The role of high-risk HPV genotyping in the detection of high-grade intraepithelial neoplasia or cancer in women with negative cytology but positivity for HPV: A hospital-based investigation in northeastern China

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Abstract

Background: The high-risk human papillomavirus (hrHPV) test has a higher sensitivity for the detection of cervical precancerous lesions than cytology can provide. The present study aimed to analyze the prevalence of hrHPV genotypes and evaluate the role of HPV genotyping triage in the detection of high-grade squamous intraepithelial lesions, adenocarcinoma in situ and cervical cancer (HSIL+) in women with negative cytology but hrHPV positivity. Methods: A retrospective study was performed in women who underwent co-screening at the China Medical University-affiliated Shengjing Hospital between 2012 and 2014. Results: Of the 34,587 women, 2,665 women were eligible for analysis with negative cytology and hrHPV positivity. In HSIL+ groups of 204 women, the common genotypes were HPV16, HPV52, HPV58, HPV33, HPV31 and HPV18. The detection rate of histological HSIL+ in women with HPV16 or HPV33 was significantly higher than that in patients with other hrHPV genotypes (P = 0.00, P = 0.03, respectively). The detection rates of histological HSIL+ in women infected with HPV33 or HPV31 had no significantly difference compared to women infected with HPV16 (P = 0.29, P = 0.19, respectively).The odds ratio (OR) for histological HSIL+ in women with HPV16/18/31/33 was higher than that in women with HPV16/18 (4.21 vs. 3.26). The OR for histological HSIL+ was 5.73 in women with HPV16/18/31/33/52/58. The addition of HPV31/33 genotyping to that of HPV16/18 increased the rate of HSIL+ detection from 63.2% to 77.5% (P = 0.002). Moreover, the colposcopy per HSIL+ detection ratio only increased slightly from 7.7 to 8.1. Conclusion: HPV genotyping played an important role in managing women with negative cytology but hrHPV positivity. In northeastern China, the addition of HPV31/33 genotyping to that of HPV16/18 is deemed necessary in triaging women with a positive HPV test.

Background

Cervical cancer is the fourth most common cancer among women worldwide and the leading cause of death from cancer in developing countries [1]. Approximately 40 human papillomavirus (HPV) genotypes are associated with infection of the lower genital tract [2]. HPVs are classified as high- or low-risk according to their oncogenic potential [3]. Persistent infection of high-risk HPV (hrHPV) is necessary for the development of high-grade squamous intraepithelial lesions, adenocarcinoma *in situ* and cervical cancer (HSIL+) [4].

Recently, HPV genotyping has gained acceptance due to having a higher sensitivity for the detection of cervical precancerous lesions than cytology can provide [5]. Based on guidelines published in 2012 by the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP), a combination of cervical cytology and HPV genotyping (co-screening) is the preferred screening method for women aged 30–65 years old. Women with negative cytology but positivity for the HPV16/18 genotype should be referred for immediate colposcopy, whereas those with positivity for other hrHPV genotypes should be followed up [6]. Recently, the American Food and Drug Administration (FDA) approved hrHPV test as an option for primary screening, which also use of HPV16/18 genotyping; therefore, women with potential positivity for the 12

other possible hrHPV genotypes, being triaged by cytology [7]. Thus, whether adopting co-screening or HPV primary screening, there would be certain populations with negative cytology but hrHPV positivity. On one hand, HPV genotyping has a low specificity and a low positive predictive value, which may increase colposcopy burden and overtreatment [8]. On the other hand, genotyping solely for HPV16/18 would miss a proportion of patients with high-grade cervical lesions, since mounting evidence suggests that the risk of HSIL+ in women positive for HPV31, 33, 52 and 58 is equivalent to or greater than that in women positive for HPV18 [9–11]. Therefore, the management of women with cytology-negative and hrHPV-positive results is a major issue. Furthermore, HPV genotype prevalence and vaccination rates are diverse among regions, and the data collected in other countries may not represent the situation in China [12, 13].

The application of HPV genotyping for cervical cancer screening is becoming increasingly popular in China. It is uncertain which combinations of hrHPV genotyping could provide optimal triage of women with negative cytology and hrHPV positivity in clinical practice in northeastern China. To address these concerns, a retrospective study was conducted to evaluate the prevalence of HPV genotypes and their associated risk for HSIL+ in northeastern China. Furthermore, an acceptable triage strategy to reduce the burden of cytological examination and increase the specificity of HPV screening was explored.

