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The accuracy of histopathologic examination compared with polymerase chain reaction to diagnose human papillomavirus infection in the uterine cervix

Mahendra-Dewi I G.A.S.

ABSTRACT

Introduction: Until today cancer is still the main health problem besides infectious disease in Indonesia and other developing countries. Cervical cancer is the second most common cancer, where early detection of high-risk Human Papillomavirus (HPV) infection as the causative agent is very important so that the cervical lesions do not develop into pre-cancerous lesions and cancer. Even though, Polymerase Chain Reaction (PCR) is still not possible to be used as a screening method in the wider community, because the cost is quite expensive. An easier, cheaper, and simpler method of examination is needed to detect earlier infection, with the accuracy close to gold standard examination. This study aims to determine the accuracy of histopathologic examination compared with PCR to diagnose HPV infection in the uterine cervix.

Methods: This is a cross-sectional diagnostic test, with predictor variable is conventional histopathology examination, and outcome variable is PCR examination. The samples in this study were tissue biopsy, or surgery samples of patients clinically diagnosed with cervical lesion. A 2x2 table was created to calculate the sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV).

Result: A total of 39 samples were observed in this study. The sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) were 72.73%, 58.82%, 69.57% and 62.50%, respectively.

Conclusion: This study found the accuracy of histopathologic examination compared with PCR to diagnose HPV infection in the uterine cervix is more than 50%.

Keywords: accuracy, histopathology, PCR, HPV, uterine cervix
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INTRODUCTION

Cancer is still a health problem in the world especially in developing countries including Indonesia. One of these cancers is cervical cancer, whose incidence is still high and tends to increase. Cervical cancer ranks the second most common cancer after breast cancer, which is one of the main causes of death in women.1,2,3,4

High risk oncogenic human papillomavirus (HPV) play a causative role in the development of cervical cancer.3,4,5,6

Most sexually-active women are exposed to HPV infection during their lifetimes. To date, more than 120 HPV types have been found, of which more than 40 types of HPV infect the anogenital and other mucosal body, of these, 13–18 types belonging to high-risk type.7 Approximately 90-95% of cervical cancer are caused by high-risk HPV-16 and 18.3,4,8

Early detection of this high-risk human papillomavirus infection is very important to prevent the development of cervical lesions into precancerous lesions and cancer. A study by Kose and Murat (2014) found about 15% of women infected with HPV develop cervical intraepithelial neoplasia (CIN) within 7 years. Invasive cancer developed at a rate of 1–3% after this infection, and the required period is approximately 25–40 years or a few months to several years depending on the precancerous lesion grade.7,9

These infections provide cytopathic effect i.e. changes in cervical squamous epithelial cells that are a pathognomonic sign for productive HPV infection, which can be seen in both routine cytological screening with the Papanicolaou (Pap) test and histopathologic examination.7,10 The cytopathic effect called koilocytic atypia, characterized by the presence of nuclear atypia i.e. the size of the nucleus varies and enlarging up to three times the normal nucleus size, hyperchromatic nucleus, irregular nuclear membrane, cavitation or cytoplasmic halo around the nucleus, and cell membrane thickening.4,10,11,12 The genesis of the cytoplasmic vacuole has remained unclear, particularly because both HPV DNA replication and virion assembly occur exclusively in the nucleus.4,12

Cytopathic effects related to the human papillomavirus (HPV) infection are more frequently found in cervical intraepithelial neoplasia (CIN) 1.11

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Molecular-based HPV testing such as Polymerase Chain Reaction (PCR) is not yet possible used as a screening program. An easier, cheaper and simpler method of examination is needed to detect earlier infection, which can be applied in developing countries with large populations, but still, has a sensitivity and specificity close to gold standard. This study aims to determine the accuracy of histopathologic examination compared with PCR to diagnose HPV infection in the uterine cervix.

