

# 08. p16INK4A Expression in Condyloma

*by Gondo Mastutik*

---

**Submission date:** 09-Apr-2023 09:39AM (UTC+0800)

**Submission ID:** 2059273520

**File name:** 08.\_p16INK4A\_Expression\_in\_Condyloma.pdf (452.75K)

**Word count:** 5503

**Character count:** 27493

RESEARCH ARTICLE

Editorial Process: Submission:05/05/2021 Acceptance:10/17/2021

## p16<sup>INK4A</sup> Expression in Condyloma Acuminata Lesions Associated with High-Risk Human Papillomavirus Infection

Gondo Mastutik<sup>1\*</sup>, Alphania Rahniayu<sup>1,2</sup>, Afria Arista<sup>2</sup>, Dwi Murtiastutik<sup>1,2</sup>, Nila Kurniasari<sup>1,2</sup>, Trisniartami Setyaningrum<sup>1,2</sup>, Anny Setijo Rahaju<sup>1,2</sup>, Erna Sulistyani<sup>3</sup>

### 33 Abstract

**Objective:** The objective of this study was to discover the possible correlation between p16<sup>INK4A</sup> expression and the LR/HR-HPV infection in condyloma acuminata (CA) lesions. **Materials and Method:** This cross-sectional study was conducted during January-December 2017 on 33 CA patients. The expression of p16<sup>INK4A</sup> was detected by immunohistochemistry (IHC) staining. The positive interpretation was carried out by scoring which score 0 was negative, score 1 was sporadic, score 2 was focal, and score 3 was diffuses. The HPV genotypes were identified by reverse line blot, and 40 genotypes of HPV detected, including HR-HPV (HPVs 16, 18, 26, 31, 33,35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68a, 68b, 69, 73, and 82) and LR-HPV (HPVs 6, 11, 40, 42, 43, 44, 54, 55, 61, 62, 64, 70, 71, 72, 81, 83, 84, 87, 89, and 90). **Results:** The expression of p16<sup>INK4A</sup> was significantly correlated with HR-HPV infection. Patients infected with HR-HPV had 0.644 times higher possibility to express p16<sup>INK4A</sup> gene compared to those infected with LR-HPV. LR-HPV genotypes detected in CA patients were HPV 6, 11, 42, 61, 54, 81, 87, 89, and 90 and HR-HPV genotypes were HPV 18, 26, 45, 51, 52, 67, 68B, 69, and 82. LR-HPV was found in 19/33 of patients and HR-HPV was in 14/33 of patients. The expression of p16<sup>INK4A</sup> in CA lesions was diffuse in 15.2% of patients, was focal in 24.2% of patients, was sporadic in 39.4% of patients were, and was negative in 21.2% of patients. In LR-HPV group, there was no diffuse expression, focal expression was observed in 15.8%, sporadic in 47.4%, and negative in 36.8%, while in HR-HPV group, p16<sup>INK4A</sup> expression was detected in all lesions, in a way that its expression was diffuse in 35.7%, focal in 35.7%, and sporadic in 28.6%. **Conclusion:** IHC is a routine method in histopathological diagnosis, therefore the detection of p16<sup>INK4A</sup> expression by IHC can be used as a biomarker for HR-HPV infection diagnosis.

**Keywords:** p16<sup>INK4A</sup>- high-risk HPV- low-risk HPV- condyloma- sexually transmitted diseases

*Asian Pac J Cancer Prev*, 22 (10), 3219-3225

### Introduction

51  
Condyloma acuminata (CA) is the most frequent sexually transmitted disease worldwide (Santegoets et al., 2012). It is also known as genital warts or anogenital warts. These lesions are usually single or multiple appearing in the anogenital region and causing symptoms of itching, vaginal discharge, and bleeding. CA can be flat or lobulated and appears as pearl-like, filiform, plaque eruption, or cauliflower projection (Patel et al., 2013; Léonard et al., 2014). Its prevalence is increasing worldwide. The prevalence of CA in Italian female population during 2009-2010 was 3.8 cases per 1,000 women per year (Suligoi et al., 2017), in the UK population during 2010-2012 was 3.8% in males and 4.6% in females (Sonnenberg et al., 2019), and in the US population during 2013-2014 was 2.9% (Daugherty et al.,

2018). A systematic review on the incident of anogenital warts showed that their prevalence ranged from 160 to 289 per 100,000 persons. New incident of anogenital warts ranged from 103 to 168 per 100,000 persons among males and 76 to 191 per 100,000 persons among females (Patel et al., 2013).

The most common cause of CA is Human Papillomavirus (HPV). There are two groups of HPV, including high risk (HR) HPV and low risk (LR) HPV. HR-HPV are HPV genotypes of 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 61, 73, and 82, and LR-HPV are HPV genotypes of 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, and 81 (Braaten et al., 2008; Gutiérrez-Xicoténcatl et al., 2009). LR-HPV causes CA, but a study in China showed that the infection of HR-HPV was also found in CA lesions. In some cases, CA is caused by the combination of LR and HR-HPV infections (Lu et al., 2014). Persistent

5  
<sup>1</sup>Department of Anatomic Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. <sup>2</sup>Department of Dermatology and Venereology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. <sup>3</sup>Department of Oral Medicine, Faculty Dentistry, Jember University, Jember, Indonesia \*For Correspondence: gondomastutik@fk.unair.ac.id

infection of LR or HR-HPV is a risk factor for the transformation of epithelial to benign hyperplasia or premalignant lesions. HR-HPV is related to the occurrence of malignancy in women, as cervical cancer (Santegoets et al., 2012). Some literature considers HR-HPV as the main causative agent responsible for the cervical cancer (Braaten et al., 2008). The detection of HPV genotype is very important to prevent, establish early diagnosis, and initiate the treatment in cervical cancer. Determination of LR or HR-HPV in anogenital warts can be used as a factor to predict the progression of lesions to benign or malignant lesions.

The E7 HPV protein plays a role in the cell transformation process. It binds to important proteins, such as the pRB and cyclin A/CDK2 complex, inhibiting the interaction between Rb and E2F. The E7 protein of HR-HPV deactivates pRB, resulting in the accumulation of p16<sup>INK4A</sup> protein. The expression of p16<sup>INK4A</sup> can also be considered as a marker of E7 gene activity (Izadi-Mood et al., 2012; Romagosa et al., 2011). p16<sup>INK4A</sup> plays a role in cell cycle regulation and it is involved in the processes of apoptosis, angiogenesis, cell invasion. This activity may be associated with overexpression in cancer (Romagosa et al., 2011). The expression of p16<sup>INK4A</sup> is a marker to determine the prognosis of a malignancy caused by HPV infection (Missaoui et al., 2010), suggesting that p16<sup>INK4A</sup> can be a specific marker for HPV infection and may correlate with the type of HR-HPV or LR-HPV. The objective of this study was to analyze the correlation between p16<sup>INK4A</sup> expression and the LR-HPV or HR-HPV in CA lesions. This study identified the genotype of HPV and performed immunohistochemical analysis of p16<sup>INK4A</sup> staining of.

