Characteristics of high-risk human papillomavirus infection in women with abnormal cervical cytology: a population-based study in Shanxi Province, China

Li Song
Shanxi Medical University
Yuanjing Lyu
Shanxi Medical University
Ling Ding
Shanxi Medical University
Xiaoxue Li
Shanxi Medical University
Wen Gao
Shanxi Medical University
Ming Wang
Shanxi Medical University
Min Hao
Shanxi Medical University Second Affiliated Hospital
Zhilian Wang
Shanxi Medical University Second Affiliated Hospital
Jintao Wang (wangjt59@163.com)
https://orcid.org/0000-0003-1415-584X

Research article

Keywords: HR-HPV, Distribution, Characteristics, Abnormal cervical cytology

Posted Date: October 9th, 2019

DOI: https://doi.org/10.21203/rs.2.15784/v1

Abstract

Background: High-risk human papillomavirus (HR-HPV) infection is widely known as the major cause of cervical intraepithelial neoplasia (CIN) and cervical cancer and it's characteristics vary greatly in different population. Women with abnormal cervical cytology could increase the risk of cervical cancer, however, HR-HPV infection characteristics in women with abnormal cervical cytology remains unclear.

Methods: This study was based on baseline survey of the CIN Cohort established in Shanxi Province, China. A total number of 2300 women with cervical abnormalities were enrolled in this study. All participants gave informed consent and agreed to HPV and thinprepcytologic test (TCT). Each individual completed a questionnaire about characteristics related to HPV infection.

Results: The overall prevalence of HR-HPV in 2300 women was 32.0%, and the proportion of single and multiple HR-HPV infections were 70.2% and 29.8% in HR-HPV infection women, respectively. The top five HR-HPV genotypes were ranked as HPV16, HPV58, HPV52, HPV53 and HPV51. The prevalence of HR-HPV in atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion and above(HSIL+) were 30.8%, 36.5% and 54.9%, respectively, showing an increasing trend with the severity of cervical cytology (χ 2 trend =13.952; p <0.001). The women aged 35~45 years, with lower education level, less frequency of bathing, multiple gravidity, multiple parity, history of gynecological diseases and premenopausal women were prone to HR-HPV infection.

Conclusions: We defined the characteristics related to HR-HPV infection in abnormal cervical cytology women, and provided an insight for the development and deeply research of HPV vaccine.

Background

Human papillomavirus (HPV) infection has been identified as definite human carcinogen[1], and account for more than 50% of infection-linked cancers in females[2]. Cervical cancer ranks as the fourth most common cancer amongst women worldwide, with an estimated 570,000 new cases and 311,000 deaths in 2018 worldwide[3]. High risk human papillomavirus (HR-HPV) has been identified as an etiological factor for cervical cancer and precancerous lesions[4].

To date, more than 100 HPV genotypes have been identified[5], of which approximately 40 HPV types are associated with the genital tract infection[6]. Among the numerous members of the HPV family, 15 HR-HPV genotypes (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66 and 68) are etiologically associated with more than 98% of cervical cancers. Effective prophylactic vaccines against the most important carcinogenic HPV types are available, but they do not cover main types of HPV in different countries and regions[7]. Moreover, the prevalence and genotype distribution of HPV substantially vary with ethnicities, demographic and behavioral characteristics, as well as health status[8–10]. However, few studies have been reported in women with abnormal cervical cytology.

Cervical cytology test had been used as a diagnostic aid for earlier detection of cervical cancer[11]. Some studies found that the incidence of cervical intraepithelial neoplasia (CIN) 2~3 and cervical cancer in women with smears revealing atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H) was 56.5% and 9.3%, respectively[12], the incidence of CIN 2~3 and cervical cancer in women with high-grade squamous intraepithelial lesion (HSIL) smears was 62.9% and 25.8% [13]. HPV-positive women with atypical squamous cells of undetermined significance (ASC-US)/ low-grade squamous intraepithelial lesion (LSIL) cytology had a 5~year CIN3+ risk of 22.2%, for those with normal cytology this risk was 7.9%[14].These studies clearly demonstrate that women with abnormal cervical cytology had high rate of significant cervical lesions particularly invasive cervical disease. However, women with what characteristics would be more susceptible to HR-HPV infection remains unclear.

It was reported that the prevalence of HPV infection in women with abnormal cervical cytology was 47.0% to 72.8%[15, 16]. HPV prevalence increased with increasing severity of cervical lesions from 12% in normal cytology to 89% in invasive cervical cancer[17]. Compared to the researches of general population, women with abnormal cervical cytology might be more susceptible to HR-HPV. However, the distribution of HR-HPV infection varied in different countries and regions, and weather demographic-behavioral characteristics related to HR-HPV infection in women with cervical abnormalities are poorly understood. The primary aims of this study were to describe the characteristics of HR-HPV infection in women with abnormal cervical cytology, so as to provide foundation for preventing and controlling cervical lesions.

Materials And Methods

Study Population

This study was based on data obtained from the baseline survey of the CIN Cohort established during June 2014 to December 2014 in Shanxi Province, China. Briefly, the present survey was conducted in two counties of Shanxi province. A woman was considered eligible to enter the study if she a) had resided in Shanxi province for at least 1 year; b) had current or past sexual activity; c) not pregnant; d) no prior history of cervical cancer or precancerous lesions; e) no prior history of treatments for cervix such as Loop Electrosurgical Excision Procedure (LEEP), conization, and adnexectomy; f) agreed to participate in the present study. A total of 39,988 women aged 19~65 years were included. All participants completed a demographic and behavioral characteristic related questionnaire, medical examination and Thinprepcytological test (TCT). Of them, 37,219 women were negative for intraepithelial lesion or malignancy (NILM), 2,769 women showed abnormal cervical cytology, including 2,305 with ASC-US, 82 with ASC-H, 316 with LSIL, 54 with HSIL, 10 with squamous cervical carcinoma (SCC), and 2 with atypical glandular cells (AGC). Then, 2769 participants with abnormal cervical cytology were referred to HPV testing. Of them, 68 refused, 387 had inadequate investigation, 8 had not fully completed medical examination, 6 specimens were not suitable for detection, At last, 2,300 women were included in the

present study (Fig.1). Informed consents have been signed by all the participants and this study has been approved by the Institutional Review Board of Shanxi Medical University (No: 2013–003).

