

DISTRIBUTION OF HUMAN PAPILLOMA VIRUS (HPV) IN CERVICAL ADENOCARCINOMA AND ADENOSQUAMOUS CARCINOMA

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ABSTRACT

Approximately 20-30% of all cervical cancer cases are adenocarcinoma and adenosquamous carcinoma. Around 70% of all of these types of cancer are related to infection of Human Papillomavirus (HPV). This study evaluated the distribution of HPV genotype in cervical adenocarcinoma and adenosquamous carcinoma. A cross-sectional study was conducted at the Department of Anatomic Pathology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January to December 2015. The sample were 22 formalin-fixed paraffin-embedded (FFPE) of cervical adenocarcinoma tissues and adenosquamous carcinoma tissues. FFPE was used for DNA extraction and followed with HPV genotyping to detect 40 genotypes of HPV, including low risk (LR) and high risk (HR) HPV. The histopathological types of adenocarcinoma were adenocarcinoma NOS and mucinous adenocarcinoma, while the adenosquamous carcinoma types were adenosquamous carcinoma and adenosquamous carcinoma glassy. All of the specimens were infected by HPV. In cervical adenocarcinoma, the infection was by HPV 6, 11, 16, 18, 31, 45, 68B, and 72, and in adenosquamous carcinoma by HPV 6, 16, 18, 45, and 59. HPV 18 was predominant, which was found in 13/22 (59.1%) in adenocarcinoma and 19/22 (86.4%) in adenosquamous carcinoma. Single infection and multiple infections in adenocarcinoma were 13/22 (59.1%) and 9/22 (40.9%), while in adenosquamous carcinoma were 21/22 (95.5%) and 1/22 (4.5%) respectively. The most common HR HPVs found in this study were HPV 18, HPV 45, HPV 16 and LR HPV are HPV 11, HPV 6.

Keywords: human papillomavirus; cervical cancer; cervical adenocarcinoma; cervical adenosquamous carcinoma

ABSTRAK

Sekitar 20-30% kanker serviks merupakan adenokarsinoma dan adenosquamous carcinoma. Kedua kanker ini sekitar 70-100% terkait dengan infeksi Human Papillomavirus (HPV). Tujuan penelitian ini adalah untuk mengevaluasi distribusi genotipe HPV pada adenokarsinoma serviks dan karsinoma adenosquamous serviks. Penelitian dilakukan secara potong melintang di Departemen Patologi Anatomi RSUP Dr. Soetomo Surabaya pada periode Januari-Desember 2015. Sampel penelitian adalah 22 blok parafin dari jaringan adenokarsinoma serviks dan 22 blok parafin dari jaringan adenosquamous carcinoma. Blok parafin digunakan untuk ekstraksi DNA dan dilanjutkan analisis genotipe HPV yang dilakukan dengan mendeteksi 40 genotipe HPV, termasuk HPV risiko rendah (LR) dan risiko tinggi (HR). Jenis adenokarsinoma secara histopatologi adalah adenokarsinoma NOS dan adenokarsinoma musinosa; Jenis karsinoma adenosquamous adalah adenosquamous carcinoma dan adenosquamous carcinoma glassy. Semua spesimen terinfeksi HPV, pada adenokarsinoma serviks adalah HPV 6, 11, 16, 18, 31, 45, 68B, 72 dan pada karsinoma adenosquamous adalah HPV 6, 16, 18, 45, 59. HPV 18 didominasi, yang menunjukkan 13/22 (59,1%) pada adenokarsinoma dan 19/22 (86,4%) pada karsinoma adenosquamous. Infeksi tunggal dan multipel pada adenokarsinoma sebanyak 13/22 (59,1%) dan 9/22 (40,9%) dan pada karsinoma adenosquamous adalah 21/22 (95,5%) dan 1/22 (4,5%).), masing-masing. HPV HR yang paling umum adalah HPV 18, HPV 45, HPV 16 dan HPV LR adalah HPV 11, HPV 6.

