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Risk factors of human papillomavirus-related cervical lesions in postmenopausal women: a cross-sectional study

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Abstract

Background The incidence of cervical cancer is increasing in postmenopausal women globally, particularly in less-developed nations, including China. However, research on cervical cancer screening methods and related factors in China is limited. In the present study, we aimed to identify the independent risk factors associated with cervical lesions in postmenopausal women. Additionally, we compared the clinical characteristics and demographic information between women diagnosed with low-grade squamous intraepithelial lesions (LSIL) and those with high-grade squamous intraepithelial lesions+ (HSIL+).

Methods We conducted a cross-sectional study using qualitative human papillomavirus (HPV) DNA testing for cervical cancer screening among postmenopausal women across 23 districts and counties in Chengdu, China. Multivariate logistic analysis was employed to analyze demographic information, clinical history, and auxiliary examinations to identify independent risk factors for cervical lesions in postmenopausal women.

Results A total of 917 patients participated in the study and were categorized as: 624 patients with LSIL (68.0%) and 293 patients with HSIL+ (32.0%). Multivariate analysis revealed that factors showing significant differences between two categories included co-infection with types 16 and 18 (adjusted odds ratio [aOR] = 0.348, 95% confidence interval [CI] = 0.138–0.881, $p = 0.026$), mixed infections involving other types, HPV 16/18 (aOR = 0.514, 95% CI = 0.336–0.785, $p = 0.002$), transformation zone (TZ) 3 (aOR = 1.604, 95% CI = 1.018–2.528, $p = 0.041$), and colposcopy impressions indicating high-grade features and worse (aOR = 11.846, 95% CI = 2.132–65.807, $p = 0.005$).

Conclusions Co-infection with HPV types 16 and 18, as well as mixed infections involving HPV 16/18 and other types, TZ 3, and colposcopic features indicative of high-grade lesions and cancer, were identified as independent risk factors for HPV-related cervical lesions in postmenopausal women. Therefore, postmenopausal women with these high-risk factors need to undergo frequent cervical screening, and histopathological examination, if necessary.

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Keywords Postmenopausal, Cervical lesion, Risk factors

Background

Cervical cancer is one of the leading causes of death in women worldwide, with more than 85% of cases and mortalities occurring in less-developed nations. An estimated 110,000 new diagnoses of cervical cancer and 60,000 related fatalities are reported annually in China [1]. Notably, older adults are more likely to be diagnosed with late-stage cervical cancer and to succumb to the disease [2, 3]. China bears a considerable cervical cancer burden, largely due to the widespread prevalence of high-risk HPV infections and cervical intraepithelial neoplasia grade 2 (CIN2+) among older adults [4]. Additionally, a secondary peak in high-risk HPV infections and their persistence is observed within older populations in less-developed regions [5–7]. A recent study, involving women from Chengdu, indicated that the occurrence of HPV exhibited a bimodal U-shaped distribution by age, with the first peak occurring in females under 20 years and the second peak in those aged 60 to 69 years [8].

For cervical screening, TZ is the region that is thoroughly examined as, in most cases, it usually harbors a precancerous lesion. However, age-related alterations frequently cause the TZ to retract into the cervical canal, which poses challenges and hinders the acquisition of precise biopsies, thereby increasing the likelihood of overlooking conditions within the cervical canal. Consequently, there may be up to a twofold increase in the chance of missing CIN2 + lesion diagnosis in postmenopausal women [9]. The American Cancer Society (ACS) recommended that individuals aged 25 to 65 undergo HPV testing every five years, while individuals over the age of 65, who have received sufficient negative screening results, could discontinue all cervical cancer screenings [10]. In the elderly population, the benefits of regular cervical cancer screening gradually diminish with age. Additionally, screening can lead to increased discomfort in older individuals. Therefore, one of the most effective strategies for reducing cancer risk among elderly women may be ensuring a comprehensive screening history before discontinuing screening.

High-risk HPV infection is frequently recognized as a key factor contributing to cervical intraepithelial neoplasia and carcinoma [11]. Correlation analysis of the relevant factors and cervical lesions in postmenopausal women is vital. Therefore, this study aimed to identify the independent risk factors associated with cervical lesions in postmenopausal women. Our findings may offer valuable theoretical guidance for cervical screening practices in postmenopausal women, potentially reducing the risk of missed diagnoses.