Data and Sample Collection

The information of demographic characteristics, history of gynecological diseases (including vaginitis, pelvic inflammation disease, uterine fibroids, hyperplasia endometria, and ovarian tumors), lifestyle habits, sexual and reproductive information was collected by trained interviewers using structured questionnaire. Two samples of exfoliated cervical cells were collected after visualization of the cervix. One sample was for routine TCT, another sample was for HPV testing.

TCT test

Exfoliated cervical cells were obtained from each participant using a cytobrush. All liquid-based cytology specimens were independently diagnosed by two experienced cytopathologists. If the diagnosis differed between the 2 cytopathologists, the sample was reviewed by a third cytopathologist, and a consensus diagnosis was obtained by the three cytopathologist together. The cytology results were diagnosed according to the 2001 Bethesda System and classified as NILM, ASC-US, ASC-H, LSIL, HSIL, SCC and AGC. A diagnosis of ASC-US or higher was considered cytological abnormality.

HR-HPV Detection

HPV detection and genotyping was tested using HybriMax HPV Geno-Array kit (Hybribio Biotechnology Limited Corp, Chaozhou, China) according to the manufacturer's instruction. 21 types of HPV, including 15 HR-HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66 and 68) and 6 low-risk human papillomavirus (LR-HPV) (6, 11, 42, 43, 44 and CP8304) were identified by the flow-through hybridization technique using a TC–96/G/H6 HPV DNA Amplification Analyzer and an HMM–2 fast nucleic acid molecule hybridization instrument (HybriBio Ltd). Briefly, PCR was performed in a 25μL reaction mixture containing 5μL extracted DNA,0.75μL DNA Taq polymerase and 19.25μL PCR-mix solution containing MY09/11 primer system. The PCR protocol was: denaturing at 95°C for 9 min, followed by 40 cycles of 20s at 95°C, 30s at 55°C, and 30s at 72°C, at last a finally extension at 72°C for 5 min. A positive control and a negative control were run in each PCR process. The HPV-genotype result was determined by the position of the HPV-genotype probes on the microarray chip. Adding NBT/BCIP solution to display the results, a positive result was indicated by a clearly visible indigo dot. Multiple dots indicated multiple infections. The HR-HPV single infection or multiple infections was defined as HR-HPV infection in the study.

Statistical Analyses

Statistical analyses were performed by using Statistical Package for the Social Sciences (SPSS) software version 22.0 (IBM Corporation, Armonk, New York, USA) for Windows. Count data were examined by Chi-square tests, odds ratios (*ORs)* and 95% confidence interval (*CI)* were calculated using unconditional logistic regression. Graphics were used GraphPad Prism 7 (GraphPad Software Inc, CA, USA). All reported *p* values were two-sided, and statistical significance was defined as $p<0.05$.

Results

Demographic characteristics of participants

A total of 2300 women were included in the study. Demographic characteristics were summarized in Table 1. The mean age was 50±13 (range 19~65) years, 1,462 (63.6%) women received education in junior high school and below, and only 36.4% with senior high school and above. 66.3% were housewives or farmers and 96 (4.2%) women with divorced, widowed, or separated. The average yearly income was under 10000 Chinese Yuan Renminbi (RMB).

Distribution of HR-HPV genotypes

A total of 32.0% (736/2300) women had HR-HPV infection, and showing the top five HR-HPV types with HPV16 (13.5%), HPV58 (5.7%), HPV52 (4.9%), HPV53 (2.5%), HPV51 (2.3%) (Fig.2).

Distribution of HR-HPV single/multiple infection

The prevalence of HR-HPV infection with single type and multiple types were 22.5% (517/2,300) and 9.5% (219/2,300), and with proportion of 70.2% (517/736) and 29.8% (219/736) in HR-HPV infection women. Among multiple HR-HPV types, two HR-HPV genotypes infection was most common with 76.7% (168/219). In addition, we found that the prevalence of HPV16, 58 and 39 single type were significantly higher than women with HPV16, 58 and 39 multiple types infection (Table 2).

Demographic-behavioral characteristics related to HR-HPV infection

HR-HPV infection peak age was aged 35 to 45 years, while 60 years old and over with the lowest HR-HPV infection rate (22.7%). The women with 35~45 years old, lower education level, less frequency of bathing, multiple gravidity (number of pregnancies), multiple parity (number of deliveries), history of gynecological diseases and premenopausal women have high risk to HR-HPV infection(Table 3, Fig.3), and mainly presented the highest prevalence of HR-HPV16, 58 and 52 infection. Especially, we found the high infection rate of HPV16 and HPV51 presented in the women under 35 years old. No significant

association was found between occupation, marital status, average annual income, condom use and HR-HPV infection.