Methods

1. **Study population**

We recruited women between 25 and 65 years old who underwent co-screening for cervical cancer when visiting outpatient of the Department of Obstetrics and Gynecology at the China Medical University-affiliated Shengjing Hospital between January 1st 2012 and December 31st 2014. The prevalence of hrHPV genotypes and the relationships between each genotype and histological HSIL+ were retrospectively analyzed in women with cytology-negative and hrHPV-positive results. The clinical characteristics and pathological data were obtained from the hospital's electronic files, including age at diagnosis, cytology results, HPV genotyping results, colposcopy results and histological results. The present study excluded pregnant women, women who had a previous hysterectomy, or had a history of cervical cancer, or had previous treatment for any cervical epithelial lesion. The study was approved by ethnics committee of Liaoning Cancer Hospital and Institute (20190971).

2. **Cytology**

Cytological testing was performed using ThinPrep® liquid-based cytology (Hologic Inc, USA). The cell sample was collected by a cytobrush and deposited into a tube with transport medium. From each woman, the first sample was taken for cytology. The second sample was taken for HPV genotyping test. The slides were screened by two cytotechnologists and diagnosed according to the 2001 Bethesda system.

3.HPV genotyping

HPV genotyping was identified by gene amplification using a genotype test kit (Hybribio, Guangzhou, China). A total of 21 genotypes were screened, including 15 high-risk genotypes (HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV53, HPV56, HPV58, HPV59, HPV66, and HPV68) and 6 low-risk genotypes (HPV6, HPV11, HPV42, HPV43, HPV44 and HPV CP8304).

4. **Colposcopy and biopsy**

All women who had positive cytology or hrHPV infection were referred for colposcopy. A colposcopy guided biopsy was performed if a suspicious lesion was found. Random cervical biopsy was obtained when colposcopic inspection was inadequate. If colposcopy results were normal with adequate inspection, women were followed up per year without biopsy. The grade of the cervical lesion was independently diagnosed by two expert pathologists according to the standard histomorphologic criteria. Immunohistochemical stains for p16 and Ki67 were used when a consensus was not reached.

5. **Data analysis**

Data were analyzed using the SPSS version 22.0 software (SPSS Inc, Chicago, IL, USA). An χ^2 test was used to compare the proportions between different groups. Logistic regression analysis was used to estimate the relative risk of histological HSIL+ associated with hrHPV genotypes. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated when risks were estimated. $P < 0.05$ is considered statistically significant.

Results

1. **Characteristics of study population**

A total of 34,587 women between 25 and 65 years old attended our hospital for cervical cancer co-screening, 4,198 of which (12.1%) had hrHPV infection and 1,839 (5.3%) had abnormal cytology results (Figure 1). Multiple infections were detected in 676 of the 4,198 (16.1%) infected women. The most common hrHPV genotype was HPV16 (1,373, 32.7%), followed by HPV58 (680, 16.2%), HPV52 (571, 13.6%), HP53 (504, 12.0%), HPV33 (360, 8.6%) and HPV18 (301, 7.2%).

2. **Cytology-negative and hrHPV-positive results**

A total of 2,897 of the 4,198 (69.0%) hrHPV infected women with cytology-negative and hrHPV-positive results were enrolled in the present study. The mean age of these women was 39.60 ± 8.99 years old, with a median of 40. The prevalence of hrHPV among women with negative cytology and hrHPV positivity was a little different from that among the whole population of women receiving cervical cancer co-screening. The top six hrHPV genotypes were HPV16 (874, 30.1%), HPV58 (452, 15.6%), HPV52 (395, 13.6%), HPV53 (380, 13.1%), HPV18 (224, 7.7%) and HPV33 (208, 7.2%). With respect to each hrHPV genotype, the percentage of women with negative cytology was higher in those infected with HPV59, HPV53, HPV45, HPV18 and HPV51 (Table 1).

