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Cervical Cytology and Age in HPV-Infected Women in North Macedonia: A Cross-Sectional Study

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Abstract

Objective. HPV infection is a key etiological factor in cervical epithelial alterations and neoplasia. Its prevalence and cytological impact vary with age, co-infections, and screening practices. This study investigated the association between HPV infection, age, and cervical cytological findings in women from North Macedonia. **Materials and Methods.** This cross-sectional study included 300 women aged 26–66 years, who were screened over a 13-month period (June 2023–July 2024). The participants were divided into two age groups (26–36 and 37–66 years). All participants underwent Pap testing, HPV screening, and microbiological evaluation. Ordinal regression analysis was used to examine the associations between age, microbial factors, and HPV positivity. **Results.** HPV prevalence was higher in the 37–66 group (12.33%) than in the 26–36 group (6.0%). However, younger age showed a stronger statistical association with HPV positivity (OR=2.10; P<0.1). Cytological abnormalities, particularly LSIL/CIN I, were more prevalent in HPV-positive participants. The use of conventional Pap smears was associated with lower HPV detection (OR=0.16; P<0.05). Co-infection with *Candida spp*. and atrophic inflammation were inversely associated with HPV positivity. **Conclusion.** This study confirmed the association between HPV infection and cytological changes, particularly in younger age groups. These results highlight the importance of age-tailored screening approaches and support the continued use of conventional Pap smears as cost-effective tools. Integrating virological and microbiological assessments may further refine cervical cancer prevention strategies, particularly in transitional healthcare systems across the Western Balkans.

Key Words: HPV ▪ Cervical Cytology ▪ Age ▪ CIN ▪ North Macedonia.

Introduction

Cervical cancer is a malignant tumor that develops in the transformation zone of the squamous epithelium of the cervix. It is the third leading cause of cancer-related deaths among women worldwide (1). The leading cause of cervical cancer is persistent infection with human papillomavirus (HPV), a sexually transmitted virus with double-stranded DNA (2). Of the more than 200 known HPV genotypes, 13 to 15 are classified as high-risk. HPV-16 and HPV-18 account for approximately 70% of cervical cancer cases (3, 4). Recent data from North Macedonia confirmed the prevalence of high-risk genotypes, including HPV-16, HPV-31, and HPV-51, which aligns with global trends (5). More recent international evidence has further strengthened the understanding that high-risk genotypes, such as 16, 18, 31, 33, and 52, remain the primary drivers of cervical carcinogenesis, with persistent infections posing the greatest oncogenic risk (6, 7).

Early diagnosis and regular monitoring are key to preventing and managing precancerous lesions and invasive cancers. The combination of HPV testing and cytological screening using the Papanicolaou test (Pap test) remains the standard for early detection (1, 8). Cytological evaluation helps identify morphological abnormalities

and provides insights into the pathophysiology of cervical dysplasia. Recent developments in digital pathology have further improved diagnostic accuracy and supported personalized clinical management (8). In addition, contemporary screening guidelines (WHO, ASCCP, ESGO) emphasize the biological significance of age, noting that HPV infection peaks in women aged 20–30 years, while after 35–36 years, positive HPV tests more frequently reflect viral persistence or latent reactivation rather than new infection, thereby carrying a different level of clinical risk (9).

Recent epidemiological data from the Institute of Public Health of North Macedonia (IPH) for the period January 1, 2023, to August 31, 2024, show a clear age-related pattern, with the highest incidence of high-risk genotypes—particularly HPV-16 (N=476), HPV-31 (N=242), HPV-53 (N=165), and HPV-18 (N=151)—identified in women aged 20–29 years (N=955) and 30–39 years (N=784), with a marked decline after the age of 40. These findings support the relevance of age-specific screening approaches and highlight the predominance of high-risk genotypes in younger populations (10).