Distribution of HR-HPV in various abnormal cervical cytology groups

Among the 2,300 women with abnormal cervical cytology, women with ASC-US, LSIL, and HSIL+ accounted for 86.5%, 11.3% and 2.2%, respectively. The prevalence of HR-HPV in ASC-US, LSIL and HSIL+ were 30.8% (613/1,989), 36.5% (95/260) and 54.9% (28/51), respectively, showing an increasing trend with the severity of cervical cytology (χ^2_{trend} = 13.952, p<0.001), particularly, HPV16 and HPV33 types showing a significant increase in prevalence with severity of cervical cytology. The top five HR-HPV types were HPV16 (13.1%), HPV58 (5.5%), HPV52 (4.9%), HPV53 (2.6%), and HPV51 (2.4%) in ASC-US, HPV16 (12.3%), HPV58 (8.1%), HPV52 (5.8%), HPV33 (3.1%), and HPV18 (2.7%) in LSIL, HPV16 (33.3%), HPV33 (7.8%), HPV31 (3.9%), HPV56 (3.9%) and HPV58 (2.0%) in HSIL+ women (Table 4).

Discussion

In the present study, we found that women with abnormal cervical cytology had a relatively higher prevalence of HR-HPV with 32.0%, which was higher than population-based prevalence observed in Shanxi Province (15.2%)[18], Jiangxi Province (12.3%)[19], Guangdong Province (15.7%)[20] and Yunnan Province (18.1%)[21]. X. Castellsagué et al[22] reported that HPV16, 18, 31, 58, 52 were the top five HR-HPV types in both women with normal and abnormal cervical cytology according to estimates from 193 countries. Hernan et al[23] found HPV16, 53, 52, 58 and 59 were the top five genotypes in women with abnormal cervical cytology from Bogota, Columbia. Our finding indicated that the top five HR-HPV genotypes were HPV16, 58, 52, 53 and 51 in women with abnormal cervical cytology in Shanxi Province, China, while HPV18 was in the 12th position. The distribution of HR-HPV genotypes vary greatly worldwide, and these differences might be related to the complex geographical and biological interplay between different HPV genotypes and host immunogenetic factors.

Our results showed that the proportion of single and multiple HR-HPV infections were 70.2% and 29.8%, respectively. HPV16, 58 and 39 were significantly more prevalent in women with single HR-HPV infection than multiple HR-HPV infections, suggested that HPV16, 58 and 39 might have stronger pathogenicity than other HR-HPV genotypes. A study conducted in Cyprus also showed that single HR-HPV infection accounted for 77.2% and multiple HR-HPV infections reached 22.8% in women HR-HPV infection combining with abnormal cervical cytology[16]. To date, there are three prophylactic vaccines targeting various HPV types, including the bivalent vaccine (HPV16/18), the quadrivalent vaccine (HPV16/18/6/11) and the nonavalent vaccine (HPV16/18/6/11/31/33/45/52/58)[24], but they do not cover the most frequent HR-HPV genotypes such as HR-HPV53, 51 in Shanxi province, China from our present study. Therefore, further work will be needed to develop the next generation vaccine which can target at more HR-HPV types.

Jing Li et al[25] reported the HR-HPV prevalence presented two age peaks in general population of China, one at age 15~24 years and the other in women aged 35~49 years, respectively. HR-HPV infection is a sexually transmitted disease, and the higher rate of infection in these women might have more frequent sexual intercourse, the cervical cells might be more vulnerable to damage and HR-HPV infection. In our study, the prevalence of HR-HPV was much higher in aged 35~45 years of women with abnormal cervical cytology. The results were inconsistent with those in the general women, suggested that women with aged 35~45 years should be regarded as high-risk groups and the focus of prevention among women with abnormal cervical cytology. Additionally, we observed that HPV16, 58 and 52 presented the highest prevalence in women aged 35~45 years, suggested that HPV16, 58 and 52 infection in this region should be given attention. Moreover, the nonavalent vaccine appears to be more valuable than quadrivalent vaccine in abnormal cervical cytology women.

Remarkably, it should be noted that HR-HPV infection rate decreased with increasing education level, the same result was demonstrated from study conducted in Yunnan Province, China[26]. The women with junior high school and below had limited knowledge about cervical cancer and its prevention. It will be necessary to improve education level of women to prevent HR-HPV infection and cervical lesions. Our findings provided evidence that women bathing less frequent were more vulnerable to HR-HPV infection. A possible reason was that in the surveyed area where lack of water resources. Bathing infrequently results in increasing viral or bacterial reproduction, which can be curbed by frequently cleaning the lower genital tract[27].

We found that the prevalence of HR-HPV significantly increased with increasing gravidity and parity, which might because of the hormonal changes of pregnancy. The female sex hormones, estrogen and progesterone, might influence susceptibility for HR-HPV infection. The changes in susceptibility to HR-HPV might also be the result of hormone-induced changes in the host adaptive immune response[28]. Our previous studies have shown that menopause was a protective factor of HR-HPV infection, which could be ascribed to the decreased estrogen level of postmenopausal women[29–31]. These results indicated that HPV DNA testing and effective HPV vaccines should be implemented in premenopausal women. Several studies reported that women with gynecological diseases were prone to HR-HPV infection due to unstable sexual hormone levels, poor function of immune system, lower resistance to HR-HPV and weak ability of viral clearance[32, 33].

Our finding indicated that HPV16 was the most frequently identified type in the women with ASC-US, LSIL and HSIL+, confirming that HPV16 was the main HR-HPV type associated with cervical lesions. Furthermore, we found that the infection rate of HPV16 and 33 increased significantly with the degree of cytological abnormality. Our analyses suggested HPV16 and HPV33 infection may be biomarker to predict cervical lesions progression in women with abnormal cervical cytology.

Conclusion

In conclusion, our finding indicated that the top five HR-HPV genotypes were HPV16, 58, 52, 53 and 51 in women with abnormal cervical cytology in Shanxi Province, China. High-risk individuals were aged 35~45 years, lower education level, less frequency of bathing, multiple gravidity, multiple parity, history of gynecological diseases and premenopausal women. Our results provided insight into HR-HPV infection related demographic-behavioral characteristics in women with abnormal cervical cytology. Based on these important leads, the prospective cohort studies are needed to provide powerful evidence.