3. **hrHPV genotype and HSIL+ incidence**

Colposcopy was performed in 2665 women with negative cytology and hrHPV positivity. Colposcopy-guided biopsy and random biopsy was performed in 1,742 (1742/2665, 65.4%) women. A total of 204 women (204/2665, 7.7%) had HSIL+, including 26 women with cervical carcinoma (14 women with early stage infiltration, 53.8%, 14/26), 173 women (173/2665, 6.5%) had low-grade intraepithelial neoplasia (LSIL), and 2,288 women (2288/2665, 85.8%) had negative histology results or normal colposcopic results. In the HSIL+ group, the prevalence of the hrHPV genotypes was HPV16 (119, 58.3%), HPV52 (28, 13.7%), HPV58 (26, 12.7%), HPV33 (22, 10.8%), HPV31 (15, 7.4%) and HPV18 (12, 5.9%). The percentage of women infected with multiple hrHPV genotypes was 19.1% (39/204) in the HSIL+ group. In the squamous cervical cancer group, the prevalence of HPV16 (75%, 18/24) was prominent. Among the 7 cases of adenocarcinoma *in situ* and adenocarcinoma, 5 cases were HPV18-positive and 2 cases were HPV16-positive, including one case HPV18 and HPV33 dual infection (Table 1).

4. **hrHPV genotypes and their risk for the detection of HSIL+**

The rate of histological HSIL+ did not differ significantly by age group (25–34, 35–44, 45–54 and 55–65 years old. P = 0.14, 0.16, 0.83, and 0.79, respectively). Of the 801 women with negative cytology and HPV16 positivity, 119 (119/801, 14.9%) women were confirmed as HSIL+ by histological diagnosis. Besides HPV16, the rate of histologic HSIL+ in each genotype was above 10% for HPV33 (22/187, 11.8%) and HPV31 (15/142, 10.6%). The rate of histologic HSIL+ in each genotype was lower than 10% for HPV52 (28/362, 7.7%), HPV58 (26/414, 6.3%), HPV18 (12/206, 5.8%) and et al. The detection rate of histological HSIL+ in women infected with HPV16 or HPV33 was significantly higher than that in women infected with the other hrHPV genotypes (P = 0.00, P = 0.03, respectively) (Table 2). The difference between the rate of histological HSIL+ in women infected with HPV18 and those infected with the other hrHPV genotypes was not statistically significant (P = 0.30) (Table 2). Compared to women infected with HPV16, the detection rates of histological HSIL+ had no significantly difference in women infected with HPV33 or HPV31 (P = 0.29, P = 0.19, respectively). Although HPV58, HPV52, HPV53 and HPV18 were four of the top six most common genotypes in women with negative cytology and hrHPV positivity, the detection rates of histological HSIL+ in each of these four HPV genotypes were significantly lower than those in women infected with HPV16 (P = 0.00, P = 0.001, P = 0.00 and P = 0.00, respectively). The detection rate of histological HSIL+ in women infected with multiple genotypes was significantly higher than those with a single infection (P = 0.03).

Among all 2,665 women with hrHPV-positive and cytology-negative results, following adjustment for age, the odds ratio (OR) for histological HSIL+ was 3.75 (95% CI = 2.79–5.05) in women with HPV16 infection. In women infected with HPV33, the OR for histological HSIL+ was 1.69 (95% CI = 1.04–2.72). And in women infected with HPV31, the OR for histological HSIL+ was 1.46 (95% CI = 0.83–2.57). Infection with HPV genotypes 18, 52 or 58 did not increase the risk of HSIL+ (OR = 0.72, 1.03, 0.78, 95% CI = 0.39–1.32, 0.68–1.57, 0.51–1.20, respectively). The OR for histological HSIL+ in women with HPV16/18/33 infection was higher than that in women with HPV16/18 infection (3.85 vs. 3.26, 95% CI = 2.79–5.31, 2.41–4.40,

respectively). The odds ratio (OR) for histological HSIL+ was 4.21 (95% CI = 2.99–5.93) in women infected with HPV16/18/31/33. The odds ratio (OR) for histological HSIL+ was 5.73 (95% CI = 3.30–9.97) in women infected with HPV16/18/31/33/52/58 (Table 3).

HPV16/18 were detected in 129 of 204 (63.2%) women with histological HSIL+; by contrast, the top six hrHPV genotypes (HPV16/18/31/33/52/58) were detected in 190 (190/204, 93.1%) women. The difference was statistically significant (P = 0.00); however, the colposcopy per HSIL+ detection ratio also increased from 7.7 to 10.2. The addition of the HPV31/33 genotype to that of HPV16/18 increased the percentage of HSIL+ detection from 63.2% to 77.5% (P = 0.002), and the colposcopy per HSIL+ detection ratio only increased slightly from 7.7 to 8.1 (Table 3).