Kata kunci: human papillomavirus; kanker serviks; adenokarsinoma serviks; karsinoma adenosquamous serviks

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INTRODUCTION

Cervical cancer is the fourth most common cancer that diagnosed in women after breast, colorectal, and lung cancer in the world. Based on data of the International Agency for Research on Cancer (IARC) in 2018, there was approximately 570 000 cervical cancer cases and 311 000 deaths occurred due to this disease. The incidence rate was 13.1 per 100 000 women and the mortality rate was 6.9 per 100 000 women (Bray et al 2018, Arbyn et al 2020). In 2020, IARC estimated that the number of new cervical cancer cases and mortality in the world was also in the fourth rank of all cancer cases, which was 604 127 (6.5%) for incidence and 341 831 (7.7%) for mortality (Globocan 2020a). In Indonesia, with total populations around 273 523 621 peoples, the incidence and mortality of cervical cancer was the second most common cancer after breast cancer at 2020. The incidence rate of cervical cancer was 36 633 cases (9.2%) and breast cancer was 65 858 (16.6%) (Globocan 2020b). In addition, these data also showed that cervical cancer in Indonesia was high and its incidence and mortality occupied the third rank in the world after India and China (Globocan 2020a).

Based on histopathological feature, there are three main types of cervical cancer, the squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma (Fujiwara et al 2014, Siriaunkgul et al 2013). The most common type of cervical cancer is squamous cell carcinoma, that approximately 70-75% of all cervical cancer. The remaining is cervical adenocarcinoma and adenosquamous carcinoma that around 20 -25% of cervical cancer (Fujiwara et al 2014, Siriaunkgul et al 2013). In the last decades, the incidence of squamous cell carcinoma tends to decrease, but adenocarcinoma and adenosquamous carcinoma tend to increase (Gien et al 2010, Zhang et al 2020). Recently, both adenocarcinoma and adenosquamous carcinoma is still treated in the same way as squamous cell carcinoma, although it has a different microscopic appearance. Squamous cell carcinoma contains many squamous cell components, while adenocarcinoma contains more glandular components and adenosquamous carcinoma contains glandular components as well as squamous cell components. Both of adenocarcinoma or adenosquamous carcinoma are located deeper than the ectocervix (Stolnicu et al 2018, Kurman et al 2011).

Some studies showed that the prognosis of adenocarcinoma and adenosquamous carcinoma is worse than squamous cell carcinoma (Gien et al 2010, Fujiwara et al 2014), so that early detection and histopathological diagnosis are important to use as the basis for determining the management of this cancer therapy.

Both adenocarcinoma and adenosquamous carcinoma is associated with infection of Human Papillomavirus (HPV) (Fujiwara et al 2014). There are two groups HPV, the High Risk (HR) HPV and Low Risk (LR) HPV. HR HPV, including HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 61, 73, and 81, is associated with cervical cancer development (Gutiérrez-Xicoténcatl et al 2009). LR HPV, consisting of HPV 6, 11, 40, 42, 43, 44, 54, 61, 72, and 81, is associated with the incidence of benign warts on oral and urogenital epithelium in adults and children (Zaravinos et al 2009). Several studies have shown that HPV DNA is found in 95- 100% of all cervical cancer (Gutiérrez-Xicoténcatl et al 2009, Izadi-Mood N et al 2012). Meta-analysis studies showed the genotypes of HPV that cause invasive cervical cancer in the world were HPV 16, 18, 33, 45, and 31 (Smith et al 2007).

The most common genotype of HPV in squamous cell carcinoma in Bandung Indonesia were HPV 16, 18, 45, and 52 (Panigoro et al 2013). Some studies showed that cervical adenocarcinoma and adenosquamous carcinoma were related with the HPV infection, with the most common were HPV 18 (Fujiwara et al 2014) or not related to HPV infection (Pirog 2017). Therefore, identification of HPV genotype infected in cervical adenocarcinoma and adenosquamous carcinoma is very important to be known and analyzed as a basis for determining the appropriate treatment of the cervical cancer.

The objective of this study was to evaluate the distribution of HPV genotype in cervical adenocarcinoma and adenosquamous carcinoma. This study detected 40 genotypes of HPV, including LR and HR-HPV from formalin fixed paraffin embedded (FFPE) specimens of cervical cancer types of adenocarcinoma and adenosquamous carcinoma.

