

Original Article

Detection and genotyping of human papillomavirus virus (HPV): a comparative analysis of clinical performance in cervical and urine samples in Chilean women

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Abstract: Human papillomavirus (HPV) is the most common sexually transmitted infectious agent and is the main cause of cervical cancer (CC). In Chile, CC is the second leading cause of death by cancer in women aged 20-44 years, four times higher than in developed countries. Currently, the detection of HPV infection using a cervical brush is recommended; however, this is an invasive procedure that many women try to avoid. The aim of this study was to evaluate the clinical performance of a self-collected, urine-based HPV detection method using conventional PCR followed by a reverse line blot. A PCR-based HPV genotyping was performed on 190 paired cervical and urine samples from gynecological exams at public health centers in the Araucanía Region, Chile. HPV DNA detection and genotyping were performed by PCR and reverse line blot assay. Carcinogenic HPV types were present in 64.7% and 65.8% of the cervical and urine samples; the infection rates of HPV16 were 34.7% and 33.2%, respectively. The overall percent agreement between carcinogenic HPV detection in cervical and urine samples was 73.7%, with a moderate concordance rate of carcinogenic HPV detection ($\kappa = 0.42$). Clinical sensitivities for cervical and urine-based sampling methods to diagnose cervical intraepithelial neoplasia 2/3 (CIN2/3) by histology were 93.4% and 90.2%, respectively. These results suggest that both cervical brush and urine-based sampling show a good clinical performance in the detection of HPV infection. The urine-based sampling method represents a valuable alternative with a great impact on public health, allowing increased cervical cancer screening coverage among women who do not undergo pelvic examinations.

Keywords: Human papillomavirus, cervical intraepithelial neoplasia, cervical cancer, urine-based sampling method

Introduction

Human papillomavirus (HPV) represents the most common sexually transmitted infectious agent throughout the world; the major risk factors are behaviors associated with sexual activity [1]. The etiological cause of nearly 100% of cervical cancers (CC) is being associated significantly with vulvar and vaginal cancers in

women, penile cancer in men, and anal cancer [2-5]. In Chile, the incidence rate of CC was estimated at 12.8 per 100.000 women with a mortality rate of 6.64 per 100.000 women, making it the second leading cause of death by cancer in women aged 20-44 years, with a total of 584 deaths in 2012 [6, 7]. The mortality rate for this neoplasm in our country is four times higher than in developed countries [8].

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Screening efforts are focused on preventing CC, primarily by Pap test, which can detect abnormal cellular changes or pre-malignant lesions in cervical tissues [9]. Since the Pap test came into use, mortality rates from CC have decreased dramatically [10]. Nevertheless, the PAP test has several disadvantages; it requires a pelvic examination, a procedure that is invasive and uncomfortable for the patient, time consuming for healthcare providers, and cannot be carried out easily [11]. In addition, cervical cytology is susceptible to technical limitations such as the inadequate transfer of cells to the slide with homogenous distribution of abnormal cells, the presence of obscuring blood, and inflammation or thick areas of overlapping epithelial cells. Also, it is subject to interpretation errors, resulting in false negative results associated with relatively low sensitivity (less than 50%) [12, 13]. In the last two decades, interest in molecular techniques for identifying HPV DNA present in infected tissues has increased, because it enables the identification of women at risk of developing CC due to its higher sensitivity of detection with only a small amount of viral DNA [14-16].

Actually, more than 200 HPV types have been reported, which can be grouped into high oncogenic risk (HR-HPV) and low oncogenic risk HPV (LR-HPV) [17, 18]. HR-HPV types have been detected in more than 99% of invasive cancer cases and in the vast majority of pre-neoplastic lesions cases [19]. Therefore, detection of HR-HPV or individual HPV-16/HPV-18 is considered as the best method of CC screening, even better than liquid-based cytology [16, 20, 21].

In 2005, the International Agency for Research on Cancer (IARC) made recommendations that supported primary screening based on cytology or HPV-DNA testing [22]. In 2015, the Chilean Department of Health incorporated an algorithm in its clinical guide for the screening of CC in women aged 30-64 years using a method of detecting clinically validated HPV, followed by cytology [23]. However, detection of HPV DNA in cervical samples requires the same collection procedure used in Pap smears. Therefore, the development of a non-invasive self-sample collection method would have the potential to increase the screening of HPV infection in women [15]. Actually, several studies have demonstrated that urine-based HPV screening

shows similar sensitivity and specificity to cervical-based sampling [15, 24-26]. Our study was performed in the Araucania Region, a high-risk population due to its sociodemographic features; one of the highest native populations in the country, 30% of women living in non-urbanized areas, and high rates of incidence and mortality by CC [7, 27].