Abbreviations

HR-HPV: High risk human papillomavirus; CIN: Cervical intraepithelial neoplasia; TCT: Thinprepcytologic test; NILM: Negative for intraepithelial lesion or malignancy; ASC-US: Atypical squamous cells of undetermined significance; ASC-H: Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; LSIL: Low-grade squamous intraepithelial lesion; HSIL: High-grade squamous intraepithelial lesion; LEEP: Loop Electrosurgical Excision Procedure; SCC: Squamous cervical carcinoma; AGC: Atypical glandular cell; OR: Odds ratio; CI: Confidence interval

Declarations

Acknowledgements

This subject was supported by the National Natural Science Foundation of China (No. 81872705, No. 81473060, No. 81703313) and the National Health and Family Planning Commission of the People's Republic of China (No. 201402010).

Author Contribution

All authors contributed significantly. Jintao Wang and Ling Ding designed the study; Min Hao, Zhilian Wang and Ming Wang were responsible for laboratory management; Xiaoxue Li and Wen Gao extracted and collected the data. Li Song and Yuanjing Lyu analysed the samples in the laboratory and wrote the first draft of the paper, all authors contributed to subsequent drafts. All authors read and approved the final version of the manuscript.

Founding

This study was founded by the National Natural Science Foundation of China (No. 81872705, No. 81473060, No. 81703313) and the National Health and Family Planning Commission of the People's Republic of China (No. 201402010).

Availability of data and materials

All data generated or analyzed during this study were included in this published article.

Ethical approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study has been approved by the Institutional Review Board of Shanxi Medical University (No: 2013–003). Informed consents have been signed by all the participants.

Consent for publication

All participants provided written and explicit consent for their anonymized data to be used in publications.

Competing Interests

The authors declared no competing interest.

References

1.Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, Vignat J, Ferlay J, Bray F, Plummer M, Franceschi S. Global burden of human papillomavirus and related diseases. Vaccine. 2012;30 Suppl 5:F12–23.

2.zur Hausen H. Papillomaviruses in the causation of human cancers - a brief historical account. Virology. 2009;384(2):260–265.

3.Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.

4.Tota JE, Chevarie-Davis M, Richardson LA, Devries M, Franco EL. Epidemiology and burden of HPV infection and related diseases: implications for prevention strategies. Prev Med. 2011;53 Suppl 1:S12–21.

5.Bernard HU, Burk RD, Chen Z, van Doorslaer K, zur Hausen H, de Villiers EM. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology. 2010;401(1):70–79.

6.Munoz N, Castellsague X, de Gonzalez AB, Gissmann L. Chapter 1: HPV in the etiology of human cancer. Vaccine. 2006;24 Suppl 3:S3/1–10.

7.Nicol AF, Andrade CV, Russomano FB, Rodrigues LL, Oliveira NS, Provance DW, Jr. HPV vaccines: a controversial issue? Braz J Med Biol Res. 2016;49(5):e5060.

8.de Sanjosé S, Diaz M, Castellsagué X, Clifford G, Bruni L, Muñoz N, Bosch FX. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. The Lancet Infectious Diseases. 2007;7(7):453–459.

9.Jalilvand S, Shoja Z, Nourijelyani K, Tohidi HR, Hamkar R. Meta-analysis of type-specific human papillomavirus prevalence in Iranian women with normal cytology, precancerous cervical lesions and invasive cervical cancer: Implications for screening and vaccination. J Med Virol. 2015;87(2):287–295.

10.Chelimo C, Wouldes TA, Cameron LD, Elwood JM. Risk factors for and prevention of human papillomaviruses (HPV), genital warts and cervical cancer. J Infect. 2013;66(3):207–217.

11.Lim AW, Landy R, Castanon A, Hollingworth A, Hamilton W, Dudding N, Sasieni P. Cytology in the diagnosis of cervical cancer in symptomatic young women: a retrospective review. Br J Gen Pract. 2016;66(653):e871-e879.

12.Kietpeerakool C, Cheewakriangkrai C, Suprasert P, Srisomboon J. Feasibility of the ‘see and treat’ approach in management of women with ‘atypical squamous cell, cannot exclude high-grade squamous intraepithelial lesion’ smears. J Obstet Gynaecol Res. 2009;35(3):507–513.

13.Aue-Aungkul A PS, Natprathan A, Srisomboon J, Kietpeerakool C. “See and Treat” Approach is Appropriate in Women with Highgrade Lesions on either Cervical Cytology or Colposcopy. Asian Pacific Journal of Cancer Prevention Apjcp. 2011;12(7):1723–1726.

14.Uijterwaal MH, Polman NJ, Van Kemenade FJ, Van Den Haselkamp S, Witte BI, Rijkaart D, Berkhof J, Snijders PJ, Meijer CJ. Five-Year Cervical (Pre)Cancer Risk of Women Screened by HPV and Cytology Testing. Cancer Prev Res (Phila). 2015;8(6):502–508.

15.Tsedenbal B, Yoshida T, Enkhbat B, Gotov U, Sharkhuu E, Saio M, Fukuda T. Human papillomavirus genotyping among women with cervical abnormalities in Ulaanbaatar, Mongolia. Int J Infect Dis. 2018;77:8–13.

16.Krashias G, Koptides D, Christodoulou C. HPV prevalence and type distribution in Cypriot women with cervical cytological abnormalities. BMC Infect Dis. 2017;17(1):346.

17.Guan P, Howell-Jones R, Li N, Bruni L, de Sanjose S, Franceschi S, Clifford GM. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. Int J Cancer. 2012;131(10):2349–2359.

18.Zhao X-L, Hu S-Y, Zhang Q, Dong L, Feng R-M, Han R, Zhao F-H. High-risk human papillomavirus genotype distribution and attribution to cervical cancer and precancerous lesions in a rural Chinese population. Journal of Gynecologic Oncology. 2017;28(4).