## Materials and Methods

### The samples collection

This cross-sectional study was conducted at Outpatient Clinic of Department Dermatology and Venereology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January 2017 to December 2017. The study was ethically approved by the Medical Ethic Research at Dr. Soetomo General Academic Hospital, Surabaya (ethical code: 382/Panke.KKE/V/2016).

All patients with CA, both male and female, who were willing to participate in the study, were included. Informed consent was obtained from the participants. Menstruating and pregnant women, those who suffered from an active pelvis and / or acute cervicitis, men or women with a diagnosis of HIV and AIDS, and those who were not willing to participate in the study were excluded.

The specimens were 33 tissues of CA. Tissue from each patient was divided into 2 parts, one part for tissue processing into paraffin block preparations followed by histopathological diagnosis and immunohistochemistry (IHC) staining, while another for the examination of the HPV genotype. Histopathological diagnosis of CA and analysis of IHC staining was performed by a pathologist.

### Expression of p16<sup>INK4A</sup>

The expression of p16<sup>INK4A</sup> was detected by

IHC staining using Anti-CDKN2A/ p16<sup>INK4A</sup> Antibody (clone 1E12E10) IHC-plus™ LS-B5261 (LS Bio). The interpretation was positive if cells were stained in the nucleus or combined in the nucleus and cytoplasm. The assessment was carried out based on guidelines presented by Klaes et al. (2001) as follows:

Score 0 (negative): if cells were stained positive <1% of all cells

Score 1 (sporadic): if cells were stained positive <5% of all cells

Score 2 (focal): if cells were stained positive <25% of all cells

Score 3 (diffuses): if cells were stained positive > 25% of all cells.

### Genotyping of HPV

Virus extraction was carried out from CA tissues using the QIAamp DNA Mini Kit (Qiagen) kit and according to the manufacturer's protocol. Genotyping of HPV was performed by Polymerase Chain Reaction (PCR), then followed by reverse line blot using the Ampliquity HPV type express v 3.0 kit (Ab Analitica). This kit could detect 40 genotypes of HPV, including HR-HPV were HPV 16, 18, 26, 31, 33,35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68 (68a, 68b), 69, 73, and 82 and LR-HPV were HPV 6, 11, 40, 42, 43, 44, 54, 55, 61, 62, 64, 70, 71, 72, 81, 83, 84, 87, 89, and 90.

### Statistical analysis

The difference in the expression of p16<sup>INK4A</sup> on CA patients with HR-HPV or LR-HPV groups infection was analyzed by Mann Whitney test (significant if p <0.05). The correlation between variables was analyzed by two-tailed Spearman's rho (significant if p <0.05).

## Results

### Characteristics of patient

This study was performed on 33 patients suffering from CA. Patients' characteristic, such as sex, age, sexual partner, duration of the symptoms, medical history, presence of lesion in the partner, history of treatment, and shape, type, and location of the lesion were investigated. The patients consisted of 12 (36.4%) males and 21 (63.6%) females. The patients aged from 18 to 64 years. The highest frequency was allocated to the age group of 15-24 years old (51.5%). Regarding sexual partner, it was found that 30/33 of the patients (90.9%) were heterosexual (men having sex with women), 2/33 (6.1%) were bisexual (having sex with the same and different sex), and 1/33 (3.0%) were homosexual (having sex with the same sex). Regarding symptoms duration, the highest frequency was allocated to the duration of 1 to 3 months. Mostly, the patients experienced CA for the first time, there was no lesion in their partner, and received TCA therapy, respectively. Considering the shape, type, and location of the lesion, it was revealed that the highest frequencies were allocated to papule shape, multiple type of lesions, and gland penis for male and labia majora for female (Table 1).

### HPV genotype in CA lesions

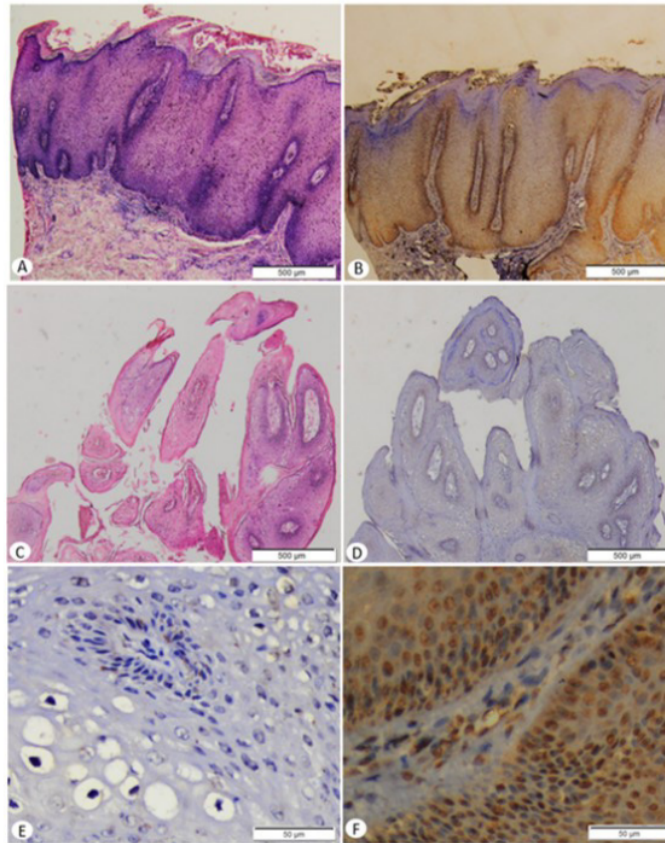


Figure 1. The Histopathological Feature and p16<sup>INK4A</sup> Expression of Condyloma Acuminata. A, Condyloma acuminata from HR-HPV infected patients, in HE staining (40 x magnification); B, In the same patients, p16<sup>INK4A</sup> expression showed in diffuse (score 3) (40 x magnification); C, Condyloma acuminata from LR-HPV infected patients, in HE staining (40 x magnification); D, In the same patients, p16<sup>INK4A</sup> expression showed negative (score 0) (40 x magnification); E, p16<sup>INK4A</sup> expression in negative (score 0) (400 x magnification); F, p16<sup>INK4A</sup> expression in diffuse (score 3) (400 x magnification).

