Research Article

Association Between High-risk HPV Infection and Cervical Precancerous Lesions

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Abstract

Introduction: More than 70% of cervical cancer cases are associated with high-risk HPV infections, especially those of type 16/18. Persistent high-risk HPV infection can cause cervical lesions and develop into cancer; therefore, early detection of HPV infection is important. Screening using HPV DNA tests, either as a single test or combined with a cervical cytological test, is recommended. This study aimed to determine the association between high-risk HPV infection and the development of cervical precancerous lesions.

Methods: This cross-sectional study was conducted on 104 patients at RSUPN Dr. Cipto Mangunkusumo in 2020-2022 using secondary data from HPV DNA test results with the DiagCor GenoFlow Human Papilloma Virus Array Test and cervical cytology results from liquid-based cytology. The data were presented in tables and analyzed using SPSS version 26.

Results: The prevalence of high-risk HPV infection was 30.8%, with the most common genotypes being HPV 18 & 52 (15.6%), HPV 51 (12.5%), and HPV 58 (9.4%). Cytological results from the high-risk HPV types showed that 16 out of 32 (50%) were abnormal. High-risk HPV caused 11 (78.6%) low-grade squamous intraepithelial lesions and 5 (83.3%) high-grade squamous intraepithelial lesions. It is known by the statistical analysis test that there was a significant relationship between high-risk HPV infection and cervical precancerous lesions (p=0.000).

Conclusion: A significant association was observed between the occurrence of high-risk HPV infection and the development of cervical precancerous lesions. Appropriate management and supervision can be carried out in accordance with risk stratification based on screening results.

Keywords: cervical precancerous lesions, high-risk HPV infection, screening.

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INTRODUCTION

Cervical cancer is one of the biggest health problems in Indonesia, ranking as the second most common cancer in the female population.[1] In 2022, there were 36,964 new cases of cervical cancer which caused 20,708 deaths in Indonesia with an incidence rate of 23.3 and a mortality rate of 13.2 out of 100,000 women.[2]

There are currently 14 high-risk HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and 5 that are likely high-risk (53, 66, 70, 73, and 82). Persistent infection with high-risk HPV genotypes has a high possibility of developing neoplasia.[3] More than 70% of cervical cancer cases are associated with infection by HPV (Human papillomavirus) types 16 and/or 18, which are the most aggressive and commonly cause cervical neoplasia.[4] Data in Indonesia also shows a high incidence of HPV infection in cervical cancer cases, 87% for HPV type 16/18.[5]

The high incidence of cervical cancer in Indonesia makes it a national concern for prevention and early detection. Cervical cancer screening has been developed since 2008 and has become a national program since 2015.[6] Well-organized screening programs have been proven to reduce the incidence and mortality of cervical cancer by 50-75% in various countries. However, cervical cancer screening coverage in Indonesia is still low, reaching only 14.6% of the target population of women aged 30-69 years

using the VIA method. This coverage is still lower than the Ministry of Health's target and the target recommended by WHO.[1]

Currently, there are three options available for cervical cancer screening, namely HPV DNA (deoxyribonucleic acid) test, cervical cytology test (Pap smear), and visual inspection with acetic acid (VIA) test. Data from clinical trials, cohorts, and modeling studies suggest that among at-risk patients aged 25—65 years, high-risk HPV DNA tests and co-testing methods may detect more cases of high-grade cervical intraepithelial neoplasia rather than a single cytology test.[7]

HPV infection has a varying prevalence based on genotype and cytology results in different populations. While most research has been conducted to assess the prevalence of HPV infection in general, only a few studies have specifically focused on high-risk types of HPV. Therefore, this study aimed to analyze the prevalence and distribution of high-risk HPV types in cervical cytology results and determine their association with the development of cervical precancerous lesions.

METHODS

This research is an analytical observational study with a cross-sectional design that aims to determine the prevalence and distribution of high-risk types of HPV in cervical cytology results and its association with the development of cervical precancerous lesions. The research was carried out at Dr. Cipto Mangunkusumo General Hospital in June–October 2023. This research was approved by the FKUI-RSCM Health Research Ethics Committee (KET-1286/UN2.F1/ETIK/PPM.00.02/2023).

The subject population of this study were patients at Dr. Cipto Mangunkusumo General Hospital who had the results of HPV DNA examination and cervical cytology in the period 2020-2022. The sample size required in this research was 104. Inclusion criteria: women aged 25—65 years, not a cervical cancer patient. Exclusion criteria: pregnant, have had treatment for SIL (squamous intraepithelial lesion) on the cervix, infected with several high-risk HPV genotypes (multiple infections).