**RESEARCH DESIGN AND METHODS**

**Specimen collection**

This study design was a cross-sectional diagnostic test that was conducted during the years 2013-2014. The materials of this study were the paraffin-embedded tissue biopsy, or surgery of patients with clinically diagnosed have a cervical lesion at Obstetric and Gynecologic Department Faculty of Medicine Udayana University/ Sanglah General Hospital. Samples were collected on a consecutive basis until the required sample size was met. The conventional histopathology examination was as the predictor variable and PCR examination as the outcome variable.

**Histopathology Examination and HPV DNA Detection**

The specimen was processed and then stained with routine Hematoxylin & Eosin. Histopathologic examination was performed to determine the presence of cytopathic effects as a sign of suspicion of HPV infection. For detection of HPV DNA, the paraffin-embedded tissues from biopsy or surgery of patients that have been examined histopathologically, either with or without cytopathic effect were sent to Molecular Biology Laboratory Unit, Faculty of Medicine Udayana University. SPF10 primers at several dilutions were used to amplify the DNA. A total of 39 cervical lesion patients were included in this study.

**Statistical Analysis**

A descriptive characteristic of the data subject was tabulated. A 2×2 table was created to calculate the sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV).

**RESULTS**

Sample distribution based on patient age display in Table 1, and the results of histopathologic and PCR examination display in Table 2 and Table 3. The positive cytopathic effect with conventional histopathologic examination show in Figure 1 and the

**Table 1** Sample Distribution Based on Patient Age

| Age range (years) | Number | Percentage (%) |
|------------------|--------|----------------|
| 21-30            | 4      | 10.26          |
| 31-40            | 12     | 30.77          |
| 41-50            | 12     | 30.77          |
| 51-60            | 7      | 17.94          |
| 61+              | 4      | 10.26          |
| Total            | 39     | 100.00         |

**Table 2** Sample Distribution Based on Patient Age, Histopathologic and PCR Examination

| Age range (years) | Histopathology | PCR |
|-------------------|----------------|-----|
|                   | Positive       | Negative | Total | Positive       | Negative | Total |
| 21-30             | 2              | 5.13     | 2     | 5.13           | 4        | 10.26 |
| 31-40             | 7              | 17.95    | 5     | 12.82          | 12       | 30.77 |
| 41-50             | 6              | 15.38    | 6     | 15.38          | 12       | 30.77 |
| 51-60             | 5              | 12.82    | 2     | 5.13           | 7        | 17.95 |
| 61+               | 3              | 7.69     | 1     | 2.56           | 4        | 10.25 |
| Total             | 23             | 58.97    | 16    | 41.03          | 9        | 100.00 |

**Table 3** Sample Distribution Based on Histopathologic and PCR Examination

| PCR | Positive | Negative | Total | Se (%) | Sp (%) | PPV (%) | NPV (%) |
|-----|----------|----------|-------|--------|--------|---------|---------|
|     |          |          |       |        |        |         |         |
| Histopathology | 16      | 7        | 23    | 72.73  | 58.82  | 69.57   | 62.50   |
| Negative       | 6       | 10       | 16    |        |        |         |         |
| Total          | 22      | 17       | 39    |        |        |         |         |
positive result of DNA HPV with PCR examination shown in Figure 2.

A total of 39 cervical lesion patients were included in this study. Of these patients, the most distribution was obtained in the 31-40 and 41-50 year age group of 12 samples (30.77%) each. This study is in accordance with the result of previous studies. A study by Ting et al. (2010) found age range of low-grade lesions occurred at 20-30 years age groups.14 A cross-sectional study in Indonesia to evaluate the performance of a single-visit approach of cervical cancer screening, using visual inspection with acetic acid (VIA), histology and cryotherapy in low-resource settings, found 64.4% high-risk women were in the age group of 30–49 years.15 Young sexually active women are the highest risk for acquiring HPV infection.7

Examination with conventional histopathology to determine the positive cytopathic effect as an indication of suspicion HPV infection was found in 23 samples (58.97%). Examination with PCR for positive DNA HPV was found in 22 samples (56.41%). The most prevalence of positive patients with conventional histopathology and PCR examination was in the 31-40 years age group, each of 7 samples (17.95%) and 8 samples (20.51%).