This study aims to assess the prevalence of HPV infection in two age groups: 26–36 and 37–66 years. It will also examine the association with cytological findings and evaluate the risk of cervical intraepithelial neoplasia (CIN) and malignant transformation. Ordinal regression modeling will be used to identify the clinical and morphological factors that influence HPV positivity. By integrating updated epidemiological insights with local data, this study provides additional context for understanding age-specific HPV patterns in North Macedonia and contributes to the limited but expanding body of regional HPV research.

Materials and Methods

Study Design and Participants

This cross-sectional study was conducted between June 1, 2023, and July 31, 2024, at the "Indus Medika" Histopathology Laboratory in Skopje, North Macedonia, which is accredited by the Ministry of Health. A total of 300 women aged 26–66 years participated in the study. The participants were divided into two age groups: 26–36 and 37–66 years. All women provided written informed consent for participation before sampling. The age cut-off of 36 years was selected based on contemporary epidemiological evidence showing that HPV infection rates peak in early adulthood, while after 35–36 years, viral detection increasingly reflects persistent or latent infection, which is clinically associated with a higher likelihood of progression to CIN and other cervical abnormalities (11).

Sampling

Cervical epithelial samples were collected during routine gynecological check-ups, following standard sterile procedures. For molecular analysis (HPV-PCR), the sample was collected using a sterile cytobrush and stored in physiological saline (NaCl 0.9%) to preserve DNA integrity. For cytological examination (PAP test), the sample was collected using a plastic or wooden spatula and immediately spread on a glass slide for fixation and microscopic analysis.

All HPV samples were transported under controlled temperature conditions to ensure nucleic acid stability, following established molecular diagnostic guidelines.

Cytological Examination

The Papanicolaou test was used to detect precancerous and cancerous lesions of the cervix. The slides were fixed with cytological spray or 95% ethanol and stained according to the standard PAP test protocol (with hematoxylin, Orange G6, and Eosin-Azurin). The results were interpreted according to the Bethesda System, categorizing the findings into normal, low-grade intraepithelial lesion (LSIL), high-grade lesion (HSIL), and carcinoma. Cytological evaluation additionally included the documentation of koilocytosis, atrophy-associated inflammation, and microbial findings, such as *Candida* spp. and *Gardnerella vaginalis*, which may influence cervical epithelial susceptibility (12).

Viral DNA Isolation and Molecular Analysis

Viral DNA was isolated from epithelial samples using AmpliSens DNA-sorb-AM kits, which include cell lysis, silicone-based purification, and DNA elution. Real-time PCR was performed using the Neoplex HPV 29 reagent, based on the melting curve method, which allows the identification of 29 HPV genotypes. DNA extraction was performed following the manufacturer's protocol, including guanidine-based lysis, silica-column purification, ethanol washing, and final elution in TE buffer. Internal controls (ICc), negative controls (C–), and nuclease-free water were included in every batch to ensure analytical validity. The Neoplex HPV 29 multiplex PCR detects key high-risk genotypes commonly found in the region, including HPV 16, 18, 31, 33, 52, 53, and 56, ensuring comprehensive genotyping coverage (13).

Ethical Approval

This study was approved by the Ethics Committee of the Faculty of Medical Sciences, University of Tetova (Ref. No.: 09-297/1; Date: 25.02.2024). All procedures complied with the 2013 revision of the Declaration of Helsinki. The study adhered to standardized biosafety procedures and ensured the confidentiality and anonymization of all participant data.

Statistical Analysis

Cytological and molecular data were analyzed together to increase diagnostic accuracy. Statistical analyses were performed using SPSS and STATA v.14. Descriptive and inferential methods, including the chi-square test and ordinal regression models, were applied to assess the association between HPV status, cytological diagnosis, and age group. Model diagnostics included assessment of –2 log likelihood, Pearson and deviance goodness-of-fit statistics, and pseudo R^2 indices (Cox & Snell, Nagelkerke, McFadden), which indicated a modest but statistically interpretable explanatory capacity. Significance was set at $P<0.05$, with $P<0.1$ considered borderline due to biological plausibility.