Discussion

Cervical cancer screening has regional differences in China. In relatively developed areas of China, co-screening is commonly performed in hospitals [9], and it is clear that women with abnormal cytology and hrHPV positivity should be referred for colposcopy [14]; however, the management of women with cytology-negative and hrHPV-positive results remains controversial. The triage of HPV primary screening faces the same problem. Several studies have shown that the current cervical screening strategy with HPV16/18 genotyping misses the majority of hrHPV-infected women who progress to high-grade cervical lesions or cancer [15, 16]. The present study was a real-world study and evaluated the prevalence and HSIL+ risk of hrHPV genotypes, especially in women with negative cytology and hrHPV positivity.

The prevalence of hrHPV (12.1%) obtained in the present study was lower than that reported in many Chinese cities [18]; however, it was slightly higher than that (9.5%) reported in a previous study from the same region [17]. Moreover, previous population-based screening results have demonstrated that the overall prevalence of hrHPV varies from 9.9–27.5% across China [19]. A previous study suggested possible reasons for this inconsistency, including different study populations, geographical prevalence, and differences in detection methods [20]. In accordance with previous data reported by Chinese population-based investigations [17–19], HPV16, HPV58 and HPV52 were found to be the dominant hrHPV types in the present study, followed by HPV53, HPV33 and HPV18. However, the results were distinctly different from those reported by a summarized global meta-analysis, in which HPV16, HPV18 and HPV45; HPV16, HPV18 and HPV33; or HPV16, HPV18 and HPV58 were the most common genotypes [21]. In the present study, the most common genotypes in women with negative cytology and hrHPV positivity were mostly in accordance with those in all hrHPV-positive women, with the exception that HPV18 was moved up to fifth place and HPV33 was moved down to sixth place.

The oncogenic potential varies with different hrHPV genotypes. A population-based study showed that HPV16, 58, 18, 52 and 33 were most common in persistent infection [22]. Another study showed that HPV16, 33 and 58 increase the risk of HSIL+ as compared with hrHPV-negative women [23]. Moreover, it has been shown by Bayesian probability modeling that the HSIL+ risk of HPV16 is the highest, and the HSIL+ risk of HPV31 and HPV33/58 is higher than that of HPV18 [24]. A European study showed that the

most common HPV types in women with HSIL+ and cervical cancer were HPV16/33/31 (59.9/10.5/9.0%) and HPV16/18/45 (63.3/15.2/5.3%), respectively [25]. In the present study, in women with negative cytology, HPV16 was the most common genotype in histological HSIL+; however, HPV52, 58, 33 and 31 were more common than HPV18. Moreover, HPV33 was associated with a significantly higher risk of developing HSIL+ than other non-HPV16 types. The detection rates of histological HSIL+ had no significantly difference between women who infected with HPV33 or HPV31 and women who infected with HPV16. Although the prevalence of HPV53 was common, it held a low risk of developing HSIL+.

HPV genotyping will enable more precise characterization of cervical disease risk, but genotyping for only HPV16/18 is not sufficient. Although the prevalence and risk of HSIL+ in women with HPV18 did not rank high among non-HPV16 types, HPV18 was one of the most common genotypes in adenoepithelial lesions. In the present study, HPV16/18 was positive in 63.2% of women with histological HSIL+. The addition of HPV31/33 genotyping to that of HPV16/18 could detect 14.3% more women with histological HSIL+. The OR for histological HSIL+ in women infected with HPV16/18/31/33 was higher than that in women infected with HPV16/18 (4.21 vs. 3.26). The addition of HPV31/33/52/58 genotyping to that of HPV16/18 could detect 93.1% of histological HSIL+ in the present study. The risk of histological HSIL+ (OR) was 5.73 in women infected with HPV16/18/31/33/52/58. A previous population-based, prospective, observational study suggested that HPV16/18/31/33/52/58 infection could be immediately referred to colposcopy [26]. However, in the present study, women infected with HPV16/18/31/33/52/58 accounted for 72.7% (1,938/2,665) of all women with negative cytology and hrHPV positivity; therefore, the burden of colposcopy would increase. Our results support the need for immediate colposcopy in women infected with HPV16/18/31/33 in order to detect more HSIL+ cases, in addition the colposcopy burden didn't increase significantly. If colposcopy resource is sufficient, women with HPV16/18/31/33/52/58 infection can also be recommended for immediate colposcopy.