The data collected is secondary data originating from the anatomical pathology laboratory at Dr. Cipto Mangunkusumo General Hospital in the form of results of HPV DNA examination and cervical cytology. Results data were presented in the form of a descriptive table, using percentages, and analysis was carried out using the SPSS version 26.

RESULTS

Characteristics of Research Subjects

The research subjects consisted of 104 patients who had HPV DNA and cervical cytology examination results at Dr. Cipto Mangunkusumo General Hospital. The average age of the subjects was 45.64 (± 9.68) with a minimum age of 25 years and a maximum age of 64 years, with the majority in the 36–45-year age group (32.7%). Most of the subjects live in Jabodetabek (85.6%), work as housewives (38.5%), are married (68.3%), 59.1% have given birth more than once (multiparous), and 39.7% use intrauterine device (IUD) contraception. The sociodemographic characteristics of the subjects are listed in **Table 1.**

Table 1. Characteristics of Research Subjects

Variable	Frequency (%)
Age	
25—35 years	18 (17.3%)
36—45 years	34 (32.7%)
46—55 years	31 (29.8%)
56—65 years	21 (20.2%)
Domicile	
Jabodetabek	89 (85.6%)
Outside Jabodetabek	15 (14.4%)
Occupation	
Unemployed	9 (8.7%)
Housewives	40 (38.5%)
Goverment employees	8 (7.7%)
Private employees	16 (15.4%)
Others	31 (29.8%)
Marital Status	
Unmarried	23 (22.1%)
Married	71 (68.3%)
Divorced	10 (9.6%)
Parity	
Nuliparous	18 (19.4%)
Primiparous	20 (21.5%)
Multiparous	55 (59.1%)
Contraception Use	
Sterilization	4 (5.1%)
Intrauterine device	31 (39.7%)
Depo-Medroxyprogesterone Acetate	14 (17.9%)
Condom	4 (5.1%)
Oral contraception pills	10 (12.8%)
Implant	3 (3.8%)
Not using contraception	12 (15.4%)

Prevalence of High-risk Type HPV Infection in Subjects' Cervical Cytology Results

Cervical cytology showed abnormal results in 20.3% of cases, with a distribution of 13.5% in low-grade squamous intraepithelial lesions (LSIL), 5.8% in high-grade squamous intraepithelial lesions (HSIL), and 1% in squamous cell carcinoma (SCC). Based on the results of the HPV DNA examination, it was found that 32 (30.8%) subjects were infected with high-risk types of HPV. Cytological results from the high-risk HPV types showed that 16 out of 32 (50%) were abnormal with 11 (34.4%) LSIL and 5 (15.6%) HSIL. The frequency and percentage of HPV types and cytology results can be seen in **Table 2.**

Table 2. Prevalence of High-risk Type HPV Infection in Subjects' Cervical Cytology Results

HPV Types	Cytology Results				Total
	Frequency (%)				
	NILM	LSIL	HSIL	SCC	
High-risk	16 (15.4%)	11 (10.6%)	5 (4.8%)	0 (0%)	32 (30.8%)
Low-risk/negative	67 (64.4%)	3 (2.9%)	1 (1.0%)	1 (1.0%)	72 (69.2%)
Total	83 (79.8%)	14 (13.5%)	6 (5.8%)	1 (1.0%)	104 (100%)

Distribution of High-risk Type HPV Genotypes in Cervical Cytology Sample Results

From the HPV DNA examination which can detect 17 high-risk HPV genotypes, it was found that HPV 18 and 52 were the genotypes that most frequently infected subjects 5 (15.6%), followed by HPV 51 with 4 (12.5%), and HPV 58 as many as 3 (9.4%). The most HPV infections detected based on cytology results were HPV 18 and 51 as many as 3 (9.4%) in the LSIL cytology results. Meanwhile, the HPV genotypes in the HSIL cytology results were evenly distributed between HPV 16, 18, 35, 45, and 58 as many as 1 (3.1%). The distribution of high-risk type HPV genotypes in cervical cytology results can be seen in **Table 3.**

Table 3. Distribution of High-risk Type HPV Genotypes in Cervical Cytology Sample Results