The aim of this study was to evaluate the clinical performance of a self-collected, urine-based HPV detection method using conventional PCR followed by reverse line blot that could be used as a non-invasive method for the early detection of CC, thereby allowing an increase in screening among populations of women at a high risk of the disease.

Material and methods

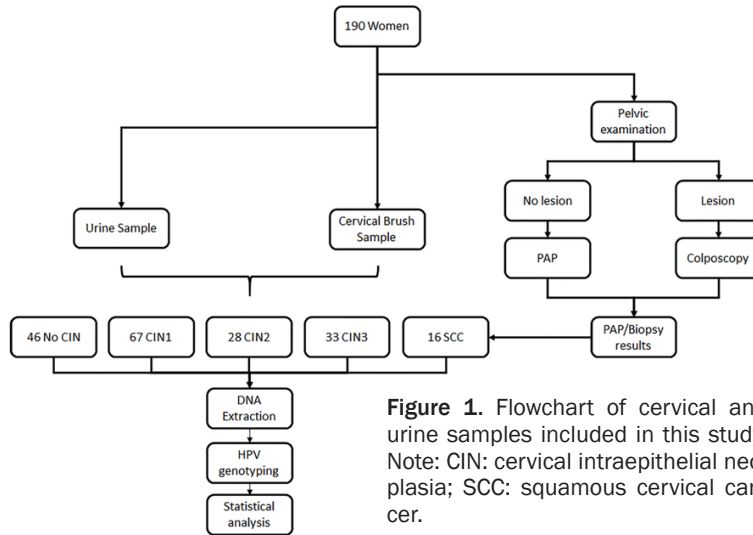
Study design

We analyzed a cohort of 190 women with cytology and histological diagnosis of cervical lesions conducted by specialized clinicians performed at the Unit of Pathological Anatomy and Cytology of the Hernán Henríquez Aravena Hospital (Temuco, Chile). To perform this study, three paired samples were collected from women referred for a gynecological exam at public health centers in the Araucania Region; one for diagnostic purposes and the other two for research purposes (cervical and urine samples). Subsequently, these were classified as no cervical Intraepithelial neoplasia (No CIN), cervical intraepithelial neoplasia grade 1 (CIN1), grade 2 (CIN2), grade 3 (CIN3) and squamous cervical cancer (SCC), according to the results of the histological diagnosis. At the same time - without knowing the diagnosis -DNA was extracted from each sample for HPV genotyping (**Figure 1**).

Clinical sample collections

Cervical samples were collected by a physician using a cervical brush and placed in a Tris-EDTA buffer solution and transported immediately to the lab for further processing. On the same day, prior to undergoing a pelvic examination, 60 mL of first-stream urine samples were collected at home in a sterile container with crystal violet (10%) and then transported immediately to the lab.

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DNA extraction from cervical and urine samples

DNA extraction from the cervical and urine samples was performed using the *Tissue DNA Kit E.Z.N.A. (Zymo Research)*, according to the manufacturer's instructions. DNA was evaluated by amplification of a 268 bp fragment of the β -globin gene using the GH20 and PCO4 primers and PCR conditions previously described [28, 29].

HPV genotyping

HPV genotyping was performed by conventional PCR amplification followed by non-radioactive hybridization, which enables the detection of HPV carcinogenic genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66) and HPV non-carcinogenic genotypes (6, 11, 42, 53, 70). The PCR reaction for the L1 gene was performed using the specific primers GP5+ and biotinylated GP6+ as previously described [30]. Subsequently, a reverse line blot was performed to identify the HPV genotype, as previously reported [29]. The PCR product of GP5+/biotinylated GP6+ was denaturalized at 96°C and cooled in ice before starting the hybridization step. Then, the PCR products were placed in a pre-treated Biodyne C membrane (Pall Bio-Support West Chester, USA) containing non-radioactive labeled oligoprobes specific to each viral genotype. A colorimetric reaction using anti-digoxigenin conjugate with alkaline phosphatase was used to detect the presence/absence of each HPV genotype. Finally, the membranes were developed using a NBT/BCIP

substrate solution (Thermo Fisher), according to the manufacturer's protocol.

Ethics statement

This study was approved by Ethics Committee of the Faculty of Medicine of the University of La Frontera, Temuco, Chile (Resolution Number 246/006, August 25th 2010). All the women were informed of the purposes of this study and written informed consent was obtained.

Statistical analysis

The overall percent agreement (OPA), positive and negative predictive agreement (PPA and NPA), and agreement beyond chance (Cohen's kappa) were calculated as percentages with 95% confidence intervals (95% CI) for carcinogenic HPV detection in the cervical and urine samples. The kappa concordance test was interpreted according to a previous study [25]. McNemar's test was used to calculate the differences between paired proportions, with a p value less than 0.05 being considered statistically significant.

