding is 98%. Based on previous studies, high risk HPV DNA can identify 99.7% of cervical cancers and 95% of high-grade precancerous lesions.[11]

The results of this study was different compared the previous studies. The high risk type of HPV was only identified up to 50% (n = 16/32) of cervical cancers and 31.57% (n = 6/19) of high-grade precancerous lesions. The sensitivity of HPV DNA tests for the detection of CIN2+ was still better than cytology (94% vs 65%).[11]

## CONCLUSIONS

Self-administered HPV test could be used as an alternative or primary screening for cervical cancer.

## SUGGESTIONS

Government health programs should focus on prevention of cervical cancer. In addition, they should include an integrated national screening program.

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