Conclusions

In summary, wider hrHPV genotyping provides a better predictive value than HPV16/18 genotyping alone in guiding the clinical management of current cervical cancer screening. In northeastern China, the addition of HPV31/33 genotyping to that of HPV16/18 is deemed necessary in triaging women with a positive HPV test.

Declarations

Ethics approval and consent to participate:

The present study was approved by ethnics committee of Liaoning Cancer Hospital and Institute (20190971).

Consent for publication

Not applicable.

Competing interests

All authors declare there are no conflicts of interest.

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Author contributions:

Jing Zhang: Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Validation; Visualization; Writing original draft; Writing review & editing. Deyu Zhang: Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Validation; Visualization; Writing original draft; Writing review & editing. Zhuo Yang: Formal analysis; Investigation; Methodology; Software; Validation; Visualization; Writing review & editing. Xiaobin Wang: Formal analysis; Funding acquisition; Methodology; Validation; Visualization; Writing review & editing. Danbo Wang: Conceptualization; Formal analysis; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Writing review & editing.

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Figure 1. Flowchart for the study population. (hrHPV, high risk human papilloma virus; HSIL+, histologic high-grade squamous intraepithelial lesions, adenocarcinoma in situ and cervical cancer).

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Tables

Table 1 The prevalence of hrHPV genotypes in 2897 women with cytology negative and hrHPV positive

hrHPV genotypes	Total	No. of HPV positive & cytology negative(%)	No. of histological HSIL+, n=204, (%)	No. of histological high-grade squamous intraepithelial lesion,n=173,(%)	No. of histological adenocarcinoma in situ and adenocarcinoma, n=7, (%)	No. of histological squamous cervical cancer, n=24, (%)
16	1373	874(63.7)	119(58.3)	99(57.2)	2(28.6)	18(75.0)
18	301	224(74.4)	12(5.9)	6(3.5)	5(71.4)	1(4.2)
31	221	154(69.7)	15(7.4)	13(7.5)	0	2(8.3)
33	360	208(57.8)	22(10.8)	21(12.1)	1(14.3)	0
35	41	22(53.7)	0	0	0	0
39	234	169(72.2)	5(2.5)	5(2.9)	0	0
45	62	47(75.8)	2(0.1)	2(1.1)	0	0
51	143	101(70.6)	4(2.0)	3(1.7)	0	1(4.2)
52	571	395(69.2)	28(13.7)	28(16.2)	0	0(0)
53	504	380(75.4)	10(4.9)	9(5.2)	0	1(4.2)
56	75	37(49.3)	0	0	0	0
58	680	452(66.5)	26(12.7)	25(14.5)	0	1(4.2)
59	93	71(76.3)	1(0.05)	0	0	1(4.2)
66	209	143(68.4)	7(3.4)	7(4.0)	0	0
68	166	115(69.3)	4(2.0)	4(2.3)	0	0

Women with multiple HPV types detected are counted to each type, and therefore counted more than once

Table 2 Comparison of the detection rate of HSIL+ among different age groups and hrHPV genotypes.

		No. of women undergone colposcopy with HPV positive & cytology negative, n=2665	No. of histological HSIL+, (%)	χ^2 value	*P* value
Age groups	25-34	923	61(6.6)	2.19	0.14
	35-44	975	84(8.6)	2.01	0.16
	45-54	585	46(7.9)	0.05	0.83
	55-65	182	13(7.1)	0.07	0.79
HPV infection	single	2296	165(7.2)	5.15	0.03
	multiple	369	39(10.6)		
Top six hrHPV genotype	16	801	119(14.9)	84.02	0.00
	18	206	12(5.8)	1.06	0.30
	31	142	15(10.6)	1.80	0.18
	33	187	22(11.8)	4.81	0.03
	52	362	28(7.7)	0.004	0.95
	58	414	26(6.3)	1.31	0.25

Table 3 Detection of histologic high-grade squamous intraepithelial lesion or worse lesions by different hrHPV genotyping approaches in the study population.