All of the positive HPV samples in this study were low-grade precancerous lesions i.e. cervical intraepithelial neoplasia (CIN) grade 1. This result showed a higher percentage compared to the previous study i.e. the prevalence of HPV infection in precancerous lesion was 18% in CIN 1 and 66% in CIN 2-3.11,16

Study by Hu et al. (2011) found 3.4% of their samples were diagnosed as CIN grade 2 or worse lesions, and 17.1% were found to be positive for HPV DNA.17 In cervical cancer cases, infection by HPV found by 90-95% in the world,18 and 95.9% in Jakarta.19 A study by Vet et al. (2008) in three regions in Indonesia; Jakarta, Tasikmalaya, and Bali. Investigate age-specific prevalence of HPV types in a population-based sample of 2686 women, aged 15–70 years, found the overall HPV prevalence was 11.4%, and 92.9% was positive in cervical cancer patients.20

DISCUSSION

Of the 39 samples studied, the most distribution of cervical, uterine lesion either with or without suspicion for HPV infection diagnosed with conventional histopathology was obtained in the 31-40 and 41-50 year age group of 12 samples (30.77%) each. This study is in accordance with the result of previous studies. A study by Ting et al. (2010) found age range of low-grade lesions occurred at 20-30 years age groups.14 A cross-sectional study in Indonesia to evaluate the performance of a single-visit approach of cervical cancer screening, using visual inspection with acetic acid (VIA), histology and cryotherapy in low-resource settings, found 64.4% high-risk women were in the age group of 30–49 years.15 Young sexually active women are the highest risk for acquiring HPV infection.7

Examination with conventional histopathology to determine the positive cytopathic effect as an indication of suspicion HPV infection was found in 23 samples (58.97%). Examination with PCR for positive DNA HPV was found in 22 samples (56.41%). The most prevalence of positive patients with conventional histopathology and PCR examination was in the 31-40 years age group, each of 7 samples (17.95%) and 8 samples (20.51%).

All of the positive HPV samples in this study were low-grade precancerous lesions i.e. cervical intraepithelial neoplasia (CIN) grade 1. This result showed a higher percentage compared to the previous study i.e. the prevalence of HPV infection in precancerous lesion was 18% in CIN 1 and 66% in CIN 2-3.11,16

Study by Hu et al. (2011) found 3.4% of their samples were diagnosed as CIN grade 2 or worse lesions, and 17.1% were found to be positive for HPV DNA.17 In cervical cancer cases, infection by HPV found by 90-95% in the world,18 and 95.9% in Jakarta.19 A study by Vet et al. (2008) in three regions in Indonesia; Jakarta, Tasikmalaya, and Bali. Investigate age-specific prevalence of HPV types in a population-based sample of 2686 women, aged 15–70 years, found the overall HPV prevalence was 11.4%, and 92.9% was positive in cervical cancer patients.20

**Table 2** show the number of cases with positive cytopathic effect as a suspicion of HPV infection with the conventional histopathologic examination as many as 23 samples (58.97%), while with PCR were 22 samples (56.41%). The most prevalence of positive patients with conventional histopathologic and PCR examination was in the 31-40 years age group, each of 7 samples (17.95%) and 8 samples (20.51%).

**Table 3** show the accuracy of conventional histopathologic examination compared with PCR namely: sensitivity (Se) = 72.73%, specificity (Sp) = 58.82%, positive predictive value (PPV) = 69.57% and negative predictive value (NPV) = 62.50%.
Of 23 positive samples examined with conventional histopathology, only 16 samples were positive with PCR examination, so the positive predictive value (PPV) was 69.57%. Of 16 negative samples examined with conventional histopathology, only 10 samples were negative with PCR examination, so the negative predictive value (NPV) was 62.50%. This study found 16 samples were positive with conventional histopathologic examination and also positive with PCR examination of all positive samples (22 samples), so the sensitivity (Se) was 72.73%. Ten samples were negative with conventional histopathologic examination and also negative with PCR examination of all negative samples (17 samples), so the specificity (Sp) was 58.82%. The accuracy obtained in this study is lower than the previous study, i.e. sensitivity for HPV infection in the form of atypia koliocytotic as much as 88.89% and PPV 72.73%.  