19.Zhong T-Y, Zhou J-C, Hu R, Fan X-N, Xie X-Y, Liu Z-X, Lin M, Chen Y-G, Hu X-M, Wang W-H, Li L, Xiao H-P. Prevalence of human papillomavirus infection among 71,435 women in Jiangxi Province, China. Journal of Infection and Public Health. 2017;10(6):783–788.

20.Zhao P, Liu S, Zhong Z, Hou J, Lin L, Weng R, Su L, Lei N, Hou T, Yang H. Prevalence and genotype distribution of human papillomavirus infection among women in northeastern Guangdong Province of China. BMC Infect Dis. 2018;18(1):204.

21.Baloch Z, Li Y, Yuan T, Feng Y, Liu Y, Tai W, Liu L, Wang B, Zhang AM, Wu X, Xia X. Epidemiologic characterization of human papillomavirus (HPV) infection in various regions of Yunnan Province of China. BMC Infect Dis. 2016;16:228.

22.X. Castellsague SdS TA. HPV and cervical cancer in the 2007 report. Vaccine. 2007;25 Suppl 3:C1-C26.

23.Vargas H, Sanchez JP, Guerrero ML, Ortiz LT, Rodriguez DM, Amaya J, Diaz LP, Gomez SL, Golijow C. Type-Specific Identification of Genital Human Papillomavirus Infection in Women with Cytological Abnormality. Acta Cytol. 2016;60(3):211–216.

24.Shi JF, Canfell K, Lew JB, Qiao YL. The burden of cervical cancer in China: synthesis of the evidence. Int J Cancer. 2012;130(3):641–652.

25.Li J, Huang R, Schmidt JE, Qiao Y-L. Epidemiological Features of Human Papillomavirus (HPV) Infection among Women Living in Mainland China. Asian Pacific Journal of Cancer Prevention. 2013;14(7):4015–4023.

26.Baloch Z, Yasmeen N, Li Y, Ma K, Wu X, Yang SH, Xia X. Prevalence and risk factors for human papillomavirus infection among Chinese ethnic women in southern of Yunnan, China. Braz J Infect Dis. 2017;21(3):325–332.

27.Zou L BYP, Li N, Dai M, Ma CP, Zhang Y Z, Liu X F, Feinleib M, Qiao Y L. Life-style and genital human papillomavirus in a cross-sectional survey in Shanxi Province, China. Asian Pacific Journal of Cancer Prevention Apjcp. 2011;12(3):781–786.

28.Kaushic C, Roth KL, Anipindi V, Xiu F. Increased prevalence of sexually transmitted viral infections in women: the role of female sex hormones in regulating susceptibility and immune responses. J Reprod Immunol. 2011;88(2):204–209.

29.Wang J T GES, Cheng Y Y, Yan J W, Ding L. Analysis on synergistic action between estrogen, progesterone and human papillomaviruses in cervical cancer. Zhonghua Liu Xing Bing Xue Za Zhi. 2005;26(5):370–373.

30.Wang J T GES, Ding L, Cheng Y Y, Yan J W. Association between endogenous hormones, hormone receptors and cervical cancer. Chinese journal of oncology. 2006;28(7):494–497.

31.Wang J T DL, Jiang S W, Hao J X, Zhao W M, Zhou Q, Yang Z K, Zhang L. Folate Deficiency and Aberrant Expression of DNA Methyltransferase 1 were Associated with Cervical Cancerization. Curr Pharm Des. 2014;20(11):1639–1646.

32.Mongelos P, Mendoza LP, Rodriguez-Riveros I, Castro A, Gimenez G, Araujo P, Paez M, Castro W, Basiletti J, Gonzalez J, Echague G, Diaz V, Laspina F, Ever S, Marecos R, Deluca G, Picconi MA. Distribution of human papillomavirus (HPV) genotypes and bacterial vaginosis presence in cervical samples from Paraguayan indigenous. Int J Infect Dis. 2015;39:44–49.

33.McInerney KA, Hatch EE, Wesselink AK, Mikkelsen EM, Rothman KJ, Perkins RB, Wise LA. The Effect of Vaccination Against Human Papillomavirus on Fecundability. Paediatr Perinat Epidemiol. 2017;31(6):531–536.

Tables

Table 1 Demographic characteristics in the 2300 participants

Characteristics	Frequency (n)	Percent (%)
Age(years)		
<35	183	8.0
35~	497	21.6
45~	867	37.7
55~	753	32.7
Education levels		
Junior high school and below	1462	63.6
Senior high school and above	838	36.4
Marital Status		
Married/cohabitant	2204	95.8
Divorced/separated/widowed	96	4.2
Occupation		
Farmer/housewife	1525	66.3
Others	775	33.7
Average yearly income(￥)		
<3000	525	22.8
3000~	789	34.3
7000~	563	24.5
≥10000	423	18.4

Table 2 Prevalence of HR-HPV single/multiple infection in women with abnormal cervical cytology(N=2300)

Genotypes	HR-HPV infection		χ^2	P
	Single (n/%)[a]	Multiple (n/%)[a]		
HR-HPV	517(22.5)	219(9.5)	2233.010	<0.001
HPV16	202(8.8)	108(4.7)	6.621	0.010
HPV58	69(3.0)	64(2.8)	26.995	<0.001
HPV52	44(1.9)	69(3.0)	62.598	<0.001
HPV53	28(1.2)	30(1.3)	14.538	<0.001
HPV51	25(1.1)	29(1.3)	15.990	<0.001
HPV33	32(1.4)	17(0.7)	0.613	0.434
HPV31	26(1.1)	19(0.8)	3.564	0.059
HPV39	23(1.0)	20(0.9)	6.135	0.013
HPV56	10(0.4)	34(1.5)	50.553	<0.001
HPV18	15(0.7)	21(0.9)	14.790	<0.001
HPV68	15(0.7)	23(1.0)	18.151	<0.001
HPV35	7(0.3)	9(0.4)	5.493	0.026
HPV66	10(0.4)	32(1.4)	45.949	<0.001
HPV59	9(0.4)	11(0.5)	6.268	0.012
HPV45	2(0.09)	1(0.0)	0.018	1.000

Note: [a] number (%) of women who with HR-HPV single/multiple infection in abnormal cervical cytology women (N=2300).

