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

Jing Zhang
Liaoning Cancer Hospital and Institute https://orcid.org/0000-0002-5124-0288

Deyu Zhang
Shengjing Hospital of China Medical University

Zhuo Yang
Liaoning Cancer Institute and Hospital

Xiaobin Wang
Liaoning Cancer Institute and Hospital

Danbo Wang ( wangdanbo@cancerhosp-ln-cmu.com )

Research article

Keywords: Human papillomavirus; hrHPV prevalence; HPV genotyping; High-grade squamous intraepithelial lesion; Cervical cancer

Posted Date: November 25th, 2019

DOI: https://doi.org/10.21203/rs.2.17764/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Version of Record: A version of this preprint was published at BMC Cancer on May 19th, 2020. See the published version at https://doi.org/10.1186/s12885-020-06935-w.
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 $\chi^2$ 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%), HPV53 (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 2,665 women with negative cytology and hrHPV positivity. Colposcopy-guided biopsy and random biopsy was performed in 1,742 (1,742/2,665, 65.4%) women. A total of 204 women (204/2,665, 7.7%) had HSIL+, including 26 women with cervical carcinoma (14 women with early stage infiltration, 53.8%, 14/26), 173 women (173/2,665, 6.5%) had low-grade intraepithelial neoplasia (LSIL), and 2,288 women (2,288/2,665, 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.

Funding

National Key Research and Development Project "Research and Development of Digital Diagnostic and Medical Equipment" (grant number 20171FC0114204); Liaoning Province Key Research and Development Project (grant number 2018225037); Liaoning Province Natural Science Foundation (grant number 20180550748)

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.

Acknowledgements

The authors would like to thank Mr. Te Qi for his excellent assistance in this work.

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).

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65:87–108.

2. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003;348:518–527.

3. de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross- sectional worldwide study. Lancet Oncol. 2010; 11:1048-56.

4. Crosbie EJ, Einstein MH, Franceschi S, Kitchener HC. Human papillomavirus and cervical cancer. Lancet. 2013; 382: 889-99.
5. Huh WK, Ault KA, Chelmow D, Davey DD, Goulart RA, Garcia FA, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. Gynecol Oncol. 2015;136(2):178–82.

6. Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. Am J Clin Pathol. 2012;137:516-542.

7. Huh WK, Ault KA, Chelmow D, Davey DD, Goulart RA, Garcia FA, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. Gynecol Oncol. 2015;136:178-82.

8. Rijkaart DC, Berkhof J, van Kemenade FJ, Coupe VM, Hesselink AT, Rozendaal L, et al. Evaluation of 14 triage strategies for HPV DNA-positive women in population-based cervical screening. Int J Cancer. 2012;130(3):602-610.

9. Zhang Y, Wang Y, Liu L, Guo C, Liu Z, Nie S. Prevalence of human papillomavirus infection and genotypes in cervical lesions among women in Shanghai. Int J Cancer. 2015;137:522-529.

10. Cuzick J, Ho L, Terry G, Kleeman M, Giddings M, Austin J, et al. Individual detection of 14 high risk human papilloma virus genotypes by the PapType test for the prediction of high grade cervical lesions. J Clin Virol 2014; 60: 44-9.

11. Thomsen LT, Frederiksen K, Munk C, Junge J, Iftner T, Kjaer SK. Long-term risk of cervical intraepithelial neoplasia grade 3 or worse according to high-risk human papillomavirus genotype and semiquantitative viral load among 33,288 women with normal cervical cytology. Int J Cancer 2015;137:193-203.

12. Bhatla N, Lal N, Bao YP, Ng T, Qiao YL. A meta-analysis of human papillomavirus type-distribution in women from South Asia: implications for vaccination. Vaccine. 2008; 26:2811-2817.

13. Xu QX, Zhang ZY. High-risk human papillomavirus genotypes in cervical lesions and vaccination challenges in China. Asian Pacific journal of cancer prevention. 2015; 16:2193-2197.

14. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al, Conference ACG. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis 2013;17: S1-S27.

15. Khunamornpong S, Settakorn J, Sukpan K, Suprasert P, Srisomboon J, Intaraphet S, et al. Genotyping of human papillomavirus in cervical lesions in Thailand and evaluation of the PapType test. J Med Assoc Thai 2015;98(Suppl 1):S19-S23.
16. Gu L, Hong Z, Gao H, Qiu L, Di W. Incidence of cervical high-grade squamous intraepithelial lesions

17. Wang R, Guo XL, Wisman GB, Schuuring E, Wang WF, Zeng ZY, et al. Nationwide prevalence of human papillomavirus infection and viral genotype distribution in 37 cities in China. BMC Infect Dis. 2015; 15:257.

18. Xue H, Lin X, Li T, Yan X, Guo K, Zhang Y. Prevalence and genotype distribution of human papillomavirus infection in asymptomatic women in Liaoning province, China. J Med Virol. 2015 Jul;87(7):1248-53.

19. Li J, Huang R, Schmidt JE, Qiao YL. Epidemiological features of Human Papillomavirus (HPV) infection among women living in Mainland China. Asian Pacific journal of cancer prevention : APJCP. 2013;14(7):4015–23.

20. Sun P, Song Y, Ruan G, Mao X, Kang Y, Dong B, et al. Clinical validation of the PCR-reverse dot blot human papillomavirus genotyping test in cervical lesions from Chinese women in the Fujian province: a hospital-based population study. J Gynecol Oncol. 2017; 28(5):e50.

21. Guan P, Howell-Jones R, Li N, Bruni L, de Sanjosé S, Franceschi S, et al. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. Int J Cancer. 2012; 131:2349–59.

22. Wang S, Wei H, Wang N, Zhang S, Zhang Y, Ruan Q, et al. The prevalence and role of human papillomavirus infection among women living in Mainland China. Asian Pacific journal of cancer prevention : APJCP. 2013;14(7):4015–23.

23. Wang Y, Xue J, Dai X, Chen L, Li J, Wu Y, et al. Distribution and role of high-risk human papillomavirus in women living in Mainland China. Asian Pacific journal of cancer prevention : APJCP. 2013;14(7):4015–23.

24. Bonde J, Bottari F, Parvu V, Pedersen H, Yanson K, Iacobone AD, et al. Bayesian analysis of baseline

25. Tjalma WA, Fiander A, Reich Q, Powell N, Nowakowski AM, Kirschner B, et al. Differences in human papillomavirus type distribution in high-grade cervical intraepithelial neoplasia and invasive cervical cancer in Europe. Int J Cancer. 2013; 132: 854-67.

26. Xu H, Lin A, Shao X, Shi W, Zhang Y, Yan W. Diagnostic accuracy of high-risk HPV genotyping in women with high-grade cervical lesions: evidence for improving the cervical cancer screening strategy in China. Oncotarget. 2016;7:83775-83783.

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

| HPV infection | Age groups | No. of HPV positive & cytology negative, n=2665 | No. of histological HSIL+, (%) | $\chi^2$ value | P value |
|---------------|------------|-----------------------------------------------|--------------------------------|----------------|---------|
|               |            | No. | Percentage | OR | 95% CI | P value |
| single        | 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   |
| multiple      |            | 2296| 165(7.2)   | 5.15 | 0.03   |
|               | 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   |

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).