Methods

This observational study was conducted in Chengdu, covering urban and rural areas, between January 2022 and December 2023. The cervical cancer screening initiative funded by the Chengdu Municipal Health Commission (2021(1)) was offered at no cost. Postmenopausal women were invited to participate in additional HPV DNA-based primary screening. Earlier, we observed that 29.6% of incidence rates of cervical cancer occur in elderly women [12]. Based on the sample size calculation formula ($N = Z_{0.05}^2 \times (P \times (1\text{-}P))/E^2$('N' is the sample size; '$Z_{0.05}$' is 1.96; 'E' is the error value; 'P' is the probability value)), at least 914 patients would be needed to carry out the study.

Cervical samples were obtained with a brush and then placed in an elution tube filled with a cell preservation solution. The samples were stored at 4 °C, and the detection was completed within 3 days. The extracted DNA was amplified by polymerase chain reaction (PCR) techniques (Hybribio Biotech Limited Corporation, Chaozhou, China) for the identification of HPV types 16 and 18, as well as pooled detection of 12 high-risk variants (HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Quality control measures included ensuring proper collection, storage, and transport of samples to prevent degradation. Moreover, HPV-positive samples to confirm the assay's functionality, and HPV-negative samples to rule out contamination were included. Laboratory equipment was maintained and calibrated according to the manufacturer's guidelines. We participated in external quality assurance programs to compare results with other laboratories and ensure accuracy. Validated software were employed for data analysis, to minimize human error. Upon receiving informed consent, participants underwent free HPV DNA testing as part of their primary screening for cervical cancer.

Women who tested positive for HPV type 16/18 or any other high-risk HPV type, along with abnormal cytological findings, were referred for colposcopy. Further histopathological evaluation was conducted if the colposcopy findings indicated abnormalities or raised suspicion. A cervical swab was obtained from visible lesions using a single-use broom-type brush, and additional punch biopsies were collected with biopsy forceps under the guidance of a qualified gynecologist. A total of 6260 biopsies were performed in the study (Fig. 1).

Postmenopausal women with histologically confirmed cervical intraepithelial neoplasia or cancer were included, and women with a history of cervical neoplasia, previous treatments for cervical conditions, concurrent immunodeficiency, hysterectomy or incomplete medical

