Research Article

Incidence of Positive Human Papillomavirus High Risk in Negative Cytology Result

Insidensi Kejadian Human Papillomavirus RisikoTinggi Positif pada Hasil Sitologi Negatif

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Abstract

Objective : To report the incidence of positive HPV high risk in negative cytology result.

Methods : We collected 83 women underwent liquid-based cytology (LBC) and HPV DNA examination at the same time. We were using Diag Cor GenoFlow Human Papillomavirus Array Test (GenoFlow), a novel HPV test based on PCR and "Flow-through" hybridization that can identify 33 HPV subtypes: 18 types of High risk HPV such as 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 81 and 82.

Results : We grouped the subjects based on age below or equal to 30 years old (n=6) and above 30 years old (n=77). We found a significant difference in HPV DNA result within this group (P = 0.034), with 19.3% had HPV DNA type 16 and 18 in a group of age above 30 years old. Our study showed that 27 women (32.5%) underwent screening for cervical cancer having negative LBC result but showed positive HPV DNA positive.

Conclusions : We found a significant difference in HPV DNA test result among women above 30 years old. Co-testing of Pap and HPV DNA is needed, especially if HPV DNA type 16 and 18 were found among negative Pap results.

Keywords : Cervical cancer, HPV DNA, incidence, LBC, screening.

Abstrak

Tujuan : *Melaporkan insidensi dari HPV risiko tinggi yang positif pada hasil sitologi negatif.*

Metode : *Kami mengumpulkan 83 perempuan yang menjalani liquid based cytology (LBV) dan pemeriksaan HPV DNA pada waktu yang bersamaan. Dengan menggunakan DiagCor GenoFlow Human Papilloma Virus Array Test (GenoFlow), yaitu sebuah uji HPV terbaru yang berbasis PCR dan "Flow-throug" hybridization dapat mengidentifikasi 33 subtipe HPV: 18 tipe HPV risiko tinggi seperti 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 81 dan 82.*

Hasil : *Kami mengelompokkan subjek berdasarkan usia di bawah atau setara 30 tahun dan di atas 30 tahun (n=77). Kami menemukan perbedaan signifikan dari hasil HPV DNA dalam kelompok ini (P=0,034), dengan 19.3% memiliki HPV DNA tipe 16 dan 18 dalam kelompok usia diatas 30 tahun. Penelitian ini menunjukkan 27 perempuan (32,5%) menjalani skrining kanker serviks memiliki hasil LBC yang negatif namun menunjukkan HPV DNA positif.*

Kesimpulan : *Terdapat perbedaan signifikan dari uji HPV DNA pada wanita usia diatas 30 tahun. Pemeriksaan bersamaan antara Pap dan HPV DNA dibutuhkan terutama ketika HPV DNA tipe 16 dan 18 ditemukan pada hasil Pap negatif.*

Kata kunci : *HPV DNA, insidensi, kanker serviks, LBC, skrining.*

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INTRODUCTION

Indonesian population is estimated at around 93.15 million, where the majority of women with age above 15 years old, has an increased risk of cervical cancer. Cervical cancer is the second most affecting cancer in women in Indonesia, with the incidence of 20,928 per year since 2012. Based on the age category in Indonesia, cervical cancer also the second most frequent female cancer in women at the age of 14-55 years old. Approximately 4% of female in Indonesia is infected with Human Papilloma Virus (HPV) type 16/18 which cause 87% of cervical cancer.[1]

In the last 40 years in the United States, yearly screening with Pap smear will dramatically decrease the morbidity and mortality related to cervical cancer.[2] In Indonesia, the diagnostic methods such as Pap smear, Visual Inspection of acetic acid[3], and also HPV Deoxyribonucleic Acid (DNA) were also used with the screening number 24.4% until 2017, with the most common in the age 30 to 50 years old and five years screening period.1 Worldwide, two type of HPV (16 and 18) cause more than 70% of cervical cancer, 41-67% High-Grade Cervical Lesions (HSIL) and 16-32% Low-Grade Cervical Lesion (LSIL).