The genotype of HPV included the infection of HPV-HR and LR, both single and multiple infections. The single or multiple infections of HPV-LR was assumed as infection of LR-HPV. The multiple infection of LR-HPV with HR-HPV was assumed as infection of HR-HPV. The genotype of LR-HPV were HPV 6, 11, 42, 61, 54, 81, 87, 89, and 90, and of HR-HPV were 18, 26, 45, 51, 52, 67, 68B, 69, and 82. LR-HPV was found in 19/33 (57.6%) of the patients and HR-HPV was seen in 14/33 (42.4%) of the patients (Table 2). The most dominant HPV was HPV 11 that infected 24/56 (42.9%) times more, then followed by HPV 6 (16.1%) and HPV 18, HPV 51, and HPV 82 for 5.4%, respectively.

#### p16<sup>INK4A</sup> expression in CA lesions

The expression of p16<sup>INK4A</sup> in CA lesions showed that nucleus or the combination of nucleus and cytoplasm of cell was stained in brown color, indicating in sporadic, focal, or diffuse (Figure 1). The results showed that 7/33 (21.2%) of the lesions were negative, 13/33 (39.4%) were sporadic, 8/33 (24.2%) were focal, and 5/33 (15.2%)

were diffuse. In LR-HPV group, the results showed that negative, sporadic, and focal lesions were 7/19 (36.8%), 9/19 (47.4%), and 3/19 (15.8%), respectively. In HR-HPV group, it was found that the frequency of sporadic lesions was 4/14 (28.6%), focal was 5/14 (35.7%), and diffuse was 5/14 (35.7%) (Table 3). There was a significant different between LR-HPV and HR-HPV groups in terms of p16<sup>INK4A</sup> expression in CA lesion ( $p = 0,000$ ). Correlation between p16<sup>INK4A</sup> expression and LR-HPV and HR-HPV infections was moderate ( $r = 0,644$ ,  $p = 0,000$ ).

#### Discussion

The microscopic features of CA lesions based on haematoxylin eosin (HE) staining are parakeratosis, hyperkeratosis, hypergranulosis, basal cell hyperplasia, and koilocytic (Léonard et al., 2014). In this study, CA lesions were seen as papules, cauli flowers, and flat-tapping papules. The microscopic features found in this study were hyperkeratosis, parakeratosis, papillomatosis, hypergranulosis, and hyperplasia of basal

Table 1. Characteristics of Patients with Condyloma Acuminata

Characteristics of Patients	N (%)	Single or multiple infection LR/LR HPV N (%)	Multiple infection of LR/HR HPV N (%)
<b>Sex</b>			
Male	12 (36.4)	7 (21.2)	5 (15.1)
Female	21 (63.6)	12 (36.4)	9 (27.3)
<b>Age</b>			
15-24 years	17 (51.5)	10 (30.3)	7 (21.2)
25-34 years	6 (18.2)	3 (9.1)	3 (9.1)
35-44 years	7 (21.2)	4 (12.1)	3 (9.1)
45-54 years	2 (6.1)	1 (3.0)	1 (3.0)
55-64 years	1 (3.0)	1 (3.0)	0
<b>Sexual Partner</b>			
Heterosexuals	30 (90.9)	18 (54.5)	12 (36.4)
Homosexual	1 (3.0)	1 (3.0)	0
Bisexual	2 (6.1)	0	2 (6.1)
<b>Duration of symptom</b>			
< 1 month	5 (15.1)	1 (3.0)	4 (12.1)
1- 3 months	20 (61.6)	14 (42.4)	6 (18.2)
4 - 6 months	6 (18.2)	3 (9.1)	3 (9.1)
> 6 months	2 (6.1)	1 (3.0)	1 (3.0)
<b>History</b>			
First lesion	26 (78.8)	15 (45.4)	11 (33.3)
Recurrent lesion	7 (21.2)	4 (12.1)	3 (9.1)
<b>Lesion on the partner</b>			
Have lesion on the partner	4 (12.1)	2 (6.1)	2 (6.1)
No lesions on the partner	29 (87.9)	17 (51.5)	12 (36.4)
<b>Therapy</b>			
TCA	19 (57.6)	11 (33.3)	8 (24.2)
Cautery	14 (42.4)	8 (24.2)	6 (18.2)
<b>Shape</b>			
Papule	28 (84.8)	16 (48.5)	12 (36.4)
Cauli flower	4 (12.1)	2 (6.1)	2 (6.1)
Flat tapped papule	1 (3.0)	1 (3.0)	0
<b>Type</b>			
Multiple	31 (93.9)	18 (54.5)	13 (39.4)
Solitary	2 (6.1)	1 (3.0)	1 (3.0)
<b>Location</b>			
Penile	7 (21.2)	4 (12.1)	3 (9.1)
Anus	4 (12.1)	2 (6.1)	2 (6.1)
Penile and anus	1 (3.0)	1 (3.0)	0
Labia (majora and minora)	16 (48.5)	10	6 (18.2)
Vulva	3 (9.1)	1 (3.0)	2 (6.1)
Introitus vagina	1 (3.0)	0	1 (3.0)
Perineum	1 (3.0)	1 (3.0)	0

cell, as well as the koilocytes that usually is associated with HPV infection.

20 The most common cause of CA is infection by HPV. There are more than 40 genotypes of HPV that can infect the anogenital area that are usually infected by LR-HPV including HPV 6 and HPV 11 in single infection, but most commonly co-infection with LR-HPV or HR-HPV

(Léonard et al., 2014; Hasanzadeh et al., 2019). The results of this study showed that all the tissues taken from the patients, who were clinically diagnosed with CA, were positive for LR-HPV or HR-HPV infections, in single infection or multiple infection. Most of the patients were infected by LR-HPV, while 42.4% were infected by LR-HPV and co-infected with HR-HPV. In line with this