In addition, we calculated the sensitivity, specificity, positive and negative predictive values, and Youden's index with a 95% CI in the cervical and urine samples for the detection of carcinogenic HPV DNA against two histologically confirmed cervical disease endpoints: CIN2/3 and CIN3.

Results

Comparison of carcinogenic HPV detection in cervical and urine samples

All 190 paired cervical and urine samples collected were suitable for analysis in this study, and the β -globin gene was amplified in all of those. The median age of the study participants was 34 years (interquartile range: 16 years; range: 15-75 years). At least one of the detectable HPV genotypes was present in 70.5% (134/190) of the cervical samples and 71.1% (135/190) of the urine samples. At least one of the detectable HR-HPV types was present in 65.8% (125/190) of the cervical samples and

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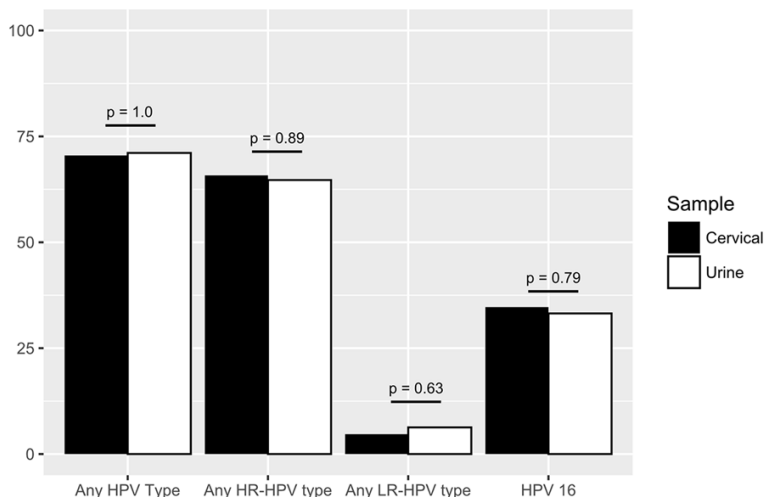


Figure 2. Prevalence of HPV genotypes detected in cervical and urine samples. Note: HR-HPV: high risk HPV; LR-HPV: low risk HPV; HPV 16: HPV genotype 16.

64.7% (123/190) of the urine samples (P -value = 0.89). The detection of LR-HPV type was practically equal in the cervical and urine samples (4.7% and 6.3%; P -value = 0.63, respectively). The HPV16 frequency was 34.7% and 33.2% (P -value = 0.79) in cervical and urine samples, respectively (**Figure 2**). In summary, there were no significant differences in HPV detection and genotyping between the cervical and urine samples.

The OPA between HR-HPV detection in the cervical and urine samples was 73.7% (95% CI: 67.0%-79.4%). The PPA between the cervical and urine samples was 80.5% (95% CI: 72.6%-86.5%). A moderate concordance rate of HR-HPV detection in the two samples was observed (kappa = 0.42; 95% CI: 0.35-0.49) (**Table 1**).

There were 50/190 (26.3%) discrepancies in the results obtained for the two types of samples. In 24 of them, the detection of carcinogenic HPV was positive in the cervical but negative in the urine samples. Conversely, 26 samples were positive for HR-HPV detection in urine but negative in cervical samples (see [Supplementary Table 1](#)).

HR-HPV detection in cervical and urine samples according to grade lesion endpoint

Histology results were available for all 190 women, which 46/190 (24.2%) were No CIN, 67/190 (35.3%) CIN1, 28/190 (14.7%) CIN2, 33/190 (17.4%) CIN3, and 16/190 (8.4%) SCC.

HR-HPV prevalence in women with CIN 2 showed similar proportions in both cervical and urine samples (89.3% and 96.4%, respectively). Nevertheless, women with CIN3 showed a higher prevalence of HR-HPV in the cervical samples than in the urine samples (90.9% versus 72.7%, respectively). Meanwhile, women with SCC have a prevalence of 96.4% in the urine samples compared to 75.0% in the cervical samples (**Table 2**).

The three cases negative for CIN2 in the cervical samples were positive for HPV 18 or 16/18 in urine samples. Similarly, the only case negative for CIN2 in the urine samples was positive for HPV16 in the cervical samples. None of the negative cases, either cervical or urine samples, were the same ([Supplementary Table 1](#)).