DiagCor GenoFlow Human Papillomavirus Array Test (Geno Flow) is a novel HPV test based on PCR and "Flow-through" hybridization that can identify 33 HPV subtypes[4], 18 types of High risk HPV such as16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58,59, 66,68, 73, 81 and 82 that count as the cause of the other 20% of cervical cancer[5,6] and the low risk HPV 15 type such as 6, 11, 26, 40, 42, 43, 44. 54, 55, 57, 61, 70, 71, 72, and 84.[6]

The newest guideline based on American Society for Colposcopy and Cervical Pathology ASCCP and American College of Obstetricians and Gynecologists ACOG recommended the DNA-HPV High-Risk examination as an additional routine examination in pap smear screening in women with the age of 30 or more. [2,7] NA-HPV has a potential role in the three main areas such as as the case triage inpatients with abnormal cytology LSIL or ASCUS, as monitoring for the post-therapy in patients with Cervical Intraepithelial Neoplasia8, and the last one as primary screening for the alternative or additional Pap smear.[7]

Food Drug Administration (FDA) in the United States agree in combination examination of DNA-HPV and cytology inpatients with the age of 30 or above. The age 30 or above was the critical ages for screening as the 30 years and below had the lower risk for invasive cervical cancer although has the high possibility to get the HPV infection temporarily.

Furthermore, the prevalence of HPV infection in women at the of 30 or above is lower than women with the younger age that causes increasing number in specificity in DNA-HPV examinaion.[9]

Although there is already an agreement in the screening age of 30, there is still an unclear issue whether there is still the same pattern in the age above 30 as long the women is still in screening methods. This is due to the score of pre-neoplastic incidence in this age group was low.[2] Based on the newest study, with Athena calculation that contributed as much as 35.000 women age 30 years and above, reported the decreasing number of high-risk DNA-HPV detection related with increasing age in all category with all degree of CIN that proves with pathological that shows the decreasing number dramatically in the HPV type 16 detection. The cohort study with high-risk DNA-HPV detection and cervical problem in perimenopause women (35 to 60 years old) shows the same results with decreasing correlation with the increasing age.[2]

The purpose of this paper is to assess the relationship between high-risk DNA HPV detection and normal cytology based on age category.

METHODS

Every woman who came to Colposcopy clinic in the department of Obstetrics and Gynecology clinic in January to December 2016 to participate in the cohort prospective study to study the natural history of HPV infection along with the transition age in perimenopause women. Inclusion criteria in this study are female age 35 to 60 years, no cervical cancer, got information about the study and willing to participate in the study. The exclusion criteria of the study were pregnant women, intending to get pregnant, history of organ transplantation, and HIV positive.

After the subject sign the informed consent, the subject will complete the basic data and gynaecology examination the ethical committee of Faculty of Medicine Universitas Indonesia. The history of sociodemographic characteristic, reproduction history and menstruation, sexual history and the latest sexual activity, cigarette history were compiled in the anamnesis. The cervical screening and medical therapy history that include the result of HPV and Pap smear before, colposcopy, and therapy-related with the condition was also collected. All of the examinations were performed by the gynaecology consultant. The examination protocol of DNA HPV was done by speculum and cervical brush examination. With transport by the standard medium transport (clinical pathology), and got approval from the research ethics committee. We were using GenoFlow Human Papillomavirus Array Test for identifying HPV DNA subtype. The lowest detection limits of the GF assay for HPV16 and HPV18 were 25 copies and 20 copies, respectively, with a sensitivity of 80% and specificity of 23%.[10]

Cervical Abnormality Detection and HPV Infection

The Pap smear classification was arranged to the severe level such as negative, ASCUS, LSIL, ASC-H, HSIL or cancer. At the cytology, classification is based on ASCUS or above ASCUS.

The extraction of the DNA-HPV detection and genotyping from the cervical specimen was by using GenoFlow Human Papillomavirus Array Test. For this analysis, HPV type 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 81 and 82 are classified as high risk HPV. The other HPV besides that type was classified as negative even the result is positive.