Table 2. Distribution of HPV in Condyloma Acuminata Lesions

Genotype of HPV	HR or LR HPV genotypes	Frequency N (%)
LR HPV		19 (57,6)
HPV 6	LR	4
HPV 11	LR	12
HPV 6, 11	LR	2
HPV 6,81,87,89	LR	1
HR HPV		14 (42,4)
HPV 6,11,18,51,82	HR	1
HPV 6,42,51,61	HR	1
HPV 11, 18	HR	2
HPV 11,18,45	HR	1
HPV 11, 26	HR	1
HPV 11,67	HR	1
HPV 11, 51, 82	HR	1
HPV 11, 52, 54	HR	1
HPV 11, 52,69,90	HR	1
HPV 11, 68B	HR	1
HPV 11, 82	HR	2
Total		33

study, a cross-sectional study in Kuwait on 156 patients with genital warts showed that 102/156 (65.4%) of the patients were infected by LR-HPV and 54/156 (34.6%) of the patients were infected by HR-HPV. About 88.4% of the patients in the aforementioned study had single infection and 11.6% had multiple infections (Al-Awadhi et al., 2019). Another study in Spain showed that the frequency of LR-HPV infection was 63/138 (45.6%) in their patients and 71/138 (41.4%) of anogenital warts patients were infected by HR-HPV (Arroyo et al., 2016). The other study on 66 anogenital warts specimens showed that LR-HPV infected 42/66 (62.1%) which was dominated by HPV 6 (47%), and HPV-11 (13.6%), as well as HPV 18 and HPV 3 (Ozaydin-Yavuz et al., 2019). We discovered that that beside LR-HPV, CA was also co-infected with HR-HPV that could develop to malignant cancer. Therefore, identification of HPV genotype can predict the risk of developing related diseases. In addition, determination of HPV genotype affects treatment management, patients' follow-up, and prevention strategies.

The findings of this study revealed that 57.6% of CA patients were infected by LR-HPV and the rest were

infected by both LR-HPV and HR-HPV infections. The most common HPV genotypes were HPV 11 and HPV 6 for LR-HPV, followed by HPV 18, HPV 51, and HPV 82 for HR-HPV. The incidence of CA and the progression of the disease can be prevented by vaccination. Recently, there are 3 commercial vaccines against HPV infection, namely Gardasil to prevent infections caused by HPV 6, 11, 16, and 18, Cervarix to prevent infections caused by HPV 16, and 18, and Gardasil 9 to prevent infections caused by HPV 6, 11, 61, 18, 31, 33, 45, 52, and 58 (Gupta et al., 2017). A previous study on anogenital benign lesions showed that HPV genotype in CA patients was dominated by HPV 11 and HPV 6 among 13 female patients (Arista et al., 2019) and 12 male patients (Murtiastutik et al., 2019). In pre-cancerous lesion and cancerous lesion of uterine cervix, those were dominated by HPV 16 (62.68%), then followed by HPV 18 (20.9%), HPV 45 (5.97%), HPV 52 (5.97%), and HPV 67 (4.48%) (Mastutik et al., 2018). Vaccination programs is expected to reduce the incidence of these diseases, but there are some genotypes of HPV that cannot be targeted by the current vaccines. Therefore, strategies to prevent the incidence of CA or the progression of malignancy still need to be developed.

Oncoprotein E6 and E7 of HR-HPV play a role in cancer development. HR-HPV E6 mediates p53 inactivation by binding to the conserved domains of E6AP (E6-linked protein) to form the E6/ E6AP/p53 complex. This complex causes degradation of p53 by ubiquitination mechanism. HR-HPV E7 targets to degrade the retinoblastoma protein (pRB). In normal cells, when cells are prevented from entering the S phase, the pRB binds to the E2F family of transcription factor, so that the cell stops at the checkpoint of G1-S phase, activating cell cycles arrest. pRb, which is phosphorylated by cyclin D1/CDK 4/6 complex, causes E2F to be released and enter the nucleus. The cell enters the S phase which then starts the activation of gene transcription (Munger et al., 2013, Pal and Kudu, 2020). Furthermore, phosphorylated pRB is a p16<sup>INK4A</sup> feedback mechanism. HPV E7 induces degradation of pRB by an ubiquitin proteasome pathway that causes the loss feedback mechanism of p16<sup>INK4A</sup> and then leads to accumulation of p16<sup>INK4A</sup>, presenting as overexpression of p16<sup>INK4A</sup> (Lassen et al., 2009; Faraji et al., 2017).

The overexpression of p16<sup>INK4A</sup> in this study was sporadic (39.4%), focal (24.2%), diffuse (15.2%), and negative (21.2%). Another study on p16<sup>INK4A</sup> expression in 24 CA specimens showed that overexpression of p16<sup>INK4A</sup> were sporadic in 11/24 of the specimens (45.8%),

Table 3. The p16<sup>INK4A</sup> Expression on Condyloma Acuminata that Infected by LR or HR-HPV

p16 <sup>INK4A</sup> expression	HPV genotype		Total N (%)	p-value
	LR-HPV N (%)	LR/HR-HPV N (%)		
Score 0 (Negative)	7 (36.8)	0 (0)	7 (21.2)	0.000*
Score 1 (Sporadic)	9 (47.4)	4 (28.6)	13 (39.4)	
Score 2 (Focal)	3 (15.8)	5 (35.7)	8 (24.2)	
Score 3 (Diffuse)	0 (0)	5 (35.7)	5 (15.2)	
Total	19 (100)	14 (100)	33 (100)	

\*Mann Whitney, Asymptotic Significance (2-tailed) with p = 0,000 (p < 0,05); Correlation is significant at the 0.01 level (2-tailed) with Spearman's rho (r) = 0,644, p = 0,000

were focal in 7/24 of the specimens (29.2%), and were negative in 6/24 of the specimens (25%) (Kazlouskaya et al., 2013). The expression of p16<sup>INK4A</sup> in cervix tended to increase from cervical normal epithelium to invasive cervical cancer (Missaoui et al., 2010; Izadi-Mood et al., 2012) and cervical adenocarcinoma (Mastutik et al., 2021). The expression of p16<sup>INK4A</sup> in HR-HPV showed that all specimens were positive ranging from sporadic to diffuse. In LR-HPV were sporadic and focal, whereas 36.8% of specimens were not expressed in p16<sup>INK4A</sup> and none of specimens expressed in diffuse category. Other study on anal lesion with HR HPV infection showed that all specimens expressed p16<sup>INK4A</sup> ranging from sporadic to diffuse, whereas those infected with LR-HPV were mostly patchy (Leeman et al., 2019). In oropharyngeal squamous cell carcinomas and tonsillar dysplasia that were positive for HPV 16, p16<sup>INK4A</sup> expression was also diffuse. However, in benign and pre-malignant lesions were positive for HPV 6 and HPV 11 showed variations from negative to strong positive (Mooren et al., 2014). All cervical lesions infected with HR-HPV had a significant, strong, and diffuse p16<sup>INK4A</sup> expression, whereas those infected with LR-HPV showed mild p16<sup>INK4A</sup> expression (score 1) (Missaoui et al., 2014).