No CIN was compared against histologically confirmed CIN2/3 or CIN3 lesions. CIN1 was not considered in this analysis because grouping it with samples from normal epithelia is an error, due to it presenting an early cervical lesion; therefore, many of those cases were positive for HR-HPV infections (74.6% of the cervical and 70.1% of the urine samples), which affects the specificity of methodology with possible "false positives". Compared to histologically confirmed CIN2/3, cervical-based detection of HR-HPV had a clinical sensitivity of 93.4% (95% CI: 84.1%-98.2%) and a clinical specificity of 80.4% (95% CI: 66.1%-90.6%). The corresponding sensitivity and specificity for urine specimens were 90.2% (95% CI: 79.8%-96.3%) and 71.7% (95% CI: 56.6%-84.0%), respectively. Moreover, the sensitivity estimated for CIN3 lesions compared to respective estimates for CIN2/3 was lower (cervical: 90.9%; 95% CI: 75.7%-98.1%; urine: 72.7%; 95% CI: 54.5%-86.7%); however, the specificity estimates were higher (cervical: 82.6%; 95% CI: 68.6%-92.2%; urine: 78.3%; 95% CI: 63.6%-89.1%) (**Table 3**).

Discussion

Cervical cancer (CC) has among the highest prevalence and incidence of neoplasia in

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Table 1. Comparative table of agreement between carcinogenic HPV detection in cervical and urine samples

	Cervical samples			Value (95% CI)				
	Negative	Positive	Total	OPA (%)	PPA (%)	NPA (%)	Cohen's kappa	
Urine samples	Negative	41	24	65	73.7 (67.0-79.4)	80.5 (72.6-86.5)	61.2 (49.2-72.0)	0.42 (0.35-0.49)
	Positive	26	99	125				
	Total	67	123	190				

Note: OPA: Overall Percent Agreement; PPA: Positive Percent Agreement; NPA: Negative Percent Agreement.

women worldwide, mostly in developing countries [31]. The main screening technique for cervical lesions is the Pap stain, which has a sensitivity that does not reach 60%. In recent years new HPV-based tests have emerged showing better sensitivity than the Pap test in CC diagnoses. It is known that almost all CCs are caused by HPV infections [32]. Consequently, in 2005, the IARC made recommendations that supported primary screening based on cytology and/or HPV-DNA testing [22]. The test for HR-HPV genotypes has recently been shown to be a better indicator of cervical cancer risk than cytology [33]. Co-testing of cytology and HPV detection at 5-year intervals is the preferred strategy for cervical cancer screening for women aged 30 to 64 years in the United States [34]. Nevertheless, the methods clinically validated for HPV detection, including the Pap test, usually require cervical brushing, a sampling method that is usually avoided in high-risk populations because of shame, religious or sociocultural background, or lack of access to health care centers. On the other hand, the urine-sampling method has some advantages over cervical scraping such as: non-invasive collection method, self-sampling method, and highly accepted among women [35], and a low amount of DNA can be detected [36]. Many reports indicates that HPV infections are very common and most women will clear HPV infections within 6-12 months, but in this sense, the presence of HR-HPV DNA does not mean that CC is present or will persist and progress to cancer [19, 37, 38]. Therefore, it is necessary for a HR-HPV test to be non-invasive, easy to use, and inexpensive, in order to increase the coverage of CC screening in high-risk populations, usually those in low-income regions.

In this framework, we evaluated the clinical performance of urine-based HPV DNA testing and its different genotypes detected in 190 paired cervical and urine samples of women refer-

red from a public health care center (Temuco, Chile). The prevalence of HR-HPV infection was increased with the grade of CIN disease. This prevalence was higher in urine than cervical samples for CIN1, CIN2, and SCC. Nevertheless, the prevalence in CIN3 was higher in the cervical than in the urine samples. Several reports indicate that HR-HPV detection in urine samples could be increased as the cervical lesion progresses due to the exfoliation of cervical cells infected with HPV DNA [24, 39-41].

Also, we found an OPA of 73.7% with a moderate concordance rate between HR-HPV infections detected in tissue samples from cervical lesions and urine. These results are similar to those reported by Sahasrabudhe *et al.*, (OPA = 79.2%; $k = 0.55$) [24], Mendez *et al.*, (OPA = 76.0%) [39], and Bisset *et al.*, ($k = 0.58$). These three studies used the Linear Array HPV Genotyping Test. On the other hand, the results obtained in this study were slightly lower than those documented by Tanzi *et al.*, with a Cohen's kappa of 0.80 obtained in a population of women infected with HIV using an in-house PCR [15], and Bernal *et al.* (OPA = 88.0%; $k = 0.76$) using a Cobas 4800 HPV test in a population of women with an abnormal PAP test [25]. One possible explanation of this variation could be the presence of DNA HPV from urethral and vulvar epithelial tissues, because these tissues are susceptible to different HPV genotype infections than cervical tissue, usually non-carcinogenic genotypes [15, 35]. The method we used detects both oncogenic and non-oncogenic HPV types, unlike the COBAS 4800 methods detect only carcinogenic HPV types; this could likely affect the OPA and Cohen's kappa value. Nevertheless, we demonstrated genotype-level similarities between sampling approaches due to infection with HR-HPV, LR-HPV and/or HPV16 being uniform across either the cervical or the urine sampling methods. This is quite interesting because it

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Table 2. HR-HPV prevalence in cervical and urine samples according different stages of the disease by histology

	No CIN (%)	CIN 1 (%)	CIN 2 (%)	CIN 3 (%)	SCC (%)	Overall (%)
Cervical	8/46 (17.4)	50/67 (74.6)	25/28 (89.3)	30/33 (90.9)	12/16 (75.0)	125/190 (65.8)
Urine	10/46 (21.7)	47/67 (70.1)	27/28 (96.4)	24/33 (72.7)	15/16 (93.8)	123/190 (64.7)

Note: CIN: Cervical intraepithelial neoplasia; SCC: Squamous cervical cancer.