	No. of HPV positive & cytology negative with availble histologic or colposcopic results	No. of histologic HSIL+	Percentage of HSIL+ detected, n=204	Ratio of colposcopy per HSIL+ detection	OR	95% CI	*P* value
HPV16/18	992	129	63.2	7.7	3.26	2.41-4.40	<0.001
PV16/18/33	1162	148	72.5	7.9	3.85	2.79-5.31	<0.001
16/18/31/33	1282	158	77.5	8.1	4.21	2.99-5.93	<0.001
18/31/33/52/58	1938	190	93.1	10.2	5.73	3.30-9.97	<0.001

Figures

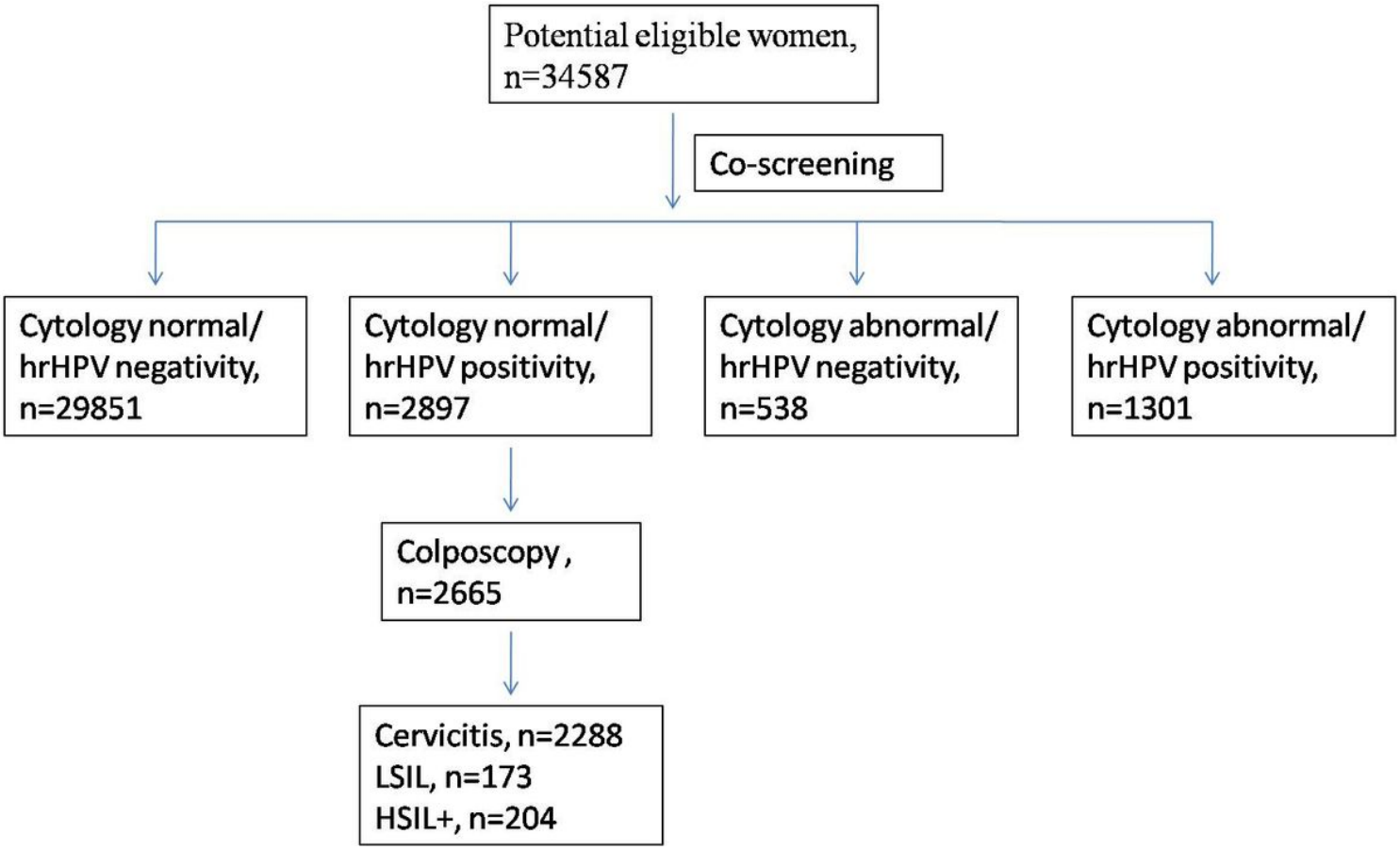

Figure 1

Flowchart for the study population. (hrHPV, high risk human papilloma virus; HSIL+, histologic high-grade squamous intraepithelial lesions, adenocarcinoma in situ and cervical cancer).