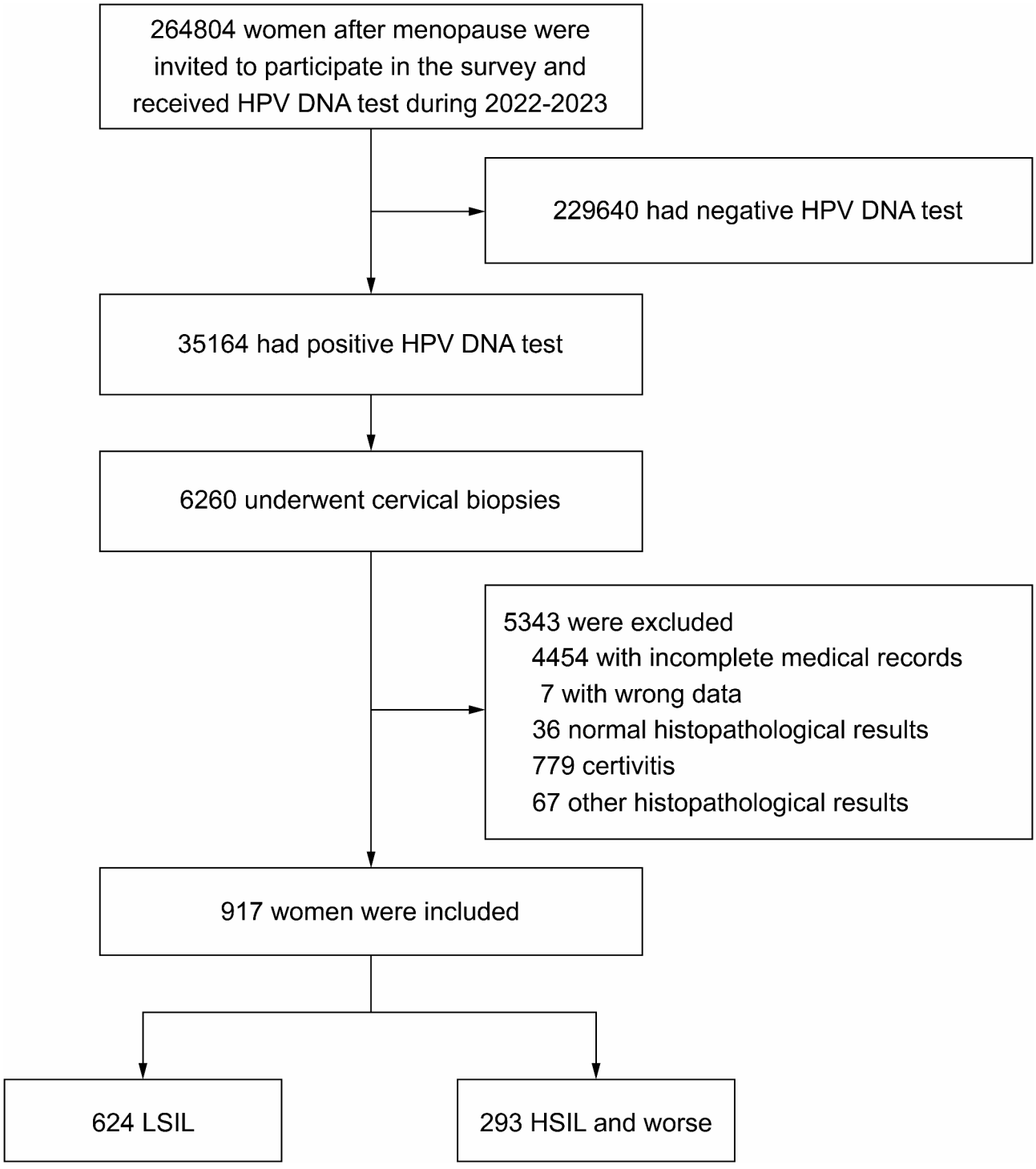

Fig. 1 Flow chart of women included in the study

records were excluded (Fig. 1). The research protocol was approved (IEC-C-007-V.02) by the Ethics Committee of Chengdu Women and Children's Central Hospital.

The electronic medical records of patients included in the study were reviewed retrospectively to gather data on demographics, clinical conditions, and laboratory findings. Histological classifications of cervical lesions were categorized according to the criteria of the WHO Classification of Tumors of Female Reproductive Organs [13]. The histological classification of the squamous intraepithelial lesion included two categories: the LSIL

(commonly referred to as CIN 1) and the HSIL (known as CIN 2 and CIN 3) [14].

All statistical analyses were performed using SPSS software (version 27.0.1; Chicago, IL, USA). The data were analyzed using independent t-tests and presented as mean ± standard deviation when the variables conformed to a normal distribution. Categorical variables were compared using the chi-square test. Additionally, a logistic regression model was employed for multivariate analysis to assess the relationship between the independent variables and cervical lesions. In the final logistic regression model, we adjusted for age, education level, high-risk HPV infection status, transformation zone type, and colposcopy impression to account for potential confounding effects. All statistical tests were two-tailed, and a p value < 0.05 was considered statistically significant unless otherwise stated.

Results

A total of 264,804 postmenopausal women with HPV DNA screening samples collected during the study, were identified. Among them, 917 met the eligibility criteria and were included in the final analysis, comprising 624 patients with LSIL (68.0%) and 293 patients with HSIL+ (32.0%) (Fig. 1). No significant differences were observed in the median age, gravidity, parity, abnormal leukorrhea, or family history of cancer between the patients with LSIL and those with HSIL+. Notably, a greater percentage of women with HSIL+ (2.4%) had lower educational levels than those with LSIL (1.4%), including no formal or primary education ($p = 0.021$). In addition, bleeding after intercourse occurred more frequently in patients with HSIL+ (5.5%) than in those with LSIL (1.9%) ($p = 0.004$). Regarding cervical screening history, a significantly higher proportion of patients with LSIL (20.2%) was noted than those with HSIL+ (14.7%) ($p = 0.045$) (Table 1).