Table 3. Comparison of test agreement between carcinogenic HPV detection in cervical and urine samples for detection of histologically confirmed CIN2/3 and CIN3 lesions

Cervical disease endpoint	No. of samples					% (95% CI)				Youden's index (95% CI)	
	Total	Lesion present	Lesion absent	TP	FN	Sensitivity	Specificity	PPV	NPV		
CIN 2/3				TP	FN						
Cervical	107/190	57	4	9	37	93.4 (84.1-98.2)	80.4 (66.1-90.6)	86.4 (75.7-93.6)	90.2 (76.9-97.3)	0.739 (0.625-0.853)	
Urine	107/190	55	6	13	33	90.2 (79.8-96.3)	71.7 (56.6-84.0)	80.9 (69.5-89.4)	84.6 (69.5-94.1)	0.619 (0.491-0.747)	
CIN 3				TP	FN						
Cervical	79/190	30	3	8	38	90.9 (75.7-98.1)	82.6 (68.6-92.2)	78.9 (62.7-90.5)	92.7 (80.1-98.5)	0.735 (0.577-0.893)	
Urine	79/190	24	9	10	36	72.7 (54.5-86.7)	78.3 (63.6-89.1)	70.6 (52.5-84.9)	80.0 (65.4-90.4)	0.51 (0.310-0.710)	

Note: TP: true positive; TN: true negative; FP: false positive; FN: false negative; PPV: positive predictive value; NPV: negative predictive value.

shows that urine samples as well as cervical samples can be used with this method.

The clinical sensitivity and specificity of urinary detection shows that 90.2% and 71.7% (cervical: 93.4% and 80.4%, respectively) of women with CIN2/3 could be accurately detected with this type of sampling. In women with CIN3, the sensibility decreased slightly to 72.7% with a specificity of 78.3% (cervical: 90.9% and 82.6%, respectively) for the urine samples. Sahasrabudhe *et al.*, [24] reported a sensitivity and specificity of 80.8% and 53.3% for women with CIN2/3 and 90.0% and 45.9% for women with CIN3 in urine samples. Another study conducted by Bernal *et al.* [25] showed a sensitivity and specificity in women with CIN2/3 of 95.0% and 51.7% and for CIN3 100% and 54.1%, respectively. Sellors *et al.* [35] obtained a sensitivity and specificity of 44.8% and 69.7% in women with HSIL (CIN2/3).

A recent meta-analysis reported that urine-based testing is an alternative to cervical sampling [42]. In this regard, our study supports the use of urine-based sampling as a viable method for screening and genotyping HPV infection in women who lack access to CC screening or that avoid pelvic examinations. Moreover, in Chile, especially in non-urbanized areas, a large number of women do not undergo CC screening due to the invasiveness of the sample collection. Therefore, this method repre-

sents an important alternative to increase coverage for those populations that are difficult to include in CC screening programs.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Characteristics of all patients include in this study