Table 3 Association between demographic-behavioral characteristics and HR-HPV infection in women with abnormal cervical cytology

Variables	n	HR-HPV infection rate (%)	$wald\chi^2$	p	OR (95%CI)
Age(years)					
<35	183	65(35.5)			1.000
35~	497	230(46.3)	6.257	0.012	1.564(1.102-2.220)
45~	867	261(30.1)	2.064	0.151	0.782(0.559-1.094)
55~	753	180(23.9)	10.123	0.001	0.570(0.403-0.806)
Education levels					
Junior high school and below	1462	492(33.7)			1.000
Senior high school and above	838	244(29.1)	5.028	0.025	0.810(0.674-0.974)
Occupation					
Farmer/housewife	1525	486(31.9)			1.000
Others	775	250(32.3)	0.036	0.850	1.018(0.846-1.225)
Marital Status					
Married/cohabitant	2204	699(31.7)			1.000
Divorced/separated/ widowed	96	37(38.5)	1.957	0.162	1.350(0.887-2.056)
Average yearly income (￥)					
<3000	525	182(34.7)			1.000
3000~	789	251(31.8)	1.162	0.281	0.879(0.696-1.111)
7000~	563	175(31.1)	1.581	0.209	0.850(0.660-1.095)
≥10000	423	128(30.3)	2.056	0.151	0.818(0.621-1.076)
Frequency of bathing					
>1/week	1570	421(26.8)			1.000
1/month~1/week	135	58(43.0)	52.794	<0.001	2.075(1.704-2.527)
<1/month	595	257(43.2)	15.515	<0.001	2.056(1.436-2.942)
Gravidity					
<2	675	197(29.2)			1.000
2~	1390	449(32.3)	2.052	0.152	1.158(0.947-1.415)
>3	235	90(38.3)	6.660	0.010	1.506(1.104-2.055)
Parity					
<2	602	171(28.4)			1.000
2~	1059	336(31.7)	1.996	0.158	1.171(0.941-1.459)
≥3	639	229(35.8)	7.812	0.005	1.408(1.108-1.789)
Menopause					
No	1124	472(42.0)			1.000
Yes	1176	264(22.4)	98.422	<0.001	0.400(0.334-0.479)
Condom use					
No	2178	703(32.3)			1.000
Yes	122	33(27.0)	1.445	0.229	0.778(0.517-1.172)
History of gynecological diseases					
No	2021	582(28.8)			1.000
Yes	279	154(55.2)	73.386	<0.001	3.046(2.361-3.930)

Table 4 Distribution of HR-HPV genotypes in various abnormal cervical cytology groups

Genotypes	Abnormal cervical cytology			χ^2	P	χ^2_{trend}	P
	ASC-US (n=1989)	LSIL (n=260)	HSIL+ (n=51)				
HR-HPV	613(30.8)	95(36.5)	28(54.9)	16.028	<0.001	13.952	<0.001
HPV16	261(13.1)	32(12.3)	17(33.3)	17.762	<0.001	6.236	0.013
HPV58	110(5.5)	21(8.1)	1(2.0)	3.709	0.149	0.225	0.345
HPV52	97(4.9)	15(5.8)	1(2.0)	1.044	0.597	0.032	0.910
HPV53	52(2.6)	5(1.9)	1(2.0)	0.272	0.882	0.453	0.539
HPV51	48(2.4)	6(2.3)	0(0.0)	0.506	0.820	0.669	0.514
HPV33	37(1.9)	8(3.1)	4(7.8)	8.016	0.014	8.090	0.008
HPV31	37(1.9)	6(2.3)	2(3.9)	1.952	0.363	1.090	0.369
HPV39	38(1.9)	4(1.5)	1(2.0)	0.266	0.929	0.079	0.859
HPV56	37(1.9)	5(1.9)	2(3.9)	1.665	0.389	0.563	0.464
HPV66	37(1.9)	4(1.5)	1(2.0)	0.268	0.854	0.051	0.860
HPV68	34(1.7)	4(1.5)	0(0.0)	0.116	1.000	0.593	0.563
HPV18	28(1.4)	7(2.7)	1(2.0)	2.980	0.173	1.772	0.223
HPV59	18(0.9)	1(0.4)	1(2.0)	1.800	0.380	0.006	1.000
HPV35	16(0.8)	0(0.0)	0(0.0)	1.592	0.472	2.254	0.149
HPV45	3(0.2)	0(0.0)	0(0.0)	1.136	1.000	0.420	1.000

HSIL+: high-grade squamous intraepithelial lesions (HSIL) and squamous cell carcinoma (SCC).