Another study found koliocytosis was found in 63% of the smears from women with a histopathological diagnosis of CIN 1.  

A study by Abdelbadia et al. (2016) who compared the results of a pap smear, histopathology, colposcopy and PCR swab with in situ hybridizations (ISH) PCR tissue. Found highly significant results, with sensitivity of 87.5%, 100%, 62.5% and 56.2% respectively, but the specificity were 78.6%, 42.9%, 28.6% and 100% respectively. The conclusion of their research that conventional cytology and histopathology were sensitive tests for detection of HPV and this may help for early detection and histopathology were sensitive tests for detection of their research that conventional cytology 42.9%, 28.6% and 100% respectively. The conclusions (ISH) PCR tissue. Found highly significant compared the results of a pap smear, histopathologic examination and also negative with PCR examination of all negative samples (22 samples), so the sensitivity (Se) was 72.73%. Ten samples were negative with conventional histopathologic examination and also positive with PCR examination of all positive samples (22 samples), so the specificity (Sp) was 58.82%. The accuracy obtained in this study is lower than the previous study, i.e. sensitivity for HPV infection in the form of atypia koliocytotic as much as 88.89% and PPV 72.73%.  

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The accuracy of histopathologic examination compared with polymerase chain reaction to diagnose human papillomavirus infection in the uterine cervix

by Mahendra Dewi
The accuracy of histopathologic examination compared with polymerase chain reaction to diagnose human papillomavirus infection in the uterine cervix

Mahendra-Dewi I G.A.S.

ABSTRACT

Introduction: Until today cancer is still the main health problem besides infectious disease in Indonesia and other developing countries. Cervical cancer is the second most common cancer, where early detection of high-risk Human Papillomavirus (HPV) infection as the causative agent is very important so that the cervical lesions do not develop into pre-cancerous lesions and cancer. Even though, Polymerase Chain Reaction (PCR) is still not possible to be used as a screening method in the wider community, because the cost is quite expensive. An easier, cheaper, and simpler method of examination is needed to detect earlier infection, with the accuracy close to gold standard examination. This study aims to determine the accuracy of histopathologic examination compared with PCR to diagnose HPV infection in the uterine cervix.

Methods: This is a cross-sectional diagnostic test, with predictor variable is conventional histopathology examination, and outcome variable is PCR examination. The samples in this study were tissue biopsy, or surgery samples of patients clinically diagnosed with cervical lesion. A 2x2 table was created to calculate the sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV).

Result: A total of 39 samples were observed in this study. The sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) were 72.73%, 58.82%, 69.57% and 62.50%, respectively.

Conclusion: This study found the accuracy of histopathologic examination compared with PCR to diagnose HPV infection in the uterine cervix is more than 50%.