Histological-ly confirmed Lesion	Age	Cervical-based sampling					Urine-based sampling				
		HPV Genotyping	ANY HPV type (0: negative; 1: positive)	ANY HR-HPV type (0: negative; 1: positive)	ANY LR-HPV type (0: negative; 1: positive)	HPV16 (0: negative; 1: positive)	HPV Genotyping	ANY HPV type (0: negative; 1: positive)	ANY HR-HPV type (0: negative; 1: positive)	ANY LR-HPV type (0: negative; 1: positive)	HPV16 (0: negative; 1: positive)
CIN 1	24	16	1	1	0	1	18	1	1	0	0
CIN 1	29	18	1	1	0	0	33, 18, 39, 53, 70	1	1	0	0
CIN 2	40	16	0	0	0	1	18, 45	0	0	0	0
CIN 1	24	58	0	0	0	0	58	0	0	0	0
CIN 2	41	56	0	0	0	0	56	0	0	0	0
CIN 1	47	18	0	0	0	0	33, 18, 45	0	0	0	0
CIN 2	29	45	1	1	0	0	18, 51, 45, 6, 42, 11, 70	1	1	0	0
CIN 2	22	58	0	0	0	0	59	0	0	0	0
CIN 2	27	16	0	0	0	1	16, 18	0	0	0	1
SCC	56	16	0	0	0	1	16, 18	0	0	0	1
CIN 1	61	16, 52	0	0	0	1	0	1	0	1	0
CIN 1	27	18	0	0	0	0	18, 45, 6, 11	0	0	0	0
CIN 1	50	16	0	0	0	1	0	0	0	0	0
CIN 1	37	83	0	0	0	0	16, 56, 59, 45	0	0	0	1
CIN 1	47	45	0	0	0	0	16, 18, 52, 35, 45, 11	0	0	0	1
CIN 3	32	18	0	0	0	0	16, 18, 35, 11	0	0	0	1
CIN 3	28	16, 18, 56	0	0	0	1	16, 56, 18	0	0	0	1
CIN 3	23	16	0	0	0	1	0	0	0	0	0
CIN 3	35	68	0	0	0	0	42	0	0	0	0
CIN 3	34	45	1	1	0	0	0	0	0	0	0
CIN 1	44	45	0	0	0	0	16, 18	0	0	0	1
CIN 2	31	16	1	1	0	1	31	0	0	0	0
CIN 3	43	45	0	0	0	0	31	0	0	0	0
CIN 3	34	16, 18, 52	0	0	0	1	16, 18, 35	0	0	0	1
CIN 1	32	66	0	0	0	0	52, 66	1	1	0	0
CIN 2	31	16	0	0	0	1	0	1	0	1	0
CIN 2	26	16	0	0	0	1	16	0	0	0	1
CIN 3	37	16	0	0	0	1	18	0	0	0	0
SCC	38	16	0	0	0	1	16	0	0	0	1
CIN 1	40	66	1	1	0	0	0	0	0	0	0
CIN 3	31	16	0	0	0	1	16, 18	1	1	0	1
CIN 2	38	66	0	0	0	0	18	1	1	0	0
CIN 1	46	45	0	0	0	0	18	0	0	0	0

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CIN 1	61	16, 45	1	1	0	1	0	1	1	0	0
SCC	35	16	0	0	0	1	16, 42	0	0	0	1
CIN 1	52	16	0	0	0	1	0	0	0	0	0
CIN 3	40	16	0	0	0	1	16, 39, 53, 11	1	1	0	1
SCC	31	16	0	0	0	1	16, 58	1	0	1	1
CIN 3	40	52, 58	0	0	0	0	18, 53, 52, 45, 16, 35, 66, 11, 58, 56	0	0	0	1
CIN 1	42	58	0	0	0	0	18, 45, 16, 52, 11, 53	0	0	0	1
CIN 1	21	16	0	0	0	1	16, 18	0	0	0	1
CIN 2	29	16	1	1	0	1	16, 18	0	0	0	1
CIN 2	26	16	0	0	0	1	16, 52, 18, 35, 53, 11	1	1	0	1
CIN 3	35	16	0	0	0	1	59, 42	0	0	0	0
CIN 1	45	45	1	0	1	0	0	0	0	0	0
CIN 3	31	16	0	0	0	1	16	1	1	0	1
CIN 3	64	16	1	1	0	1	0	1	1	0	0
CIN 3	43	45	1	1	0	0	42	0	0	0	0
CIN 1	25	45	1	1	0	0	45	1	1	0	0
CIN 1	43	45	1	1	0	0	35	1	1	0	0
CIN 1	23	16	1	0	1	1	0	0	0	0	0
CIN 1	24	16	1	1	0	1	16	0	0	0	1
CIN 3	26	16	1	1	0	1	16, 42	0	0	0	1
CIN 3	41	46	1	1	0	0	56, 18, 31, 53, 11	1	1	0	0
CIN 2	23	58	1	1	0	0	58	0	0	0	0
CIN 1	27	16, 66	1	1	0	1	16, 52, 66, 53, 18, 42	1	1	0	1
CIN 2	57	16	0	0	0	1	58	0	0	0	0
CIN 1	34	16	1	1	0	1	16, 58	1	1	0	1
CIN 1	20	16	0	0	0	1	16, 33	0	0	0	1
CIN 2	32	45	1	1	0	0	16	0	0	0	1
CIN 2	33	45	0	0	0	0	31	1	1	0	0
CIN 1	25	52	1	1	0	0	16, 33, 18, 59	1	1	0	1
CIN 1	48	16	1	1	0	1	16, 18	1	1	0	1
CIN 1	38	0	1	1	0	0	0	0	0	0	0
CIN 3	49	16	1	0	1	1	16	1	0	1	1
CIN 1	23	0	1	1	0	0	59, 42	1	1	0	0
CIN 2	25	52	0	0	0	0	31	1	1	0	0
CIN 1	24	45, 56	1	1	0	0	56, 45, 6, 53	1	1	0	0
CIN 3	60	16	1	1	0	1	16	1	1	0	1
CIN 1	21	51	1	1	0	0	53	0	0	0	0