MATERIALS AND METHODS

Sample Collection

A cross sectional study was conducted at the Department of Anatomic Pathology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Ethical clearance for this research was approved by Health Research Ethics Committee of the Faculty of Medicine, Universitas Airlangga. Data from cervical cancer patients in the period of January - December 2015 were recorded, then formalin-fixed paraffin embedded (FFPE) and Hematoxylin Eosin (HE) slides from these patients were collected. FFPE, in accordance with the inclusion criteria, was taken randomly and used for DNA extraction and HPV genotyping analysis. The

inclusion criteria were (1) specimens from cervical tissues diagnosed as adenocarcinoma and adenosquamous carcinoma by Pathologist and (2) tissue in FFPE were still adequate for immunohistochemistry staining (IHC). The exclusion criteria were (1) the cervical tissue in FFPE was completely cut or left insufficient to be used for slide processing and (2) tissue on FFPE was destroyed. In this study, there were 44 FFPE specimens from cervical tissues of adenocarcinoma and adenosquamous carcinoma patients.

HPV Genotyping

The preparation processes of FFPE for HPV genotyping were conducted as in our previous study (Mastutik et al 2018). Before use, the cutting area and the blades of the microtome was cleaned with 90% alcohol. This is useful for removing DNA residue and cell debris attached to the microtome and blade, thereby reducing DNA contamination. FFPE were cut into small pieces of ~25 μm^2 (5 μm x 5 μm). A number of 3-5 slices were used to deparaffinization by xylol and rehydration with ethanol and continued with DNA extraction process. DNA extraction was performed by using QIAamp DNA Mini Kit (Qiagen) according to the manufacture's protocol. The extraction product was used as the Polymerase Chain Reaction (PCR) template.

HPV genotyping was performed to detect HPV DNA, using *Ampliquality HPV type express v 3.0* (AB Analytica). Pre-denaturated PCR condition was performed for 10 min at 95°C, followed by denaturation at 95°C for 30 seconds, annealing at 50°C for 30 seconds, and extension at 72°C for 30 seconds. All cycles were 50 cycles. The last was final extension at 72°C for 5 minutes. This study identified 40 genotypes of HPV, including low risk (LR) and high risk (HR) HPV. There were HPV 6, 11, 16, 18, 26, 31, 33,35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59,61, 62, 64, 66, 67, 68a, 68b, 69, 70, 71, 72, 73, 81, 82, 83,84, 87, 89, 90.

RESULTS

The Characteristics of the Patients

This study was conducted in 44 FFPE from cervical tissues of adenocarcinoma and adenosquamous carcinoma patients. There were 22 adenocarcinoma patients aged 39-75 years and 22 adenosquamous patients aged 35-62 years. Histopathological diagnosis consisted of adenocarcinoma NOS and mucinous adenocarcinoma for cervical adenocarcinoma group and

adenosquamous carcinoma and adenosquamous carcinoma glassy for adenosquamous carcinoma group.

Clinical data and laboratory data profiles were presented in the table 1. The clinical data such as: temperature, heart rate and respiratory rate. Meanwhile, laboratory data that observed were white blood cell and erythrocyte sedimentation rate (ESR). Only 31 respondents from all samples were conducted respiratory check in medical record and 17 samples were checked the ESR.

Table 1. Characteristics of the patients

Type of cervical cancer	Age (year)	Number (person)
Adenocarcinoma:	39-75	22
• Adenocarcinoma NOS		20
• Mucinous Adenocarcinoma		2
Adenosquamous carcinoma:	35-62	22
• Adenosquamous carcinoma		21
• Adenosquamous carcinoma glassy		1
Total		44

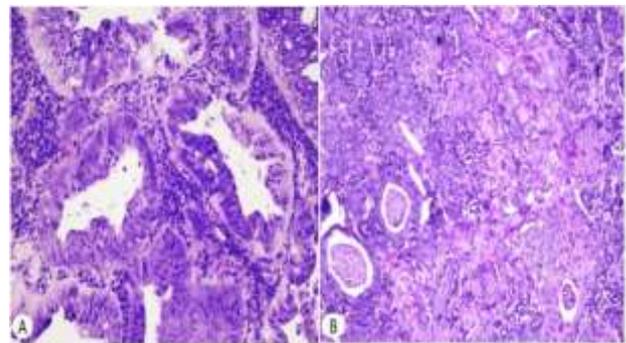


Figure 1. Histopathology of adenocarcinoma and adenosquamous carcinoma. (A) Cervical adenocarcinoma shows anaplastic epithelial cells arranged in irregular crowded glandular structure invading stroma, 200x (B) Cervical adenosquamous carcinoma shows tumor cells with biphasic pattern comprising of malignant glandular and squamous components, 200x