Keywords: accuracy, histopathology, PCR, HPV, uterine cervix

INTRODUCTION

Cancer is still a health problem in the world especially in developing countries including Indonesia. One of these cancers is cervical cancer, whose incidence is still high and tends to increase. Cervical cancer ranks the second most common cancer after breast cancer, which is one of the main causes of death in women. High risk oncogenic human papillomavirus (HPV) play a causative role in the development of cervical cancer. Most sexually-active women are exposed to HPV infection during their lifetimes. To date, more than 120 HPV types have been found, of which more than 40 types of HPV infect the anogenital and other mucosal body, of these, 13-18 types belonging to high-risk type. Approximately 90-95% of cervical cancer are caused by high-risk HPV-16 and 18. Early detection of this high-risk human papillomavirus infection is very important to prevent the development of cervical lesions into precancerous lesions and cancer. A study by Kose and Murat (2014) found about 15% of women infected with HPV develop cervical intraepithelial neoplasia (CIN) within 7 years. Invasive cancer developed at a rate of 1-3% after this infection, and the required period is approximately 25-40 years or a few months to several years depending on the precancerous lesion grade. These infections provide cytopathic effect i.e. changes in cervical squamous epithelial cells that are a pathognomonic sign for productive HPV infection, which can be seen in both routine cytological screening with the Papanicolaou (Pap) test and histopathologic examination. The cytopathic effect called koilocytotic atypia, characterized by the presence of nuclear atypia i.e. the size of the nucleus varies and enlarging up to three times the normal nucleus size, hyperchromatic nucleus, irregular nuclear membrane, cavitation or cytoplasmic halo around the nucleus, and cell membrane thickening. The genesis of the cytoplasmic vacuole has remained unclear, particularly because both HPV DNA replication and virion assembly occur exclusively in the nucleus. Cytopathic effects related to the human papillomavirus (HPV) infection are more frequently found in cervical intraepithelial neoplasia (CIN) 1-4.
Molecular-based HPV testing such as Polymerase Chain Reaction (PCR) is not yet possible as a screening program. An easier, cheaper and simpler method of examination is needed to detect earlier infection, which can be applied in developing countries with large populations, but still, has a sensitivity and specificity close to gold standard. This study aims to determine the accuracy of histopathologic examination compared with PCR to diagnose HPV infection in the uterine cervix.

**RESEARCH DESIGN AND METHODS**

**Specimen collection**

This study design was a cross-sectional diagnostic test that was conducted during the years 2013-2014. The materials of this study were the paraffin-embedded tissue biopsy, or surgery of patients with clinically diagnosed have a cervical lesion at Obstetric and Gynecologic Department Faculty of Medicine Udayana University/ Sanglah General Hospital. Samples were collected on a consecutive basis until the required sample size was met. The conventional histopathology examination was as the predictor variable and PCR examination as the outcome variable.

**Histopathology Examination and HPV DNA Detection**

The specimen was processed and then stained with routine Hematoxylin & Eosin. Histopathologic examination was performed to determine the presence of cytopathic effects as a sign of suspicion of HPV infection. For detection of HPV DNA, the paraffin-embedded tissues from biopsy or surgery of patients that have been examined histopathologically, either with or without cytopathic effect were sent to Molecular Biology Laboratory Unit, Faculty of Medicine Udayana University. SPF10 primers at several dilutions were used to amplify the DNA. A total of 39 cervical lesion patients were included in this study.

**Statistical Analysis**

A descriptive characteristic of the data subject was tabulated. A 2x2 table was created to calculate the sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV).

**RESULTS**

Sample distribution based on patient age display in Table 1, and the results of histopathologic and PCR examination display in Table 2 and Table 3. The positive cytopathic effect with conventional histopathologic examination show in Figure 1 and the

| Table 1 | Sample Distribution Based on Patient Age |
|---------|------------------------------------------|
| Age range (years) | Number | Percentage (%) |
| 21-30 | 4 | 10.26 |
| 31-40 | 12 | 30.77 |
| 41-50 | 12 | 30.77 |
| 51-60 | 7 | 17.94 |
| 61+ | 4 | 10.26 |
| Total | 39 | 100.00 |