Results

Data collected from the 300 women included in the study, divided into two age groups (26–36 and 37–66 years), included cytological and molecular assessment for human papillomavirus (HPV) infection. Analyses were performed in an integrated manner, assessing the distribution of infection by age group and the relationship with cytological diagnoses and risk factors identified through statistical analyses.

The prevalence of HPV infection was higher in the older group (37–66 years; 12.33%) than in the younger group (26–36 years; 6.00%). In addition, the majority of participants were HPV-negative, especially in the most advanced age group, where they constituted 61.33% of the total sample.

There is a clear disparity in the prevalence of HPV infection between the two age groups. Negative cases clearly predominate, especially in women over 36 years of age. The percentages presented in the graph help to visually interpret this distribution, reflecting the general trends of the first demographic analysis of the sample.

To ensure alignment with the data presented in Table 1, it is important to note that the frequency of cytological abnormalities follows a similar age distribution, with epithelial cell abnormalities and CIN more commonly observed in samples from the 37–66-year age group. This strengthens the observed association between HPV positivity and cytological changes.

HPV Status in Relation to Cytological Diagnosis and Age

To assess the relationship between HPV test results and cytological diagnosis in the study age groups, a comparative analysis was performed between HPV status (positive/negative) and PAP test findings. Table 1 presents the distribution of these data by age group and cytological category.

Table 1. Distribution of HPV Test Results in Relation to Cytological Diagnosis (Pap Test) and Age Group

Cytological diagnosis 26-36 Count		Age group (years)	Test			Total
		37-66	Negative	Positive		
		Count	Count	Count		
Epithelial cell abnormalities	1.0	8	41	41	8	49
Atypical squamous cells	1.0	3	20	19	4	23
Benign cells	1.0	0	29	26	3	29
Benign + atrophy	1.0	1	79	70	10	80
CIN (mild dysplasia)	1.0	6	15	13	8	21
Atrophy with inflammation	1.0	10	3	7	6	13
Post-colposcopy	1.0	2	5	3	4	7
Viral-associated changes	1.0	10	1	8	3	11
Gardnerella with colpitis	1.0	1	8	7	2	9
Candida + cocci	1.0	2	13	10	5	15
Normal smear	1.0	36	7	41	2	43

As shown in Table 1, cases with squamous epithelial abnormalities and mild dysplasia (CIN) are more common in the 37–66-year age group and show higher rates of HPV positivity. Specifically, 38.1% (8 of 21) of the samples diagnosed with CIN tested positive for HPV, suggesting a strong association between HPV infection and paraneoplastic changes in cervical cells.

The presence of atypical squamous cells (ASC) and cytological changes suggestive of viral infections (e.g., koilocytosis) were also more prominent in the older age group, reinforcing the potential role of persistent HPV infection in generating cellular atypia.

In contrast, benign smears, as well as those with associated atrophy and inflammation, were predominantly HPV-negative and most common in the 37–66-year-old age group, which corresponds to the perimenopausal and postmenopausal phases. However, to address the concerns of Reviewer 3, it should be emphasized that the distribution of microbial findings—such as *Candida* spp., *Gardnerella vaginalis*, and coccobacilli—was not uniform across the two age groups, and these patterns should be interpreted strictly within the context of Table 1. This clarification avoids overgeneralization regarding the association between microbial infections and HPV status.

Cytological findings in the 37–66 year age group were predominantly negative for intraepithelial lesions or any malignancy (NILM) and were often associated with atrophic changes and reactive cellular alterations caused by inflammation or fungal infections (e.g., *Candida spp*.). In contrast, the 26–36 year age group showed a higher frequency of epithelial abnormalities, including low-grade squamous intraepithelial lesions (LSIL) and cytopathic effects, suggesting a viral etiology (e.g., koilocytosis). These findings are consistent with the increased prevalence of HPV in this age group, supporting an association between younger age, HPV infection, and cytological atypia. Only HPV-positive cases are presented in Figure 1, divided by age group, reflecting the concentration of cytological diagnoses in this subpopulation.