Table 2. Distribution of HPV genotype in cervical adenocarcinoma and adenosquamous carcinoma

HPV genotype	Number (person)	Percentage (%)
Cervical adenocarcinoma	22	
HPV 18 (HR)	13	59,1
HPV 11, 18 (LR-HR)	4	18,2
HPV 6,18, 45 (LR-HR-HR)	1	4,5
HPV 11, 16 (LR-HR)	1	4,5
HPV 11, 31 (LR-HR)	1	4,5
HPV 6, 45 (LR-HR)	1	4,5
HPV 68b, 72 (HR-LR)	1	4,5
Cervical adenosquamous carcinoma	22	
HPV 16 (HR)	1	4,5
HPV 18 (HR)	19	86,4
HPV 45 (HR)	1	4,5
HPV 6, 59 (LR-HR)	1	4,5
Total	44	

HPV: Human papillomavirus, HR: high risk, LR: low risk

The Genotype of HPV in Cervical Adenocarcinoma and Adenosquamous Carcinoma

In general, the genotypes of HPV in this study were HPV 6, 11, 16, 18, 31, 45, 59, 68B, 72. The genotype of HPV in cervical adenocarcinoma were HPV 6, 11, 16, 18, 31, 45, 68B, 72. HR-HPV were HPV 16, HPV 18, HPV 31, HPV 45, HPV 68B and LR-HPV were HPV 6, HPV 11, HPV 72. The genotype of HPV in adenosquamous carcinoma were HPV 6, 16, 18, 45, 59. HR-HPV were HPV 16, HPV 18, HPV 45, HPV 59. LR-HPV were HPV 6 (Table 2). The genotype of HPV in cervical adenocarcinoma and adenosquamous carcinoma were dominated by HPV 18 that was found in 13/22 (59,1%) for cervical adenocarcinoma and in 19/22 (86,4%) for cervical adenosquamous carcinoma.

HPV infection in this study was found as single infection by HR-HPV or multiple infection by HR/LR-HPV. In cervical adenocarcinoma, single infection was found in 13/22 (59,1%) and multiple infection in 9/22 (40,9%). Single infection by HPV 18 was in 13/22, while multiple infection by HPV 11, 18 was in 4/22; HPV 6, 18, 45 in 1/22; HPV 11, 16 in 1/22; HPV 11, 31 in 1/22; HPV 6, 45 in 1/22, and HPV 68b, 72 in 1/22. In

cervical adenosquamous carcinoma, the single infection was in 21/22 (95,5%) and multiple infection was in 1/22 (4,5%). Single infection by HPV 16 was in 1/22; HPV 18 in 19/22; HPV 45 in 1/22, while multiple infection by HPV 6, 59 was in 1/22. In all of cervical cancer, both in adenocarcinoma and adenosquamous carcinoma, the single infection was found in 34/44 (77,3%) which were infected by HPV 16, 18, 45 and multiple infection was in 10/44 (22,7%) which infected were by HPV 6, 11, 31, 45, 58, 68B, 72 (Table 3).

The prevalence of HPVs that infected in cervical adenocarcinoma and adenosquamous carcinoma were HPV 18 (67,3%), HPV 45 (5,5%), HPV 16 (3,6%) for HR-HPV and HPV 11 (10,9%), HPV 6 (5,5%) for LR-HPV (Table 4).

Table 3. Single and multiples infection of HPV in cervical adenocarcinoma and adenosquamous carcinoma

HPV Genotype	Number (person)	Percentage (%)
Cervical adenocarcinoma	22	
- Single infection	13	59.1
- Multiple infection	9	40.9
Cervical adenosquamous carcinoma	22	
- Single infection	21	95.5
- Multiple infection	1	4.5
Single infection	34	77.3
- HPV 18 (HR)	32	
- HPV 16 (HR)	1	
- HPV 45 (HR)	1	
Multiple infection	10	22.7
- HPV 11, 18 (LR-HR)	4	
- HPV 11, 16 (LR-HR)	1	
- HPV 11, 31 (LR-HR)	1	
- HPV 6, 18, 45 (LR-HR-HR)	1	
- HPV 6, 45 (LR-HR)	1	
- HPV 6, 59 (LR-HR)	1	
- HPV 68B, 72 (HR-LR)	1	

Table 4. Prevalence of HPV genotype in cervical adenocarcinoma and adenosquamous carcinoma