The findings on leukorrhea in the HSIL group compared with the HSIL + group had no significant difference ($p = 0.184$). Most patients (56.8%) exhibited single high-risk genotypes other than 16/18, 20.2% had only type 16, and 16.9% presented a mixture of other types alongside HPV 16/18. Additionally, 5.3% of patients were infected solely with type 18, and co-infection with types 16 and 18 was observed in 0.8% of cases. Patients classified as HSIL + exhibited a notably higher prevalence of single type 16 infections, co-infections of types 16 and 18, and mixed infections with other types of HPV 16/18 than those with LSIL ($p < 0.001$). TZ2 and TZ3 were more frequently observed in women diagnosed

Table 1 Basic characteristics of women who were included

Characteristics	Histopathological results (*n*(%))		*p*
	LSIL (*n* = 624)	HSIL+ (*n* = 293)	
Median age (years)	56.04 ± 3.77	56.59 ± 3.72	0.40
Gravidity			0.811
≤1	188 (30.1%)	86 (29.4%)	
≥2	436 (69.9%)	207 (70.6%)	
Parity			0.788
≤1	444 (71.2%)	211 (72.0%)	
≥2	180 (28.8%)	82 (28.0%)	
Education level			**0.021**
No formal	9 (1.4%)	7 (2.4%)	
Primary	196 (31.4%)	106 (36.2%)	
Secondary	386 (61.9%)	171 (58.3%)	
Tertiary	33 (5.3%)	7 (2.4%)	
Unknown	0 (0.0%)	2 (0.7%)	
Clinical symptoms			
Bleeding after intercourse			**0.004**
Yes	12 (1.9%)	16 (5.5%)	
No	612 (98.1%)	277 (94.5%)	
Abnormal leucorrhea			0.689
Yes	36 (5.8%)	15 (5.1%)	
No	588 (94.2%)	278 (94.9%)	
History of cervical screening			**0.045**
Yes	126 (20.2%)	43 (14.7%)	
No	498 (79.8%)	250 (85.3%)	
Family history of cancer			0.067
Yes	2 (0.3%)	4 (1.4%)	
No	622 (99.7%)	289 (98.6%)	

Table 2 Results of vaginal microecology, high-risk HPV types, transformation zone type, and colposcopy findings

	Histopathological results (*n*(%))		*p*
	LSIL (*n* = 624)	HSIL+ (*n* = 293)	
Routine examination of leucorrhea			0.184
Cleanliness of grade I-II	482 (77.2%)	215 (73.4%)	
Cleanliness of grade III-IV	142 (22.8%)	77 (26.3%)	
Trichomonas vaginitis	0 (0.0%)	1 (0.3%)	
High-risk HPV infection status			**< 0.001**
Single 16	101 (16.2%)	84 (28.7%)	
Single 18	42 (6.7%)	7 (2.4%)	
16 and 18	4 (0.6%)	3 (1.0%)	
Single other high-risk genotypes	381 (61.1%)	140 (47.8%)	
Mixture of other types and HPV 16/18	96 (15.4%)	59 (20.1%)	
Transformation zone type			**0.006**
TZ1	163 (26.1%)	50 (17.1%)	
TZ2	167 (26.8%)	97 (33.1%)	
TZ3	294 (47.1%)	146 (49.8%)	
Colposcopy impression			**< 0.001**
Normal	5 (0.8%)	2 (0.7%)	
Low-grade features	538 (86.2%)	128 (43.7%)	
High-grade and cancer features	30 (4.8%)	144 (49.1%)	
Unsatisfactory	21 (3.4%)	11 (3.8%)	
Other	30 (4.8%)	8 (2.7%)	

Table 3 Multivariable logistic regression analyses of risk factors of postmenopausal patients with cervical lesions