Statistical Analysis

Analysis of statistic using SPSS version 22 for analyzing the relationship between the variables. We analyze the relationship between LBC result and HPV DNA test, and as well as LBC result and HPV DNA type.

RESULTS

We recruited 83 women who underwent LBC and HPV DNA examination. Our study showed that women having positive HPV DNA test were around 40 to 45 years of age, with the age of first sexual intercourse around 20 years old. Most of our HPV DNA positive population (56.5%) is having a one-time marriage, and work as housewives (28.9%) (Table 1).

Table 1. Demographic Data

	HPV DNA Positive %	HPV DNA Negative %	*P- value*
Age (years)	43 (95CI 40.38 – 45.62)	45 (95CI 41.16 – 48.84)	>0.05
Parity	2 (95CI 1.67 – 2.49)	2 (95CI 1.73 – 2.64)	>0.05
Abortus	0 (95CI .13 – .43)	0 (95CI .07 – .66)	>0.05
Living Child	2 (95CI 1.58 – 2.30)	2 (95CI 1.56 – 2.31)	>0.05
Sexual Partner(s)	46 (55.4)	31 (37.3)	>0.05
Single			
Multiple	4 (4.8)	2 (2.4)	
Duration of Mariage (years)	20 (95CI 17.55 – 23.97)	24 (95CI 18.01 – 25.87)	>0.05
Age of First Sexual Contact	20.5 (95CI 20.43 – 22.85)	20 (95CI 19.89 – 23.5)	>0.05
Cigarette Smoking	11 (13.3)	2 (2.4)	>0.05
yes			
no	39 (46.9)	31 (37.4)	
Occupation	24 (28.9)	18 (21.7)	>0.05
Housewife			
Private Sector	21 (25.3)	9 (10.8)	
Governmental Sector	5 (10.0)	6 (18.2)	
Contraception	24 (28.9)	14 (16.9)	>0.05
None			
Sterilization	2 (2.4)	1 (1.2)	
IUD	13 (15.7)	12 (14.5)	
DMPA	6 (7.2)	4 (4.8)	
Condom	0 (0)	1 (1.2)	
OCP	4 (4.8)	1 (1.2)	
Implant	1 (1.2)	0 (0)	

From our data, the eldest subject was 68 years old, and the youngest was 20 years old. We grouped the subjects by age below or equal to 30 years old (n=6) and above 30 years old (n=77). We found significant difference HPV DNA result within this grouping (P = 0.034), with 19.3% had HPV DNA type 16 and 18 in the group of age above 30 years old (Table 2).

Table 2. Relationship between Age below or Above 30 Years Old and HPV DNA Test

Agey o	HPV DNA High Risk		HPV DNA Low Risk/Negative	*P-value**
	HPV DNA Type 16 and/or 18	Other HPV High-Risk Type		
< 30	1 (1.2)	0 (0)	5 (6.0)	0.034
> 30	16 (19.3)	33 (39.7)	28 (33.7)	
Total	17 (20.5)	33 (39.7)	33 (39.7)	

*Chi-square test, relations between Age below or above 30 years old and HPV DNA result

Our study showed that 27 women (32.5%) underwent screening for cervical cancer having negative LBC result but showed positive HPV DNA positive. Only seven women (8.4%) that showed HSIL from LBC result, having HPV DNA test positive. There is no significant relation ($p<0.05$) between LBC result and HPV DNA result (Table 3).

Table 3. Relationship between LBC Result and HPV DNA Test

		HPV DNA Result		Total	*P-value**
		High Risk	Low Risk/Negative		
LBC Result	HSIL	7(8.4)	2 (2.4)	9 (10.8)	>0.05
	LSIL	2(2.4)	1 (1.2)	3 (3.6)	
	ASCH	7 (8.4)	8 (9.6)	15 (18.1)	
	ASCUS	7 (8.4)	1 (1.2)	8 (9.6)	
	Negative	27 (32.5)	21 (25.3)	48 (57.8)	
	Total	50 (60.2)	33 (39.8)	100 (100)	

HPV DNA type that recorded positive in our study population mostly is HPV type 59 found in 19 women (22.8%), and yet 12 (14.5%) out of them showed negative LBC result. Only three women (3.6%) with HPV DNA of type 16 showed LBC result of HSIL (Table 4).