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CIN 3	40	16	1	1	0	1	0	0	0	0	0
CIN 1	32	0	1	1	0	0	0	1	1	0	0
CIN 2	35	18	1	0	1	0	16, 58, 18, 31, 45, 11	1	0	1	1
CIN 2	19	31	1	1	0	0	18, 31, 66, 53	0	0	0	0
CIN 1	46	35	0	0	0	0	0	0	0	0	0
CIN 1	24	16	0	0	0	1	16, 59, 35, 45, 42, 53	1	1	0	1
CIN 1	49	0	1	1	0	0	16, 18, 52, 66, 45, 6, 53	1	0	1	1
CIN 1	20	18, 45	0	0	0	0	18, 45	1	1	0	0
CIN 2	30	17	1	1	0	1	16	1	1	0	1
CIN 1	22	16	1	1	0	1	18, 45	1	1	0	0
CIN 1	35	45.16	1	1	0	1	35	1	1	0	0
CIN 1	38	16	1	1	0	1	0	1	1	0	0
CIN 2	35	0	1	1	0	0	16, 56, 33, 58, 18, 35, 45, 6, 42	0	0	0	1
CIN 1	21	16	1	1	0	1	16	1	1	0	1
CIN 1	35	0	1	0	1	0	11	1	1	0	0
CIN 1	33	0	1	1	0	0	56, 51	1	1	0	0
CIN 2	30	16, 18, 37	1	1	0	1	16, 33, 35, 42	1	1	0	1
CIN 1	19	70	1	1	0	0	70	1	1	0	0
CIN 1	26	16, 52	1	1	0	1	16	1	1	0	1
CIN 1	25	0	1	1	0	0	16, 18, 31, 35, 45, 6, 70	0	0	0	1
CIN 1	42	52	1	1	0	0	31, 6, 70	1	1	0	0
CIN 1	19	16	1	1	0	1	56, 6	1	1	0	0
SCC	52	16	1	1	0	1	16, 11	1	1	0	1
CIN 1	61	45	1	1	0	0	0	1	1	0	0
CIN 1	18	51	1	1	0	0	0	1	1	0	0
CIN 1	35	18	0	0	0	0	18, 45, 35	1	1	0	0
CIN 1	27	33, 59	1	1	0	0	59, 42, 35	1	0	1	0
SCC	46	16	1	1	0	1	0	1	1	0	0
CIN 1	17	51	1	1	0	0	51	1	1	0	0
CIN 2	52	16-18	1	1	0	1	56, 18, 31, 53	1	1	0	0
CIN 3	35	16	0	0	0	1	16, 18	1	0	1	1
CIN 1	19.	70	0	0	0	0	70	1	1	0	0
CIN 3	33	16	1	1	0	1	16, 11	1	1	0	1
SCC		16	1	1	0	1	16, 18	1	1	0	1
SCC	56	16	1	1	0	1	18	1	1	0	0
CIN 1	40	16	1	0	1	1	59, 42, 53	1	1	0	0
CIN 1	48	16	0	0	0	1	0	1	1	0	0

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CIN 1	23	0	1	1	0	0	0	1	1	0	0
CIN 3	55	31	1	1	0	0	59	1	1	0	0
CIN 2	50	52	1	1	0	0	52, 42, 53, 18, 16, 59, 45, 11	1	1	0	1
CIN 2	26	33	1	1	0	0	33, 42	1	1	0	0
CIN 3	33	52	1	1	0	0	42	1	1	0	0
CIN 3	45	31	0	0	0	0	16, 18, 52	1	1	0	1
SCC	35	0	1	1	0	0	58	1	1	0	0
CIN 3	58	0	1	1	0	0	42	1	1	0	0
CIN 3	36	0	1	1	0	0	0	1	1	0	0
CIN 1	30	0	1	1	0	0	52, 66	1	1	0	0
CIN 1	50	18	1	1	0	0	11	1	1	0	0
CIN 1	23	66	1	1	0	0	52, 66, 53	1	1	0	0
CIN 3	37	16	1	1	0	1	33, 18	0	0	0	0
CIN 3	21	16	1	1	0	1	16, 18, 11	1	1	0	1
CIN 1	23	0	1	0	1	0	58, 11	1	1	0	0
CIN 2	26	16	1	1	0	1	18	1	1	0	0
CIN 3	37	16	1	1	0	1	16, 11	1	1	0	1
CIN 1	20	0	1	1	0	0	56, 11	1	1	0	0
CIN 2	24	66	1	1	0	0	16, 18, 59, 52, 66, 42, 53, 11	1	1	0	1
CIN 3	60	33	1	1	0	0	11, 16, 18, 59	1	1	0	1
CIN 1	25	16	1	1	0	1	16	1	1	0	1
CIN 3	40	31,56,58	1	1	0	0	16, 18	1	1	0	1
CIN 3	34	0	1	1	0	0	16, 18, 59, 52, 35, 66, 45, 6, 42, 11	1	1	0	1
CIN 2	31	31	1	1	0	0	31, 35, 53, 18, 16	1	1	0	1
CIN 1	51	51	1	1	0	0	18, 53, 11, 16, 45, 35	1	1	0	1
CIN 1	40	16, 52	0	0	0	1	16, 52, 42	1	1	0	1
CIN 1	24	56	1	1	0	0	56, 35	1	1	0	0
CIN 1	55	58	1	1	0	0	16, 58, 18, 52, 31, 45, 11	1	1	0	1
CIN 2	33	16	1	1	0	1	16	1	1	0	1
CIN 1	25	0	1	1	0	0	58, 18, 51, 53	1	1	0	0
SCC	38	18	1	1	0	0	18	1	1	0	0
SCC	27	53	1	0	1	0	53	1	1	0	0
SCC	43	42, 53	1	1	0	0	16, 18, 35	1	1	0	1