Figures

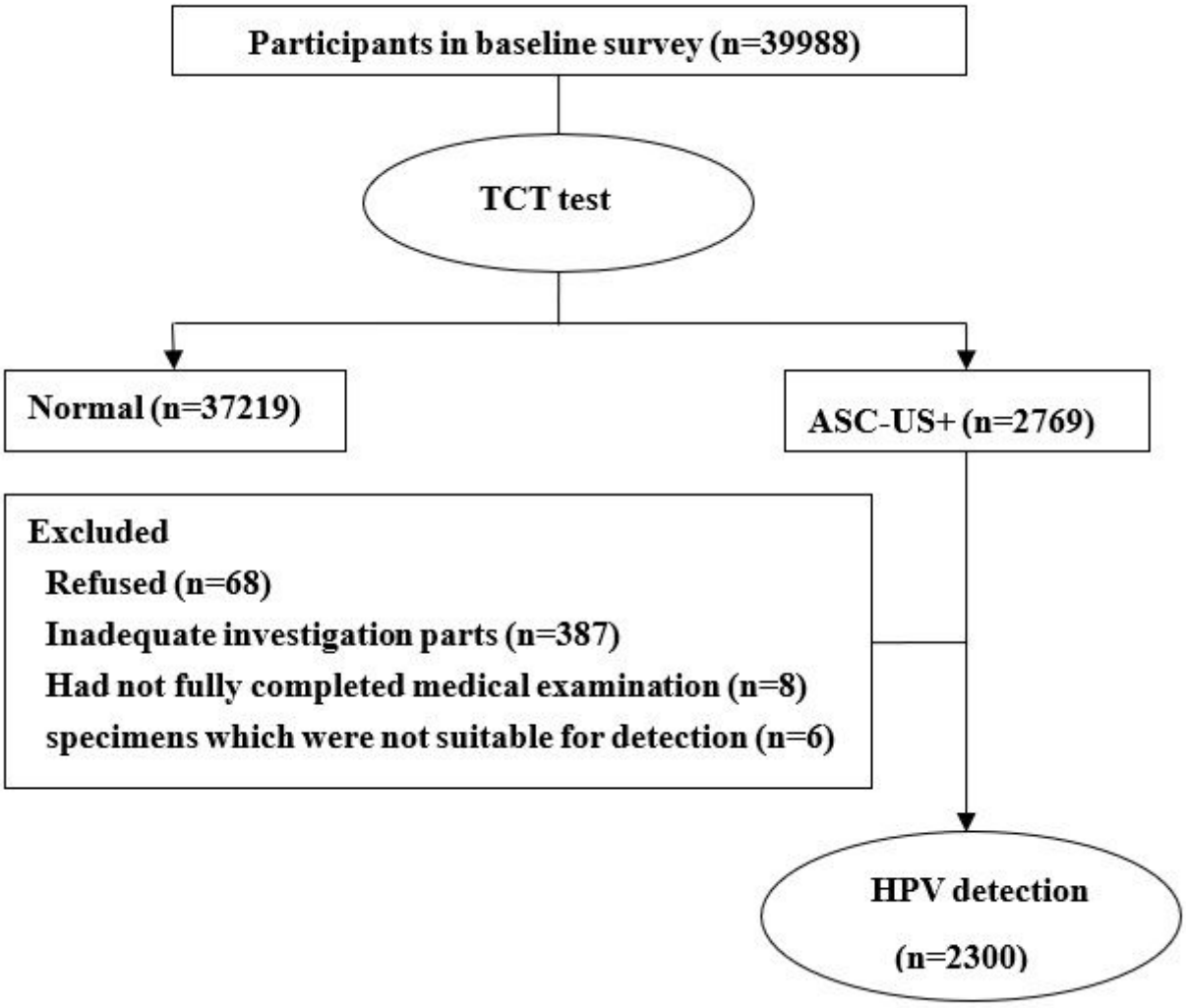

Figure 1

Flowchart of participants in the study. ASC-US+: included ASC-US, ASC-H, LSIL, HSIL, SCC and AGC.