Table 4. Relationship between HPV DNA Type and LBC Result

HPV DNA Type	LBC Result						
	HSIL	LSIL	ASCH	ASCUS	Negative	Total	*P-value*
16	3 (3.6)	1 (1.2)	1 (1.2)	1 (1.2)	8 (9.6)	14 (16.8)	>0.05
18	1 (1.2)	0 (0)	1 (1.2)	0 (0)	3 (3.6)	5 (6.0)	>0.05
58	2 (2.4)	0 (0)	0 (0)	1 (1.2)	0 (0)	3 (3.6)	>0.05
59	1 (1.2)	0 (0)	3 (3.6)	3 (3.6)	12 (14.5)	19 (22.8)	>0.05
52	1 (1.2)	1 (1.2)	3 (3.6)	2 (2.4)	11 (13.3)	18 (21.6)	>0.05
35	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.2)	1 (1.2)	>0.05
56	0 (0)	0 (0)	3 (3.6)	1 (1.2)	3 (3.6)	7 (8.4)	>0.05
66	0 (0)	0 (0)	4 (4.8)	2 (2.4)	10 (12.0)	16 (19.2)	>0.05
68	1 (1.2)	0 (0)	4 (4.8)	2 (2.4)	9 (10.8)	16 (19.2)	>0.05
51	1 (1.2)	0 (0)	1 (1.2)	0 (0)	2 (2.4)	4 (4.8)	>0.05
45	0 (0)	0 (0)	2 (2.4)	0 (0)	2 (2.4)	4 (4.8)	>0.05
81	0 (0)	0 (0)	0 (0)	1 (1.2)	0 (0)	1 (1.2)	>0.05
53	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.2)	1 (1.2)	>0.05
33	1 (1.2)	0 (0)	1 (1.2)	0 (0)	1 (1.2)	3 (3.6)	>0.05
39	1 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.2)	>0.05

DISCUSSION

In our study, women that performed the screening is between the age of 20 – 68 years old, and the first sexual intercourse is 14 – 39 years old. Based on data in Indonesia, the median age of women that performed the sexual intercourse is 19-21.8years old; the cigarette prevalence is 3.8%, hormonal contraception is 49.4%, total fertility birth 2.6.[5]

From our study, we found significant differences in HPV DNA result among a group of age below 30 years old and above 30 years old. The guideline that is used nowadays that related to the cervical cancer screening is included all women with the age of 30 and above in one category. Based on this research, make an important question of homogeneity and HPV interpretation and Pap test at this age. Although the proportion of relative abnormality in low grade and high grade do not change with increasing age. It showed the loss of conformity between HR HPV detection and cytology abnormality with the increasing of age. Decreasing of HPV prevalency between all of the cytology level also found with the increasing age in the cohort study that contributed almost 1 million women with the age of 30 to 64 years.2For patients below 30 years old, especially in adolescents and young women, screening adolescents leads to the unnecessary evaluation and potentially to the treatment of pre-invasive cervical lesions that have a high probability of regressing spontaneously.[11]

Several studies show that HR HPV examination in a low degree of the lesion in women with older age shows beneficial to differentiate HPV infection that will grow into the precancer lesion. This is opposite to the study in the USA with RCT conclude that HR HPV screening has limited access to detect in low degree lesion. The approximate age in this study relatively young (27.9 years old) that makes it difficult to conclude in women above 30 years old, although from this study report 2x decreasing HR HPV prevalence in 18% of women LSIL above 30 years.[2]HR HPV type 16 and 18 need to have our attention since women with negative Pap and also had HPV-16 or HPV-18, colposcopy is recommended. ASC-US who also had HPV-16 or HPV-18 detected had approximately twice the risk of CIN 3+ as women with ASC-US and high-risk HPV types other than 16 or 18. Therefore, this population needs further colposcopy examination.