These findings highlighted that the expression of p16<sup>INK4A</sup> significantly correlated with HR-HPV infection, in a way that CA lesions infected by HR-HPV had 0.644 times more chances to express p16<sup>INK4A</sup> compared to CA lesions infected by LR-HPV. As previous studies showed that p16<sup>INK4A</sup> expression was associated with HR-HPV infection in oropharyngeal squamous (Liu et al., 2015), mucosal squamous cell carcinomas of the head and neck (Antonsson et al., 2015), cervical squamous intraepithelial lesion (Yildiz et al., 2007), and invasive cervical and vaginal carcinomas (Missaoui et al., 2010; Missaoui et al., 2014). HR-HPV is integrated into the host cell genome, whereas LR-HPV prefers extra chromosome as episome, so that the expression of E6 and E7 oncoproteins are within the regulatory framework of E1 and E2 HPV (Boulet et al., 2007). HR-HPVs, such as HPV 18, 33, HPV 51, HPV 58, and HPV 59, were found to be integrated, while HPVs 30, 35, 39, 44, 45, 53, 56, 59, 74 and 82 did not tend to be integrated, but to be in episome form (Nkili-Meyong et al., 2019). In this study, it was found that HR-HPVs 18, 51, and 82. As reported by Nkili-Meyong et al., (2019), HPV 18 was founded to be integrated in 55% of the positive HPV 18 specimen, HPV 51 was integrated in 25% of the positive HPV 51 specimen, and HPV 82 was founded in extra chromosome. This integration was associated with partial or total deletion of E1 and E2 genes, leading to the overexpression of E6 and E7 due to loss of feedback mechanism by E2 protein (Woodman et al., 2007; Nkili-Meyong et al., 2019). In addition, the HR-HPV E7 oncoproteins have higher affinity to bind pRB than LR-HPV E7, increasing the accumulation of p16<sup>INK4A</sup>. Therefore, all specimens infected by HR-HPV in this study were positive for the expression of p16<sup>INK4A</sup> in sporadic, focal, and diffuse forms, while those infected by LR-HPV had sporadic and focal, but not diffuse expression.

In conclusion, this study found significant differences between CA specimens infected by LR-HPV (HPV 6, 11,

42, 61, 54, 81, 87, 89, 90) and HR-HPV (HPV 18, 26, 45, 51, 52, 67, 68B, 69, 82) regarding the expression of p16<sup>INK4A</sup>. p16<sup>INK4A</sup> expression was correlated with HR-HPV infection moderately. IHC is a routine method to perform the diagnostic of histopathological. Therefore, IHC of p16<sup>INK4A</sup> could be used as biomarker for HR-HPV infection to predict the malignancy development of CA lesions.

### Author Contribution Statement

Concepts, design, definition of intellectual content: Gondo Mastutik. Literature search: Gondo Mastutik, Afria Arista. Clinical studies: Gondo Mastutik, Dwi Murtiastutik, Trisniartami Setyaningrum. Experimental studies: Gondo Mastutik, Alphania Rahniayu, Afria Arista. Data acquisition: Nila Kurniasari, Alphania Rahniayu, Anny Setijo Rahaju. Data analysis: Gondo Mastutik, Alphania Rahniayu, Anny Setijo Rahaju. Statistical analysis: Gondo Mastutik, Nila Kurniasari, Anny Setijo Rahaju. Manuscript preparation and manuscript editing: Gondo Mastutik, Afria Arista, Anny Setijo Rahaju. Manuscript review: Gondo Mastutik, Alphania Rahniayu, Dwi Murtiastutik, Trisniartami Setyaningrum, Erna Sulistyani.

### Acknowledgement

We are thankful of Government of the Republic of Indonesia, the Ministry of Research, Technology and Higher Education, and the Faculty of Medicine, Airlangga University for funding in this research with the university's operational funding for the 2017 fiscal year.

### Funding statement

This study was supported by the Faculty of Medicine, Airlangga University, and the university's operational funding for the 2017 fiscal year. This manuscript have not been presented at a scientific event or submitted to any other journals.

### Ethical statement

Ethical study was approved by the Medical Ethic Research at Dr. Soetomo General Academic Hospital Surabaya, Indonesia (ethical code:382/Panke. KKE/V/2016).

### Statement conflict of interest

The authors declare no conflict of interest

### References

- Al-Awadhi R, Al-Mutairi N, Albatineh AN, Chehadeh W (2019). Association of HPV genotypes with external anogenital warts: a cross sectional study. *BMC Infect Dis*, **19**, 375-82.
- Antonsson A, Neale RE, Boros S, et al (2015). Human papillomavirus status and p16(INK4A) expression in patients with mucosal squamous cell carcinoma of the head and neck in Queensland, Australia. *Cancer Epidemiol*, **39**, 174-81.
- Arista A, Murtiastutik D, Setyaningrum T, Mastutik G (2019). Genotyping of Human Papilloma Virus (HPV) in female condyloma acuminata patient in Dr. Soetomo Hospital, Surabaya. *Dermatol Rep*, **11**, 122-3.