Variable	aOR	95% CI	*p*
Age	1.041	0.994–1.089	0.089
Education level			
Secondary	0.902	0.630–1.291	0.574
Tertiary	0.515	0.190–1.396	0.192
No formal	0.935	0.265–3.295	0.916
Bleeding after intercourse	2.092	0.798–5.486	0.133
History of cervical screening	0.873	0.558–1.368	0.555
High-risk HPV infection status			
Single 18	2.134	0.441–0.326	0.346
16 and 18	0.348	0.138–0.881	**0.026**
Other high-risk genotypes	0.748	0.440–1.272	0.284
Mixture of other types and HPV 16 and/or 18	0.514	0.336–0.785	**0.002**
Transformation zone type			
TZ2	1.558	0.954–2.545	0.076
TZ3	1.604	1.018–2.528	**0.041**
Colposcopy impression			
Low-grade features	0.674	0.125–3.625	0.646
High-grade and worse	11.846	2.132–5.807	**0.005**
Unsatisfactory	0.605	0.095–3.853	0.595
Other	1.141	0.182–7.132	0.888

with HSIL+ ($p = 0.006$). Following the guidelines of the American Society for Colposcopy and Cervical Pathology [14], colposcopic evaluations were categorized into benign, low-grade, high-grade, and cancerous features. The colposcopic findings for patients with HSIL + indicated a greater prevalence of unsatisfactory outcomes, high-grade characteristics, and cancerous features, compared with patients with LSIL, who exhibited low-grade characteristics ($p < 0.001$) (Table 2).

Table 3 presents the multivariate logistic regression models to identify factors significantly linked with cervical lesions in postmenopausal women. After accounting for the influence of covariates, the multivariate analysis revealed that notable factors included co-infection with HPV types 16 and 18 (odds ratio [OR] = 0.348,

95% confidence interval [CI] = 0.138–0.881, $p = 0.026$), mixed infection involving other types along with HPV 16/18 (OR = 0.514, 95% CI = 0.336–0.785, $p = 0.002$), TZ3 (OR = 1.604, 95% CI = 1.018–2.528, $p = 0.041$), and the presence of high-grade features as well as cancer indicated by colposcopy impression (OR = 11.846, 95% CI = 2.132–65.807, $p = 0.005$).

Discussion

This study examined the demographics, clinical histories, and additional examinations to identify independent risk factors associated with cervical lesions in postmenopausal women. These findings indicate that co-infection with HPV types 16 and 18, as well as mixed infections that include other types alongside HPV 16/18 and TZ3, and colposcopic findings of high-grade lesions and cancerous features are the most prominent risk factors.

The proportion of CIN3 lesions unrelated to genotypes detected by primary screening tests increases with age, implying that age probably modifies the risk of CIN3 and the possibility of cancer associated with HPV types [15]. In the future, we intend to perform stratified analysis and analyze the disease characteristics of different age groups.

The increase in high-risk HPV infections among postmenopausal women may be attributed to factors such as reduced levels of female sex hormones or a decline in immunity. Research suggests that HPV DNA testing serves as a primary screening tool for this population, exhibiting greater sensitivity than other first-line screening methods [16]. However, HPV16 has been implicated in progressive carcinogenic pathways, whereas HPV18 often complicates the identification of precancerous lesions. In patients diagnosed with cervical cancer in China, HPV types 16 and 18 are the most frequently identified strains, found in up to 69.1% of cases [17, 18]. Co-infection with HPV 16 and 18 may serve as one of the independent risk factors, aligning with earlier research findings. Additionally, HPV52 and HPV58 are commonly associated with cervical intraepithelial neoplasia [19]. Similarly, our findings indicated that the detection rate of isolated HPV18 in precancerous lesions and cancer was considerably lower than that in LSIL. Although our results suggest that mixed infections involving HPV types 16 and 18 are more common in HSIL+, previous research has demonstrated no significant relationship between the type of HPV infection and the severity of cervical cancer [20]. Owing to variations in HPV test kits, age, and geographical factors of the population studied, conducting a comprehensive analysis and comparison across different studies was challenging.

Menopausal women show a greater proportion of physical cervical changes (such as TZ 3, incomplete visibility of the squamocolumnar junction, and the location of endocervical lesions), that confound diagnosis and complicate the detection of cervical premalignant lesions. The proportion of TZ3 increases steadily with age, surpassing 55% in women over 50 years old. Furthermore, colposcopic diagnostic accuracy revealed that the specificity of HSIL + for TZ3 was greater than for TZ1 or TZ2 [21]. These findings support our research and suggest that older women may have an increased likelihood of undergoing undiagnosed cervical cancer screening. This age-related phenomenon may be influenced by the gradual displacement of the squamocolumnar junction into the cervical canal, which can be affected by factors such as hormonal changes, contraceptive use, and obstetric history. Our results align with previous findings, which have demonstrated that among patients with TZ3, evidence of high-grade lesions and invasive carcinoma was also observed in women with normal or low-grade absolute cytology [22]. Similarly, findings from prior research indicated that predictors of high lesions occurred at a reduced rate in older women who had severe cervical lesions [23].