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SCC	66	31	1	1	0	0	33, 58, 18, 31, 53	1	1	0	0
SCC	37	0	1	1	0	0	16, 18	1	1	0	1
SCC	75	0	1	1	0	0	16, 53	1	1	0	1
SCC	29	18	1	1	0	0	18, 42	0	0	0	0
No CIN	26	16	1	1	0	1	18	1	0	1	0
No CIN	47	16,45,58	1	1	0	1	58	0	0	0	0
No CIN	38	0	1	1	0	0	0	1	1	0	0
No CIN	39	0	1	1	0	0	0	1	1	0	0
No CIN	42	0	1	1	0	0	0	1	1	0	0
No CIN	32	0	1	1	0	0	0	1	1	0	0
No CIN	22	53	1	1	0	1	16	1	1	0	1
No CIN	27	0	1	1	0	0	0	1	1	0	0
No CIN	36	0	1	1	0	0	0	1	1	0	0
No CIN	38	0	1	1	0	0	0	1	1	0	0
No CIN	28	0	1	1	0	0	53	0	0	0	0
No CIN	49	0	1	1	0	0	0	1	0	1	0
No CIN	36	0	1	1	0	0	0	1	1	0	0
No CIN	22	0	1	1	0	0	0	1	1	0	0
No CIN	28	0	1	1	0	0	0	1	1	0	0
No CIN	43	0	1	1	0	0	0	1	1	0	0
No CIN	15	0	1	1	0	0	0	0	0	0	0
No CIN	41	0	1	1	0	0	0	1	1	0	0
No CIN	47	0	1	1	0	0	0	1	1	0	0
No CIN	32	11	1	1	0	0	0	1	1	0	0
No CIN	19	0	1	1	0	0	0	1	0	1	0
No CIN	28	56	1	1	0	0	0	1	1	0	0
No CIN	26	0	0	0	0	0	0	1	0	1	0
No CIN	20	0	0	0	0	0	0	0	0	0	0
No CIN	53	0	1	1	0	0	52	1	1	0	0
No CIN	40	0	1	1	0	0	42	1	1	0	0
No CIN	37	0	1	1	0	0	0	1	1	0	0
No CIN	34	0	1	1	0	0	0	1	1	0	0
No CIN	47	0	1	1	0	0	0	1	1	0	0
No CIN	27	58	0	0	0	0	0	1	1	0	0
No CIN	50	0	1	1	0	0	56	1	1	0	0
No CIN	21	0	1	1	0	0	16, 18, 51	1	1	0	1
No CIN	20	0	1	1	0	0	0	1	1	0	0
No CIN	21	35	1	1	0	0	16, 35	1	1	0	1
No CIN	24	0	1	1	0	0	0	1	1	0	0
No CIN	32	0	1	1	0	0	0	0	0	0	0

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No CIN	31	0	1	1	0	0	51	1	1	0	0
No CIN	53	0	1	1	0	0	53	1	1	0	0
No CIN	41	0	0	0	0	0	0	1	1	0	0
No CIN	42	0	1	1	0	0	0	1	1	0	0
No CIN	40	0	1	1	0	0	0	1	1	0	0
No CIN	56	16	1	0	1	1	0	1	1	0	0
No CIN	39	0	1	1	0	0	18	1	1	0	0
No CIN	24	0	0	0	0	0	0	1	1	0	0
No CIN	28	53	0	0	0	0	0	1	1	0	0
No CIN	28	0	1	1	0	0	18	1	1	0	0

CIN: Cervical Intraepithelial Neoplasia; SCC: Squamous Cervical Cancer