- Arroyo LS, Basaras M, Arrese E, et al (2016). Distribution of genital human papillomavirus genotypes in benign clinical manifestations among men from Northern Spain. *BMC Public Health*, **16**, 81-8.
- Boulet G, Horvath C, Vanden Broeck D, Sahebali S, Bogers J (2007). Human papillomavirus: E6 and E7 oncogenes. *Int J Biochem Cell Biol*, **39**, 2006-11.
- Braaten KP, Laufer MR (2008). Human Papillomavirus (HPV), HPV-Related Disease, and the HPV Vaccine. *Rev Obstet Gynecol*, **1**, 2-10.
- Daugherty M, Byler T (2018). Genital Wart and Human Papillomavirus Prevalence in Men in the United States From Penile Swabs: Results From National Health and Nutrition Examination Surveys. *Sex Transm Dis*, **45**, 412-6.
- Faraji F, Zaidi M, Fakhry C, Gaykalova DA (2017). Gaykalova DA. Molecular mechanisms of human papillomavirus-related carcinogenesis in head and neck cancer. *Microbes Infect*, **19**, 464-75.
- Gupta G, Glueck R, Patel PR (2017). HPV vaccines: Global perspectives. *Hum Vaccin Immunother*, **13**, 1421-24.
- Gutiérrez-Xicoténcatl L, Plett-Torres T, Madrid-González CL, Madrid-Marina V (2009). Molecular diagnosis of human papillomavirus in the development of cervical cancer. *Salud Publica Mex*, **51**, S479-88.
- Hasanzadeh M, Rejali M, Mehramiz M, et al (2019). The interaction of high and low-risk human papillomavirus genotypes increases the risk of developing genital warts: A population-based cohort study. *J Cell Biochem*, **120**, 12870-4.
- Izadi-Mood N, Asadi K, Shojaei H, et al (2012). Potential diagnostic value of P16 expression in premalignant and malignant cervical lesions. *J Res Med Sci*, **17**, 428-33.
- Kazlouskaya V, Shustef E, Allam SH, Lal K, Elston D (2013). Expression of p16 protein in lesional and perilesional condyloma acuminata and Bowenoid papulosis: clinical significance and diagnostic implications. *J Am Acad Dermatol*, **69**, 444-9.
- Klaes R, Friedrich T, Spitkovsky D, et al (2001). Overexpression of p16(INK4A) as a specific marker for dysplastic and neoplastic epithelial cells of the cervix uteri. *Int J Cancer*, **92**, 276-84.
- Lassen P, Eriksen JG, Hamilton-Dutoit S, et al (2009). Effect of HPV-associated p16<sup>INK4A</sup> expression on response to radiotherapy and survival in squamous cell carcinoma of the head and neck. *J Clin Oncol*, **27**, 1992-8.
- Leeman A, Jenkins D, Marra E, et al (2019). Grading immunohistochemical markers p16<sup>INK4a</sup> and HPV E4 identifies productive and transforming lesions caused by low- and high-risk HPV within high-grade anal squamous intraepithelial lesions. *Br J Dermatol*, **182**, 1026-33.
- Léonard B, Kridelka F, Delbecq K, et al (2014). A clinical and pathological overview of vulvar condyloma acuminatum, intraepithelial neoplasia, and squamous cell carcinoma. *Biomed Res Int*, **2014**, 1-11.
- Liu SZ, Zandberg DP, Schumaker LM, Papadimitriou JC, Cullen KJ (2015). Correlation of p16 expression and HPV type with survival in oropharyngeal squamous cell cancer. *Oral Oncol*, **51**, 862-9.
- Lu LH, Yu J, Zhang YH, Wu XF, Liu XY (2014). HPV Infection and Distribution of HPV Genotypes on Patients with Condyloma Acuminatum. *J Reproduct Contraception*, **25**, 26-31.
- Mastutik G, Alia R, Rahniayu A, et al (2018). Genotyping of human papillomavirus in cervical precancerous lesion and squamous cell carcinoma at Dr. Soetomo Hospital, Surabaya, Indonesia. *Afr J Infect Dis*, **12**, 7-12.
- Mastutik G, Rahniayu A, Kurniasari N, Rahaju AS, Alia R (2021). Correlation between the expression of E6 HPV with P53 and P16<sup>INK4A</sup> at cervical adenocarcinoma and cervical normal. *Indian J Forensic Med Toxicol*, **15**, 1827-34.
- Missaoui N, Trabelsi A, Hmissa S, et al (2010). p16<sup>INK4A</sup> overexpression in precancerous and cancerous lesions of the uterine cervix in Tunisian women. *Pathol Res Pract*, **206**, 550-5.
- Missaoui N, Abdelkarim SB, Mokni M, Hmissa S (2014). p16<sup>INK4A</sup> expression in squamous cell carcinomas of the vagina and the vulva in Tunisian women. *Asian Pac J Cancer Prev*, **15**, 10803-8.
- Mooren JJ, Gültekin SE, Straetmans JM, et al (2013). P16(INK4A) immunostaining is a strong indicator for high-risk-HPV-associated oropharyngeal carcinomas and dysplasias, but is unreliable to predict low-risk-HPV-infection in head and neck papillomas and laryngeal dysplasias. *Int J Cancer*, **134**, 2108-17.
- Munger K, Gwin TK, McLaughlin-Drubin ME (2020). p16 in HPV-associated cancers. *Oncotarget*, **4**, 1864-5.
- Murtiastutik D, Mastutik G, Rahniayu A, Arista A, Setyaningrum T (2019). The Genotype of Human Papilloma Virus of Male Patients with Anogenital Warts. *Folia Med Indonesiana*, **55**, 100-6.
- Nkili-Meyong AA, Moussavou-Boundzanga P, Labouba I, et al (2019). Genome-wide profiling of human papillomavirus DNA integration in liquid-based cytology specimens from a Gabonese female population using HPV capture technology. *Sci Rep*, **9**, 1504-14.
- Ozaydin-Yavuz G, Bilgili SG, Guducuoglu H, et al (2019). Determinants of high-risk human papillomavirus infection in anogenital warts. *Postepy Dermatol Alergol*, **36**, 76-81.
- Pal A, Kundu R (2020). Human Papillomavirus E6 and E7: The Cervical Cancer Hallmarks and Targets for Therapy. *Front Microbiol*, **10**, 1-15.
- Patel H, Wagner M, Singhal P, Kothari S (2013). Systematic review of the incidence and prevalence of genital warts. *BMC Infect Dis*, **13**, 39-52.
- Romagosa C, Simonetti S, López-Vicente L, et al (2011). p16(INK4a) overexpression in cancer: a tumor suppressor gene associated with senescence and high-grade tumors. *Oncogene*, **30**, 2087-97.
- Santegoets LA, van Baars R, Terlou A, et al (2012). Different DNA damage and cell cycle checkpoint control in low- and high-risk human papillomavirus infections of the vulva. *Int J Cancer*, **130**, 2874-85.
- Sonnenberg P, Tanton C, Mesher D, et al (2019). Epidemiology of genital warts in the British population: implications for HPV vaccination programmes. *Sex Transm Infect*, **95**, 386-90.
- Suligoi B, Vittori G, Salfa MC, et al (2017). Prevalence and incidence of external genital warts in a sample of Italian general female population. *BMC Infect Dis*, **17**, 126-33.
- Woodman CB, Collins SI, Young LS (2007). The natural history of cervical HPV infection: unresolved issues. *Nat Rev Cancer*, **7**, 11-22.
- Yildiz IZ, Usubütün A, Firat P, Ayhan A, Küçükali T (2007). Efficiency of immunohistochemical p16 expression and HPV typing in cervical squamous intraepithelial lesion grading and review of the p16 literature. *Pathol Res Pract*, **203**, 445-9.



This work is licensed under a Creative Commons Attribution-Non Commercial 4.0 International License.