Although the presentation of HR HPV decrease in linear shape as related with age in the cytology abnormality, HPV prevalence with U shape and highest in the older age group. This pattern suggests that LR HPV dan HR HPV contributed to detection in patients with an older age group. Moreover, there is a strong relationship between the infection with low lever HPV and cervical abnormality in women with age above 45 years old that not seen in women with a younger age group. This condition is corresponding with observaional study before that mention the cervical transformation regression zone in older women and the high prevalence in LR HPV in vagina compare in cervical ephitelial.[2]

DNA HPV has better sensitivity. Therefore this could be an optional method in the HPV screening. A report in a cohort study with 324 women. Sensitivity and specivicity in cervical cytology, colposcopy, and DNA HPV is 66.66% and 93.54%, 86.84% and 86.32%, and 90% and 84.61%. With the false-negative as much as 33.3%, 8.95%, and 10%.[12] In a meta-analysis that compared the DNA HPV examination and cervical cytology with contribute 39050 participant with the asymptomatic clinic and 2% of pathological result NIS 1-2 from 11 studies, mentioned that the sensitivity and specificity of DNA HPV is 94% and 90%, with cervical cytology 70% and 95%. The false-negative in DNA HPV is 1/1000 women, and in cytology, the cervix is 6/1000 women.[13]The epidemiology data in Indonesia, the HPV type 16 and 18 prevalence in Indonesia is 4% in normal cytology and 87% in cervical cancer, and there is no data in HSIL and LSIL.[1]

The false negative in cervical cytology is caused by the 4 main problems, which are the error in the taking the sample with not taking the lesion part, tranfer error form the taking sample until the microsopic examination, error in the cell detection when the abnormal cell does not identify during the screening, the interpretation error when the abnormal cell detected but wrong interpretation. The minimal abnormal cell in the media could cause the false negative that frequently happen in the conventional Pap smear, with the highest error in the number of the abnormal cell< 30. The availability of micro

biopsy or Liquid-Based Cytology (LBC)group has a relatively smaller false negative, which is 6% if compared to conventional Pap smear (14%). Categorized the cause od the false negative in the cytology interpretation into; the high density of the micro biopsy and hyperchromatic material (27.3%), discariotic cell that broken, small or pale (37.8%), foreign material (8.4%), low level of contrast (7.4%), unexplainable (5.3%).[14]False negative is more frequent to be found in tumour type glandular than in squamosa (52% compare to 16%).[15]

The cervical cytology and DNA HPV has better accuracy. In a meta-analysis of two RCTs and six cross-sectional studies in women with NIS ≥2 mention that cytology examination only will show sensitivity (74.3%), specificity (95.1%) and false-negative(22.6%). On the other hand, in combination examination (cytology and DNA HPV) will give sensitivity (93.7%), specificity (85.8%) and false negative (8.3%).[16]A report in the cross-sectional study with 615 samples showed that DNA HPV positive in the negative cytology occurred in the HPV type based on the most frequent: 16,18, 51, 52, 6,56, 90, 39, 66, 33, dan 526.

This study reported routine examination in cervical cancer screening (cytology and DNA HPV) could give a different result. The HPV DNA test is having better sensitivity compare to citology. We found 32.5% of our study showed negative in cytology but having high-risk DNA result. A review reports that comparing HPV test and cervical smear with pooled sensitivity 94% and 70% respectively and specificity of 90% and 95% respectively.[13] Other studies reported this discrepancy occurred among their study population varies around 2.2% - 6.7%.2,6,[17]Several factors including a number of subject studies, preparation of patients, sampling, adequacy in samples and pathology reading, contribute to our result with the previous study as our HR HPV (+) with Pap (-) number considered higher. This may increase our awareness for screening of precancerous lesion of the cervix.

CONCLUSION

From Pap examination, we found 32.5% negative cytology result with high-risk HPV DNA result. The highest findings of HPV DNA type in our study was type 59 (22.8%). We found a significant difference in HPV DNA test result among women above 30 years old. Co-testing of Pap and HPV DNA is needed, especially if HPV DNA type 16 and 18 was found among negative Pap results.