High-risk HPV *Genotypes*	Cytology Results				Total
	Frequency (%)				
	NILM	LSIL	HSIL	SCC	
16	1 (3.1%)	0 (0%)	1 (3.1%)	0 (0%)	2 (6.2%)
18	1 (3.1%)	3 (9.4%)	1 (3.1%)	0 (0%)	5 (15.6%)
31	0 (0%)	1 (3.1%)	0 (0%)	0 (0%)	1 (3.1%)
33	0 (0%)	2 (6.3%)	0 (0%)	0 (0%)	2 (6.3%)
35	1 (3.1%)	0 (0%)	1 (3.1%)	0 (0%)	2 (6.2%)
39	2 (6.3%)	0 (0%)	0 (0%)	0 (0%)	2 (6.3%)
45	1 (3.1%)	0 (0%)	1 (3.2%)	0 (0%)	2 (6.3%)
51	1 (3.1%)	3 (9.4%)	0 (0%)	0 (0%)	4 (12.5%)
52	4 (12.5%)	1 (3.1%)	0 (0%)	0 (0%)	5 (15.6%)
53	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
56	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
58	2 (6.3%)	0 (0%)	1 (3.1%)	0 (0%)	3 (9.4%)
59	2 (6.3%)	0 (0%)	0 (0%)	0 (0%)	2 (6.3%)
66	1 (3.1%)	1 (3.1%)	0 (0%)	0 (0%)	2 (6.2%)
68	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
73	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
82	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	16 (50%)	11 (34.4%)	5 (15.6%)	0 (0%)	32 (100%)

Analysis of the Relationship between High-Risk Type HPV Infection and the Development of Cervical Precancerous Lesions

High-risk HPV caused 11 (78.6%) LSIL and 5 (83.3%) HSIL. Based on the results of statistical tests, it was found that there was a significant relationship between high-risk type HPV infection and the degree of cervical precancerous lesions on cytology results ($p<0.05$). The relationship between high-risk type HPV infection and the development of cervical precancerous lesions on cytology results can be seen in **Table 4.**

Table 4. Analysis of the Relationship between High-Risk Type HPV Infection and the Development of Cervical Precancerous Lesions

HPV Types	Cytology Results				*P-value*
	NILM	LSIL	HSIL	SCC	
High-risk	16 (19.3%)	11 (78.6%)	5 (83.3%)	0 (0%)	0.000
*Low-risk/*negative	67 (80.7%)	3 (21.4%)	1 (16.7%)	1 (100%)	

DISCUSSION

Our research subjects consisted of 104 patients who had HPV DNA and cervical cytology examination at Dr. Cipto Mangunkusumo General Hospital. The combination test of high-risk HPV DNA and cytology provides data regarding the prevalence of high-risk HPV infection in various cervical cytological findings. Based on the results of cervical cytology, our study showed abnormal results in 20.3% of cases, with a distribution of 13.5% in LSIL, 5.8% in HSIL, and 1% in SCC. Meanwhile, in the HPV DNA examination, it was found that 30.8% of the subjects of our study were infected with high-risk types of HPV. Cytological results from the high-risk HPV types showed that 50% were abnormal with 34.4% LSIL and 15.6% HSIL.

The prevalence of infection by this high-risk HPV type was higher than that reported by Ali M et al. with a prevalence of 21%. This study also reported the results of cervical cytology which found abnormal results in 17.5% of the total research subjects.[8] Another study by Ali K, et al. observed that there were 13.1% abnormal cervical cytology with LSIL.[9] Both studies show a lower rate of abnormal cervical cytology results but are in line with the results that LSIL has the largest percentage of the other abnormal categories.

Different HPV genotypes show different risks for high-grade cervical lesions.[10] Infections with HPV 16 and 18 are known to have a higher risk of developing into cancer, so positive results from these two genotypes must be treated differently compared to other high-risk genotypes.[11] Since 2015, the identification of HPV genotypes has expanded beyond HPV 16 and 18 for cervical cancer screening. Reporting HPV genotypes can improve risk stratification and help optimize the detection of clinically important cervical neoplasia while minimizing unnecessary colposcopy referrals.[12] Several research results reported that HPV genotypes other than HPV 16 and 18 have the highest frequency among positive cases of high-risk type HPV.[9,10]

Based on this study, which identified high-risk HPV genotypes, it was found that HPV 18 and 52 were the most common HPV genotypes that infected research subjects at 15.6%, followed by HPV 51 at 12.5% and 58 at 9.4%, apart from the finding that HPV 16 was not found frequently, only 6.2% in this study. These results are similar to the results of research by Zhang W, et al. and Jiang L, et al. which reported that HPV 16, 52, 58, and 51 are the most frequently identified high-risk HPV genotypes.[13,14] One of the studies conducted in Surabaya in 2018 also obtained the prevalence of HPV infection from cytology samples of LSIL, HSIL, and SCC. The most frequently identified HPV genotype in the study was HPV 16 (62.68%), followed by 18 (20.9%), 45 (5.97%), 52 (5.97%), and 67 (4.48%).[15]