## 08. p16INK4A Expression in Condyloma

---

### ORIGINALITY REPORT

---

18%

SIMILARITY INDEX

11%

INTERNET SOURCES

15%

PUBLICATIONS

0%

STUDENT PAPERS

---

### PRIMARY SOURCES

---

1

[www.scielosp.org](http://www.scielosp.org)

Internet Source

1%

---

2

Jingying Wang, Songshan Li, Junpeng Li, Zhijia Li et al. "Evaluation of human papillomavirus DNA detection-guided aminolaevulinic acid-mediated photodynamic therapy for the treatment of condyloma acuminata", Photodiagnosis and Photodynamic Therapy, 2019

Publication

<1%

---

3

Yung-Taek Ouh, Kyung-Jin Min, Hyun Woong Cho, Moran Ki, Jin-Kyoung Oh, Sang Yop Shin, Jin Hwa Hong, Jae-Kwan Lee. "Prevalence of human papillomavirus genotypes and precancerous cervical lesions in a screening population in the Republic of Korea, 2014–2016", Journal of Gynecologic Oncology, 2018

Publication

<1%

---

4

[nust.edu.pk](http://nust.edu.pk)

Internet Source

<1%

---

[www.rjptonline.org](http://www.rjptonline.org)

5

Internet Source

&lt;1 %

6

Kenji Furui. "Cell Proliferation and apoptosis: Detection of apoptosis in human endometriotic tissues", *Molecular Human Reproduction*, 1996

Publication

&lt;1 %

7

[www.mdpi.com](http://www.mdpi.com)

Internet Source

&lt;1 %

8

[www.pagepressjournals.org](http://www.pagepressjournals.org)

Internet Source

&lt;1 %

9

[api.crossref.org](http://api.crossref.org)

Internet Source

&lt;1 %

10

[biblio.ugent.be](http://biblio.ugent.be)

Internet Source

&lt;1 %

11

Dina Angelika, Risa Etika, Muhammad Pradhika Mapindra, Martono Tri Utomo, Paulus Rahardjo, I Dewa Gede Ugrasena. "Associated neonatal and maternal factors of osteopenia of prematurity in low resource setting: A cross-sectional study", *Annals of Medicine and Surgery*, 2021

Publication

&lt;1 %

12

Feiyan Xiang, Qing Guan, Xinwen Liu, Han Xiao et al. "Distribution characteristics of different human papillomavirus genotypes in women in

&lt;1 %

# Wuhan, China", Journal of Clinical Laboratory Analysis, 2018

Publication

13

Pornjarim Nilyanimit, Jira Chansaenroj, Jatupol Srisomboon, Wanida Rodrangnok et al. "Human Papillomavirus in Thai Women and Men with Anogenital Warts", Intervirology, 2018

Publication

<1 %

14

[journal.uad.ac.id](http://journal.uad.ac.id)

Internet Source

<1 %

15

[jas.uitm.edu.my](http://jas.uitm.edu.my)

Internet Source

<1 %

16

[www.nature.com](http://www.nature.com)

Internet Source

<1 %

17

Linhong Liao, Hui Cheng, Fansheng Zeng, Weijie Zhou, Yanqing Ding. "Prevalence and distribution of human papillomavirus genotypes among women with high - grade squamous intraepithelial lesion and invasive cervical cancer in Ganzhou, China", Journal of Clinical Laboratory Analysis, 2018

Publication

<1 %

18

Mariusz Skoczyński, Anna Goździcka-Józefiak, Anna Kwaśniewska. "The Prevalence of Human Papillomavirus between the Neonates

<1 %

and Their Mothers", BioMed Research International, 2015

Publication

19

[repository.uin-malang.ac.id](http://repository.uin-malang.ac.id)

Internet Source

<1 %

20

[files.cercomp.ufg.br](http://files.cercomp.ufg.br)

Internet Source

<1 %

21

[hal.umontpellier.fr](http://hal.umontpellier.fr)

Internet Source

<1 %

22

[repository.unair.ac.id](http://repository.unair.ac.id)

Internet Source

<1 %

23

[www.anst.uu.se](http://www.anst.uu.se)

Internet Source

<1 %

24

Nimisha Tripathi, Sneha Keshari, Pallavi Shahi, Poonam Maurya, Atanu Bhattacharjee, Kushal Gupta, Sanjay Talole, Mukesh Kumar. "Human papillomavirus elevated genetic biomarker signature by statistical algorithm", Journal of Cellular Physiology, 2020

Publication

<1 %

25

Suresh Yadav, Ritu Sehra, Shashank Nath Singh, Sunita Agarwal, Pawan Singhal, Ramkalyan Meena. "An Observational Study Depicting Role of p16 in Detecting Human Papilloma Virus in Oral and Oropharyngeal Cancer and Associated Factors", Indian

<1 %

# Journal of Otolaryngology and Head & Neck Surgery, 2020

Publication

26

[worldwidescience.org](http://worldwidescience.org)

Internet Source

<1 %

27

Ana E Zacapala-Gómez, Luz del C Alarcón-Romero, Miguel A Mendoza-Catalán, Eric G Salmerón-Bárceñas et al. "Integrin subunit $\beta$ 1 and laminin  $\gamma$ 1 chain expression: a potential prognostic biomarker in cervical cancer", Biomarkers in Medicine, 2020

Publication

<1 %

28

Kim, Yong-Hee. "Current and Next-generation Vaccines against Human Papillomaviruses", Journal of Bacteriology and Virology, 2015.

Publication

<1 %

29

W. Glenn McCluggage. "Immunohistochemistry as a diagnostic aid in cervical pathology", Pathology, 2007

Publication

<1 %

30

[bmcinfectdis.biomedcentral.com](http://bmcinfectdis.biomedcentral.com)

Internet Source

<1 %

31

[bmcpregnancychildbirth.biomedcentral.com](http://bmcpregnancychildbirth.biomedcentral.com)

Internet Source

<1 %

32

[doi.org](http://doi.org)

Internet Source

<1 %

33

[revista-agroproductividad.org](http://revista-agroproductividad.org)

Internet Source

&lt;1 %

34

[store.ihcworld.com](http://store.ihcworld.com)

Internet Source

&lt;1 %

35

[www.beautyjapan.net](http://www.beautyjapan.net)

Internet Source

&lt;1 %

36

[www.dovepress.com](http://www.dovepress.com)

Internet Source

&lt;1 %

37

Chonlaphat Sukasem. "Molecular epidemiology of human papillomavirus genotype in women with high-grade squamous intraepithelial lesion and cervical cancer: Will a quadrivalent vaccine be necessary in Thailand?", *Journal of Medical Virology*, 01/2011

Publication

&lt;1 %

38

Zeyi Deng, Taro Ikegami, Asanori Kiyuna, Chunlin Zhang et al. "Methylation of CpG sites in the upstream regulatory region, physical status and mRNA expression of HPV-6 in adult-onset laryngeal papilloma", *Oncotarget*, 2017

Publication

&lt;1 %

39

[cris.maastrichtuniversity.nl](http://cris.maastrichtuniversity.nl)