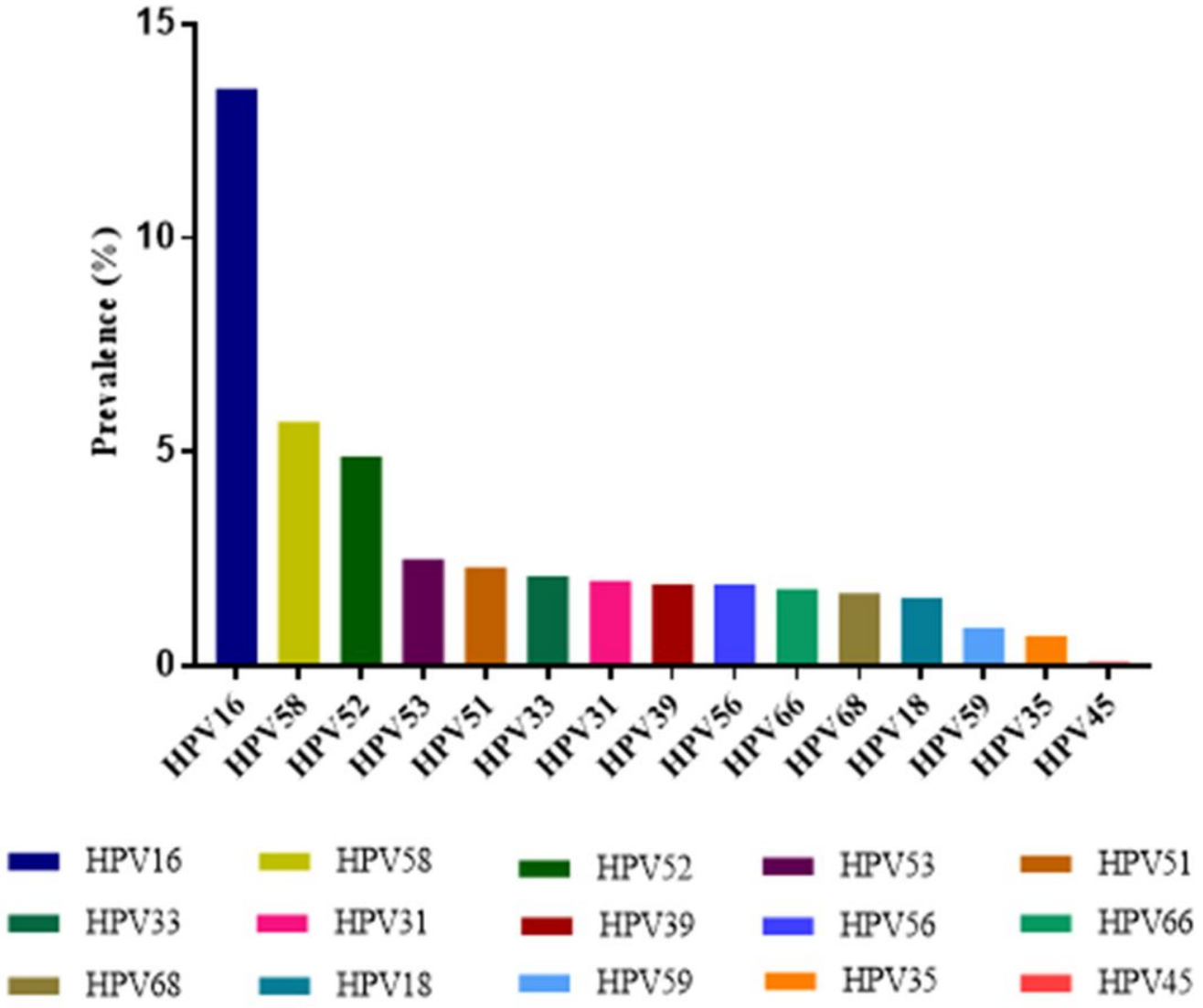

Figure 2

Prevalence of HR-HPV infection in women with abnormal cervical cytology

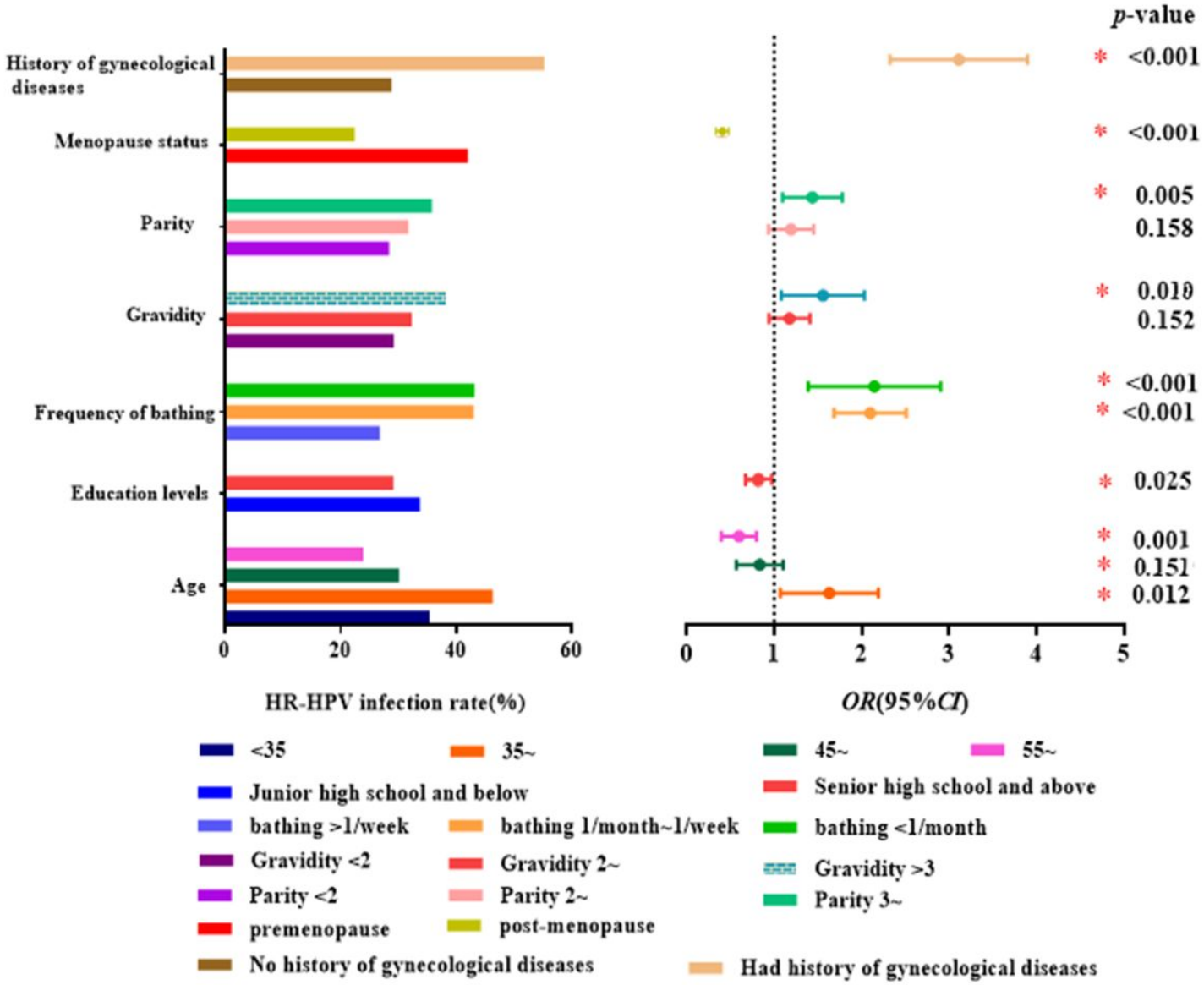

Figure 3

Association between demographic-behavioral characteristics and HR-HPV infection in women with abnormal cervical cytology. Women aged 35~45 years old, with lower education level, less frequency of bathing, multiple gravidity, multiple parity, history of gynecological diseases and premenopausal women have relatively higher risk for HR-HPV infection.