HPV Genotype	Number (time)	Percentage (%)
- HPV 18	37	67.3
- HPV 11	6	10.9
- HPV 45	3	5.5
- HPV 6	3	5.5
- HPV 16	2	3.6
- HPV 31	1	1.8
- HPV 59	1	1.8
- HPV 68B	1	1.8
- HPV 72	1	1.8
Total	55	100

DISCUSSION

The incidence of cervical adenocarcinoma and other type epithelial cancer, including adenosquamous carcinoma, was approximately 20-30% of cervical cancer. Both are rarely found so that guidelines in the management of therapy have not been established yet (Molijn et al 2016, Georgescu et al 2020). However, the incidence of cervical adenocarcinoma tends to increase, including in 13 European countries (Bray et al 2005), as well as in the Netherlands (Horst et al 2017). This was predominant in young women, age around 25-39 years old (Horst et al 2017). The survival rate and clinical outcome of cervical adenocarcinoma is worse than those in squamous cell carcinoma (Fujiwara et al 2014).

The World Health Organization was classified cervical cancer in three groups, the squamous cell carcinoma, adenocarcinoma, and other epithelial tumours. Adenocarcinoma consists of usual type adenocarcinoma, mucinous adenocarcinoma (endocervical type, intestinal type, signet-ring type), minimal deviation, villoglandular endometrioid adenocarcinoma, clear cell adenocarcinoma, serous adenocarcinoma, mesonephric adenocarcinoma. Another epithelial tumor is adenosquamous carcinoma that consists of adenosquamous carcinoma and adenosquamous carcinoma glassy variant (Kurman et al 2011, Stolnicu et al 2018). Based on histopathological type of cervical adenocarcinoma, the types of adenocarcinoma in this study belonged to adenocarcinoma of not otherwise specified (NOS) and mucinous adenocarcinoma. The adenosquamous carcinoma were adenosquamous carcinoma and adenosquamous carcinoma glassy.

Many studies found that HPV infection was associated with cervical cancer, including cervical adenocarcinoma and adenosquamous carcinoma. Study using in situ polymerase chain reaction on invasive adenocarcinoma glass slide showed that HPV DNA was detected underlying on adenocarcinoma cells and in squamous epithelium, while on adenosquamous carcinoma glass slide showed that HPV DNA was found mostly in pure squamous epithelium and small amount in the cervical gland (Ogura et al 2006). The prevalence of HPV infection varies around 60-100% (Ogura et al 2006, Molijn et al 2016). This was in accordance with the results of this study. We found that all of cervical cancer tissues in this study that consisted of 22 cervical adenocarcinomas and 22 cervical adenosquamous carcinoma showed 100% positively infected by HPV.

Other study showed that in cervical adenocarcinoma, including adenocarcinoma usual type, adenocarcinoma NOS, adenocarcinoma minimal deviation, clear cell

adenocarcinoma, endometrioid adenocarcinoma, serous adenocarcinoma, 426 of 596 cases (71.5%) were positively infected by HPV (Molijn et al 2016). In addition, in 110 specimens of cervical adenosquamous carcinoma showed that 97/110 (88%) were positive for HPV (Molijn et al 2016). A study in Thailand showed that HPV DNA was detected in 145/150 (97%) FFPE specimens from cervical adenocarcinoma tissues (Siriaungkul et al 2013) and in China from 121 cervical adenocarcinoma cases, 113 (93,4%) was positive for HPV infection (Wang et al 2018).

HPV infection is usually found in single infection by HR-HPV or multiple infection by HR/LR-HPV. In this study, the single infection of HPV both in adenocarcinoma and adenosquamous carcinoma was dominated by single infection of HR HPV that was 77.3% and followed by multiple infection of HR/LR HPV or HR/HR HPV of 22.7%. In addition, single infection in cervical adenosquamous carcinoma (95.5%) was higher than in cervical adenocarcinoma. (59.1%). This in accordance with another study that also showed that single infection in cervical adenocarcinoma was 375/596 (62,9%) and in multiple infection was 51/596 (8,6%) and single infection in cervical adenosquamous carcinoma was 88/110 (91%) and 9/110 (9%) in multiple infection (Molijn et al 2016). A study by Schellekens et al (2004) showed that single infection in adenocarcinoma was 93% and in adenosquamous carcinoma was 62%. Cervical adenocarcinoma in Thailand showed that single infection was 132/145 (91%) and multiple infection was 11/145 (8%) (Siriaungkul et al 2013), while in China, single infection was 91 (75,3%) and multiple infection was 22 (18,1%) (Wang et al 2018).