Internet Source

&lt;1 %

40

[jurnal.ugm.ac.id](http://jurnal.ugm.ac.id)

Internet Source

<1 %

41

[spiral.imperial.ac.uk](http://spiral.imperial.ac.uk)

Internet Source

<1 %

42

[test.dovepress.com](http://test.dovepress.com)

Internet Source

<1 %

43

[www.termedia.pl](http://www.termedia.pl)

Internet Source

<1 %

44

"Sexually Transmitted Infections", Springer  
Science and Business Media LLC, 2020

Publication

<1 %

45

A N Fiander. "Human papillomavirus infection:  
an Anonymous Prevalence Study in South  
Wales, UK", British Journal of Cancer,  
07/17/2006

Publication

<1 %

46

Andersson, S.. "Expression of p16<sup>INK4a</sup>  
in relation to histopathology and viral load of  
'high-risk' HPV types in cervical neoplastic  
lesions", European Journal of Cancer, 200611

Publication

<1 %

47

Boulet, G.. "Human papillomavirus: E6 and E7  
oncogenes", International Journal of  
Biochemistry and Cell Biology, 2007

Publication

<1 %

48

Enas Tantawy, Abdallah El-Beyali, Maha Gohar, Mohamed Nasr, Zynab Ibrahim, Ayman Marie. "Genotyping of Human papilloma virus from warts in Egyptian patients", Egyptian Journal of Medical Microbiology, 2020

Publication

&lt;1 %

49

L.N. Calil, M.I.A. Edelweiss, L. Meurer, C.N. Igansi, M.C. Bozzetti. "p16INK4a and Ki67 expression in normal, dysplastic and neoplastic uterine cervical epithelium and human papillomavirus (HPV) infection", Pathology - Research and Practice, 2014

Publication

&lt;1 %

50

Saavedra, Kathleen P, Priscilla M Brebi, and Juan Carlos S Roa. "Epigenetic alterations in preneoplastic and neoplastic lesions of the cervix", Clinical Epigenetics, 2012.

Publication

&lt;1 %

51

Serena Bellaminutti, Silva Seraceni, Francesco De Seta, Tarik Gheit, Massimo Tommasino, Manola Comar. " HPV and co-detection in young asymptomatic women from high incidence area for cervical cancer ", Journal of Medical Virology, 2014

Publication

&lt;1 %

52

Vahap Eldem, Selim Can Kuralay, Gülperi Özdoğan, Gökçe Has Özçelik et al.

&lt;1 %



"Comprehensive analysis of circulating viral DNA in maternal plasma at population-scale using low-pass whole-genome sequencing",  
Genomics, 2023

Publication

---

53

Witold Owczarek, Monika Slowinska, Irena Walecka, Magdalena Ciazynska, Dorota Nowicka, Leszek Walczak, Elwira Paluchowska. "Correlation of the ALA-PDT Treatment Efficacy and the HPV Genotype Profile of Genital Warts after Cryotherapy Failure and Podophyllotoxin Therapy in Male Patients",  
Life, 2021

Publication

---

54

Ying Gan, Wanru Ma, Xiuhong Wang, Juanli Qiao, Baozhen Zhang, Chenghua Cui, Zhaojun Liu, Dajun Deng. "Coordinated transcription of ANRIL and P16 genes is silenced by P16 DNA methylation", Chinese Journal of Cancer Research, 2018

Publication

---

55

Yonghong Xie, Peng Shen, Linlong Chen, Fumei Zhu, Guangtao Xu, Xiaoyan Pan, Ruilin Yan, Yanping Zhang. "Clinical role of hWAPL in histologic diagnosis of cervical cancer and cervical intraepithelial neoplasia: Correlation with p16INK4a expression and HPV testing",  
Proceedings 2011 International Conference

<1 %

<1 %

<1 %

# on Human Health and Biomedical Engineering, 2011

Publication

---

56	<a href="http://diposit.ub.edu">diposit.ub.edu</a> Internet Source	<1 %
57	<a href="http://docksci.com">docksci.com</a> Internet Source	<1 %
58	<a href="http://dokumen.pub">dokumen.pub</a> Internet Source	<1 %
59	<a href="http://e-century.us">e-century.us</a> Internet Source	<1 %
60	<a href="http://edepositireland.ie">edepositireland.ie</a> Internet Source	<1 %
61	<a href="http://hdl.handle.net">hdl.handle.net</a> Internet Source	<1 %
62	<a href="http://www.etnomatematica.org">www.etnomatematica.org</a> Internet Source	<1 %
63	<a href="http://www.oncotarget.com">www.oncotarget.com</a> Internet Source	<1 %
64	<a href="http://www.tandfonline.com">www.tandfonline.com</a> Internet Source	<1 %
65	Fernanda Pessi de Abreu, Pedro Lenz Casa, Marcos Vinicius Rossetto, Nikael Souza de Oliveira et al. "Gene expression analysis in cervical cancer progression: Towards	<1 %

## unveiling alterations from normal to tumoral tissue", Human Gene, 2022

Publication

---

66

J P A Baak. "Dynamic behavioural interpretation of cervical intraepithelial neoplasia with molecular biomarkers", Journal of Clinical Pathology, 10/1/2006

Publication

---

<1 %

67

Okadome, Masao, Toshiaki Saito, Hideyuki Tanaka, Takayoshi Nogawa, Reiko Furuta, Kayoko Watanabe, Tsunekazu Kita, Kaichiro Yamamoto, Mikio Mikami, and Ken Takizawa. "Potential impact of combined high- and low-risk human papillomavirus infection on the progression of cervical intraepithelial neoplasia 2 : High-/low-risk HPV infection and CIN2", Journal of Obstetrics and Gynaecology Research, 2014.

Publication

---

<1 %

68

"20th ECP", Virchows Archiv, 2005

Publication

---

<1 %

69

"Cytopathology", Modern Pathology, 02/2005

Publication

---

<1 %

70

HPV and Cervical Cancer, 2012.

Publication

---

<1 %

71

Marius Alexandru Moga, Marius Irimie, Alexandru Oanta, Alina Pascu, Victoria Burtea.

<1 %

# "Type-specific Prevalence of Human Papillomavirus by Cervical Cytology among Women in Brasov, Romania", Asian Pacific Journal of Cancer Prevention, 2014

Publication

---

---

Exclude quotes      On

Exclude matches      Off

Exclude bibliography      On

# 08. p16INK4A Expression in Condyloma

GRADEMARK REPORT

FINAL GRADE

**/100**

GENERAL COMMENTS

**Instructor**

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7