In the clinical management of postmenopausal women with primary screening abnormalities who are referred for colposcopy, it is essential to balance the risks of potential overtreatment with underdiagnosis. This study demonstrated that a high-grade assessment during colposcopy is an independent risk factor for cervical lesions, highlighting its importance in cervical cancer screening. The diagnostic accuracy of colposcopy is inherently influenced by colposcopists. Variations in training, experience, and adherence to standardized protocols may lead to discrepancies in lesion classification. For instance, retrospective research reported that in terms of women evaluated by various colposcopists regarding their ability to identify HSIL+, the accuracy and sensitivity levels were notably superior among senior colposcopists compared to their junior counterparts [24]. However, undergoing colposcopy may lead to adverse psychological effects and strong emotional reactions related to referrals and attendance at colposcopy appointments [25, 26]. Particularly in postmenopausal women, issues such as vaginal atrophy and dryness can increase the stress associated with colposcopy. The role of healthcare professionals to thoroughly explain the diagnosis and consider patients' preferences regarding different aspects of their consultations, can lead to a significant reduction in anxiety levels. The sensitivity of detecting precancers during colposcopy, and the reassurance provided for a negative outcome, require careful study and improvement, partly due to a shortage of specialists in this area. Recommendations addressing these independent risk factors may play a vital role in minimizing overtreatment, while concurrently decreasing the risk of underdiagnosis. Before enhanced screening techniques become widely available, it is crucial to establish clear consensus guidelines for

the optimal screening and follow-up of postmenopausal women.

This study addresses a frequently overlooked topic—independent risk factor associated with HPV-related cervical lesions in postmenopausal women. We report various aspects related to women, adjusted for factors such as HPV infection status, TZ, and colposcopic assessment that influence cervical lesions. While this retrospective observational study design has its inherent limitations, we acknowledge that our research also presents several shortcomings. Including only women in screening programs may lead to selection bias. Moreover, those who participated in screening may have different health-seeking behaviors, socioeconomic conditions, or access to healthcare services compared to non-participants, potentially restricting the applicability of our findings to larger populations. Additionally, this study did not explore cervical cytology or the correlation between cervical lesions and cytological findings. Furthermore, the impact of geographic regions on disease prevalence is yet to be thoroughly examined.

Conclusions

This study identified multiple risk factors associated with cervical lesions in postmenopausal women, including co-infections with HPV types 16 and 18, mixed infections that involve HPV types 16/18 along with other variants, TZ3, and high-grade or more severe lesions detected through colposcopy. Postmenopausal women exhibiting these high-risk factors should be incorporated into the routine screening schedule, and the screening interval should be reduced. This improvement could potentially reduce the chances of missed diagnoses of cervical epithelial abnormalities, such as intraepithelial neoplasia and even invasive cancer. Future studies should focus on individuals with different cytological abnormalities, particularly those classified as atypical squamous cells of undetermined significance and above, to reduce the likelihood of misdiagnosis or missed cases and support early intervention of cervical lesions.

Abbreviations

CIN2+	Cervical intraepithelial neoplasia grade 2 or worse
HPV	Human papillomavirus
HSIL+	High-grade squamous intraepithelial lesions or worse
LSIL	Low-grade squamous intraepithelial lesions
OR	Odds ratio
TZ	Transformation zone

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Author contributions

HZ conceptualized the study, performed formal analysis, and was responsible for writing the original draft and reviewing and editing the manuscript. QD contributed to the conceptualization and methodology. JP handled data curation and software development. JL and JC contributed to the investigation. ZL, TS, and WL provided resources for the study. XW, LY, and ML were involved in the visualization. XY and YL managed the project administration, supervision, and validation of the study, with XY also securing funding acquisition. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Chengdu Women and Children's Central Hospital (approval number: IEC-C-007-V.02). Informed consent was waived because this is a retrospective cohort study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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