| Table 2 | Sample Distribution Based on Patient Age, Histopathologic and PCR Examination |
|---------|--------------------------------------------------|
| Age range (years) | Histopathology | PCR |
|              | Positive | Negative | Total | Positive | Negative | Total | Number | Total |
| 21-30 | 2 | 10.26 | 4 | 10.26 | 2 | 5.13 | 4 | 10.26 |
| 31-40 | 7 | 30.77 | 12 | 30.77 | 8 | 20.51 | 12 | 30.77 |
| 41-50 | 6 | 30.77 | 12 | 30.77 | 5 | 12.82 | 12 | 30.77 |
| 51-60 | 5 | 12.82 | 7 | 17.94 | 4 | 10.25 | 7 | 17.94 |
| 61+ | 3 | 7.69 | 1 | 2.56 | 4 | 10.25 | 7 | 17.94 |
| Total | 23 | 58.97 | 16 | 41.03 | 9 | 100.00 | 22 | 56.41 | 17 | 43.59 | 39 | 100.00 |

| Table 3 | Sample Distribution Based on Histopathologic and PCR Examination |
|---------|--------------------------------------------------|
| PCR | Positive | Negative | Total | Se (%) | Sp (%) | PPV (%) | NPV (%) |
| Histopathology | 16 | 7 | 23 | 72.73 | 58.82 | 69.57 | 62.50 |
| Negative | 6 | 10 | 16 | |
| Total | 22 | 17 | 39 | | | | |
Figure 1  Positive cytopathic effect as a suspicion of HPV infection with conventional histopathologic examination (×400) (H & E, 450x).

Figure 2  HPV DNA amplification products by PCR examination in the uterine cervix. Line 1 standard DNA, line 2 positive control, line 3 negative control, line 4 sample with positive HPV DNA positive result of DNA HPV with PCR examination shown in Figure 2.

A total of 39 cervical lesion patients were included in this study. Of these patients, the most distribution was obtained in the 31-40 and 41-50 year age group of 12 samples (30.77%) each.

Table 2 show the number of cases with positive cytopathic effect as a suspicion of HPV infection with the conventional histopathologic examination as many as 23 samples (58.97%), while with PCR were 22 samples (56.41%). The most prevalence of positive patients with conventional histopathologic and PCR examination was in the 31-40 years age group, each of 7 samples (17.95%) and 8 samples (20.51%).

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DISCUSSION

Of the 39 samples studied, the most distribution of cervical, uterine lesion either with or without suspicion for HPV infection diagnosed with conventional histopathology was obtained in the 31-40 and 41-50 year age group of 12 samples (30.77%) each. This study is in accordance with the result of previous studies. A study by Ting et al. (2010) found a range of low-grade lesions occurred at 20-30 years age groups. A cross-sectional study in Indonesia to evaluate the performance of a single-visit approach of cervical cancer screening, using visual inspection with acetic acid (VIA), histology and cryotherapy in low-resource settings, found 64.4% high-risk women were in the age group of 30-49 years. Young sexually active women are the highest risk for acquiring HPV infection.

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Study by Hu et al. (2011) found 3.4% of their samples were diagnosed as CIN grade 2 or worse lesions, and 17.1% were found to be positive for HPV DNA. In cervical cancer cases, infection by HPV found by 90-95% in the world, and 95.9% in Jakarta.

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Studi by Matala and Sareen (2011) found 66.6% of the low-grade squamous intraepithelial lesion (LSIL) were HPV positive, 33.3% of koilocytosis were HPV positive.

Another study found koilocytosis was found in 63% of the smear from women with a histopathological diagnosis of CIN 1.

A study by Abdelbadiaa et al. (2016) who compared the results of a pap smear, histopathology, colposcopy and PCR swab with situ hybridizations (ISH) PCR tissue. Found highly significant results, with sensitivity of 87.5%, 100%, 62.5% and 56.2% respectively, but the specificity was 78.6%, 42.9%, 28.6% and 100% respectively. The conclusion of their research that conventional cytology and histopathology were sensitive tests for detection of HPV and this may help for early detection of cancer cervix in a developing country.

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| 8  | Kyung Jin Eoh, Hee Jung Kim, Jung-Yun Lee, Eun Ji Nam, Sunghoon Kim, Sang Wun Kim, Young Tae Kim. "Upregulation of homeobox gene is correlated with poor survival outcomes in cervical cancer", Oncotarget, 2017 | Publication          | 1%         |
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