CONFLICT of INTEREST

None to declare.

FUNDING STATEMENT

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Data Avaibility

The master data used to support the findings of this study are available from the corresponding author upon request.

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REFERENCES

1. Indonesia Human Papillomavirus and Related Cancers [Internet]. ICO/IARC Information Centre on HPV and Cancer. 2017. Available from: http://www.hpvcentre.net/statistics/reports/IDN.pdf.
2. Rositch AF, Silver MI, Burke A, Viscidi R, Chang K, Duke CM, et al. The correlation between human papillomavirus positivity and abnormal cervical cytology result differs by age among perimenopausal women. J Low Genit Tract Dis. 2013;17(1):38-47.
3. Weimann A, Braga M, Carli F, Higashiguchi T, Hubner M, Klek S, et al. ESPEN guideline: Clinical nutrition in surgery. ClinNut. 2017;36(3):623-50.
4. Wong FK, Ching JC, Chow JK. Comparison of the DiagCor GenoFlow Human Papillomavirus Array Test and Roche Linear Array HPV Genotyping Test. Open Virol J. 2010;4:169-74.
5. Human Papillomavirus and Related Diseases Report. ICO/IARC. 2017
6. Ozalp SS, Us T, Arslan E, Oge T, Kasifoglu N. HPV DNA and Pap smear test results in cases with and without cervical pathology. J Turk Ger Gynecol Associat. 2012;13(1):8-14.
7. El Banna N, Al Eyd G, Saeed R. High-risk human papillomavirus infection among women with pap smear tests negative for intraepithelial lesions or malignancy. Int J Med Public Health. 2014;4(1:.102-106

8. Gogacz M, Sarzynski M, Napierala R, Sierocinska-Sawa J, Semczuk A. Ovarian endometrioma in an 11-year-old girl before menarche: a case study with literature review. JPediatAdol Gynecol. 2012;25(1):e5-e7.
9. Thrall MJ, Russell DK, Facik MS, Yao JL, Warner JN, Bonfiglio TA, et al. High-risk HPV testing in women 30 years or older with negative Papanicolaou tests: initial clinical experience with 18-month follow-up. Am J Clin Pathol. 2010;133(6):894-8.
10. Wong OG, Lo CK, Chow JN, Tsun OK, Szeto E, Liu SS, et al. Comparison of the GenoFlow human papillomavirus (HPV) test and the Linear Array assay for HPV screening in an Asian population. JClinMicrobiol. 2012;50(5):1691-7.
11. Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. AmJClinPathol. 2012;137(4):516-42.
12. Gupta V, Tandon A, Nanda A, Sharma A, Bansai N, Singhal M. Correlation between Cytology, HPV-DNA Test and Colposcopy in Evaluation of Cervical Intraepithelial Lesions. J South Asian Fed Menopouse Soc. 2014;2(2):71-4.
13. Mustafa RA, Santesso N, Khatib R, Mustafa AA, Wiercioch W, Kehar R, et al. Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy. Int J Gynecol Obstet. 2016;132(3):259-65.
14. Gupta N, John D, Dudding N, Crossley J, Smith JH. Factors contributing to false-negative and potential false-negative cytology reports in SurePath liquid-based cervical cytology. Cytopathol. 2013;24(1):39-43.
15. Castillo M, Astudillo A, Clavero O, Velasco J, Ibanez R, de Sanjose S. Poor Cervical Cancer Screening Attendance and False Negatives. A Call for Organized Screening. PLoS One. 2016;11(8):e0161403.
16. Li T, Li Y, Yang GX, Shi P, Sun XY, Yang Y, et al. Diagnostic value of combination of HPV testing and cytology as compared to isolated cytology in screening cervical cancer: A meta-analysis. J Cancer Res Ther. 2016;12(1):283-9.
17. Louvanto K, Chevarie-Davis M, Ramanakumar AV, Franco EL, Ferenczy A. HPV testing with cytology triage for cervical cancer screening in routine practice. AmJObstetGynecol. 2014;210(5):474 e1-7.