If identified based on cervical cytology results, this study found that HPV 18 and 51 of 9.4% were detected in LSIL, and the HSIL cytology results the HPV genotypes were evenly distributed between HPV 16, 18, 35, 45, and 58 as many as 1 (3.1%). World population data from 2021 show that the prevalence of HPV types 16 and/or 18 infection is 51.9% in LSIL and 25.8% in HSIL cytology results.[16] In Indonesia, the prevalence of HPV type 16/18 infection in LSIL and HSIL cytology results was 21.2% and 42.1%, respectively.[5] Song et al. also reported the distribution of HPV genotypes in

the cervical cytology results. From the abnormal cytology, it was found that HPV 16 was 12.3% dominant in LSIL, followed by 58, 52, and 33. In HSIL, HPV 16 was also found the most at 33.3%, followed by 33, 31, and 56.[17] Research in China in 2020 showed the most common HPV genotypes were HPV 16 (20.19%) and 52 (17.34%) in patients with LSIL, and HPV 16 (49.09%), 52 (14.55%) and 18 (10.91%) in patients with HSIL.[18]

Based on the results of this study, high-risk HPV caused 11 (78.6%) LSIL and 5 (83.3%) HSIL, which results in 50% abnormal cytology results. This relationship was also supported by statistical analysis, which showed a significant relationship ($p<0.05$) between high-risk HPV infection and the development of cervical precancerous lesions. The overall positive rate for high-risk type HPV infection studied by Ali M, et al. among women with abnormal cytology was 50.6%, which is approximately 3.5 times greater than women with normal cytology of 14.7 %.[9] This shows that women with abnormal cytology have a much higher positive rate for high-risk type HPV infection compared to those with normal cytology. The study also reported the prevalence of high-risk HPV infection among LSIL cytology results of 40.6% and 60% in HSIL. Both studies by Ali M, et al. and Ma X, et al. showed results that were in line with the results of this study that there was a significant relationship and an increase in the positive rate of high-risk HPV infection along with the development of the degree of cervical precancerous lesions.[10,19]

The discovery of the relationship between high-risk HPV infection and the development of cervical precancerous lesions has become a basis for creating guidelines for the management of abnormalities in cervical cancer screening by the American Society of Colposcopy and Cervical Pathology (ASCCP). The guidelines updated in 2019 are necessary to accommodate the three available cervical cancer screening strategies, namely primary HPV testing, co-testing with HPV testing and cervical cytology, and cervical cytology only.[20] The management recommendations in these guidelines are based on risks, not outcomes. Recommendations for colposcopy, therapy, or monitoring are based on the patient's risk of developing HSIL.

Repeat HPV testing or co-testing at one-year intervals is recommended for patients with minor screening abnormalities indicating low-risk HPV infection with a cytology grade lower than HSIL. Meanwhile, the presence of HPV 16 and 18 infections, which have the highest risk of developing cancer, requires further evaluation (e.g., colposcopy with biopsy), even if the cytology results are negative. HSIL cytology results also require further evaluation in the form of colposcopy. Continued surveillance with HPV testing or co-testing at three-year intervals for a minimum of 25 years is recommended after undergoing histological therapy for cervical lesions.

Strengths and Limitations

Research on the prevalence and distribution of high-risk HPV genotypes in cervical cytology results has not yet been conducted in Indonesia. Most similar studies have only assessed the prevalence of HPV infection in general, and not specifically high-risk HPV types. In addition, this study examined the relationship between high-risk HPV infection and the development of cervical precancerous lesions. These results can strengthen the knowledge from previous research and provide a basis for risk stratification in patients undergoing cervical cancer screening.

However, this study had some limitations. Secondary data obtained from medical records cannot fully meet data needs on the variables of parity and contraceptive use (obtained by 93 of the main sample of 104); therefore, there were missing data in analyzing the sociodemographic characteristics of the subjects. Future research could carry out analyses related to various risk factors associated with high-risk HPV infection, cervical cytology abnormalities, or cervical cancer, such as age at first sexual intercourse, number of sexual partners, smoking habits, history of sexually transmitted infection, and oral contraception, using questionnaires. Another suggestion is to analyze multiple high-risk types of HPV infections, because a large amount of data on subjects with multiple infections has been found.

CONCLUSION

A significant association was observed between the occurrence of high-risk HPV infection and development of cervical precancerous lesions. Appropriate management and supervision can be carried out in accordance with risk stratification based on screening results.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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Data Availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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