This study was found that the most predominant HPV single infection both in cervical adenocarcinoma and adenosquamous carcinoma was HPV 18. The other study from 16 specimens of cervical adenocarcinoma cases in Indonesia that showed single infection were HPV 18 (9/16 cases), HPV 45 (2/16 cases), HPV 16 (1/16 cases), HPV 52 (1/16 cases), HPV 59 (1/16 cases) and multiple infection with HPV 16/ HPV 18 (1/16 cases), and 1 specimen negative for HPV, while from 13 cervical adenosquamous carcinoma cases showed that single infection of HPV 18 (6/13), and HPV 16 (1/13), HPV 59 (1/13), and multiple infection by HPV 16/18, HPV 16/52, HPV 18/45, HPV 18/52, HPV 18/52/5 (1/13) (Schellekens et al 2004). In Thailand, the most predominant HPV single infection in cervical adenocarcinoma was HPV 18 was 86/132 (65.2%) and followed by HPV 16 was 40/132 (30,3%) (Siriaungkul et al 2013).

We found HPV 6, 11, 16, 18, 31, 45, 68B, 72 in cervical adenocarcinoma and HPV 6, 16, 18, 45, 59 in cervical adenosquamous carcinoma. In cervical adenocarcinoma, 59.1% were infected by HPV 18 and in cervical adenosquamous carcinoma, 86.4% were infected by HPV 18. This result was in accordance with other studies. Adenocarcinoma was associated with HPV 16 and HPV 18, but 50-58% was associated with HPV 18 (Fujiwara et al 2014).

A study in China from 718 specimens of cervical adenocarcinoma consisted of cervical adenocarcinoma usual mucinous type of 59%, adenosquamous of 15%, and other type of adenocarcinoma showing that infection of HPV had a clear relationship to HPV infection, particularly HPV 16, HPV 18, and HPV 45 (Molijn et al 2016). In Thailand, HPV 18 (95/145 66%) is the most common HPV in adenocarcinoma, followed by HPV 16 (44/145 30%), HPV 45 (5/145 3%) (Siriaunkgul et al 2013). In China, HPV 18 was identified in 35.8%, followed by HPV52 (21.6%), HPV 16 (17.4%), and HPV 58 (16.9%) (Wang et al 2018).

The most frequent of HR HPV in this study was HPV 18 (67.3%), HPV 45 (5.5%), HPV 16 (3.6%) and the LR HPV was HPV 11 (10.9%) and HPV 6 (5.5%). Another study in preinvasive and invasive cervical cancer showed that the most frequent HPV was HPV 16, HPV 18, HPV 45, HPV 52, HPV 67 (Mastutik et al 2018). The most common HPV that cause invasive cervical cancer in Asia are HPV 16, 18, 58, 33, 52, which HPV 52 and 58 are specific in Asia (Smith et al 2007). Most types of HPV in Indonesia were HPV 18, 16, 52, 45, 82 (Smith et al 2007). It was also found that the most often HPV found in invasive cervical cancer cases in Jakarta were HPV 16, 18, 52 (Schellenkens et al 2004), and in Bandung were HPV 16, 18, 45, 52 (Panigoro et al 2013, Tobing et al 2014). Furthermore, in Jakarta, Tasikmalaya, and Bali, Indonesia, the most common HPV were found to be HPV 52, 16, 18, and 39 (Vet et al 2008). This indicate that HPV 16 and HPV 18 is the most common causes of cervical cancer in Indonesia.

CONCLUSION

HPV DNA was detected in 100% of cervical adenocarcinoma and adenosquamous carcinoma, in single infection (77.3%) or multiple infection (22.7%) by HR/LR HPV or HR/HR HPV. The most common HPV in cervical adenocarcinoma, as well as in adenosquamous carcinoma, is HPV 18. In general, the most common HR HPV are HPV 18, HPV 45, HPV 16 and the most common LR HPV are HPV 11 and HPV 6. Based on this data, we suggest that the current use of a

bivalent or quadrivalent vaccine can be used to prevent this type of cervical cancer, including cervical adenocarcinoma and adenosquamous carcinoma in Indonesia.

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