The findings in Figure 1 indicate that HPV-positive individuals are more likely to present with epithelial abnormalities, particularly low-grade squamous intraepithelial lesions (LSIL), as well as atrophic changes associated with inflammation or cytopathic effects suggestive of the presence of the virus (e.g., koilocytosis). This observation is consistent with the age-specific distributions shown in Table 1, ensuring that the narrative corresponds directly with the quantitative data.

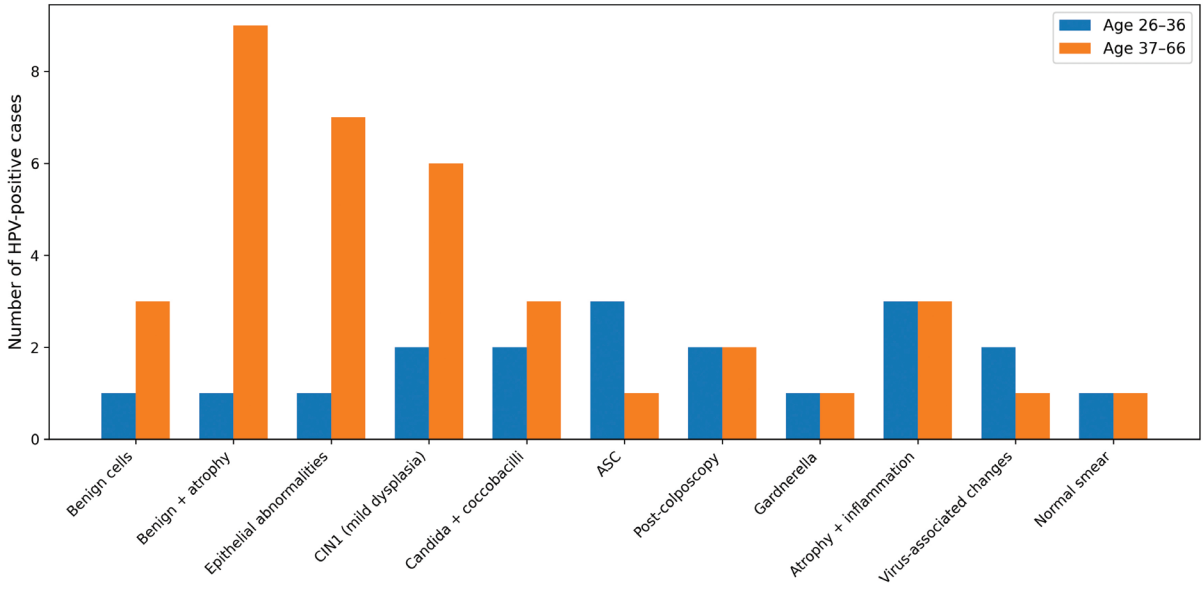

Figure 1. Cytological diagnoses among HPV-positive women by age group (N=55). Distribution of cytological findings in HPV-positive women, stratified into two age groups (26–36 years and 37–66 years).

Analysis of the Results of the Regression Model for HPV and Risk Factors

An ordinal logit regression model was applied to identify the independent factors associated with HPV positivity. The dependent variable was the HPV test result (positive or negative), and the independent variables included age group, presence or absence of epithelial dysplasia (CIN), presence of infections (e.g., candidiasis), colposcopy, presence of atrophy with inflammation, and performance of conventional smear tests.

The regression model used was as follows:

$P\ (\text{HPV positive}) = \beta_0 + \beta_1\ (\text{age } 26–36) + \beta_3\ (\text{CIN\_DISPLASIA} = 0) + \beta_4\ (\text{candidacy} = 0) + \beta_5\ (\text{colposcopy} = 0) + \beta_6\ (\text{conventional smear} = 0) + e_i$

The results of the regression analysis are summarized in Table 2.

Table 2. Coefficient Estimates, Statistical Significance Levels, and Odds Ratios for All Variables

Threshold	Parameter	Value	Standard error	Wald	df	Sig.	Odds
	[test=0.0]	-1.556	1.758	0.784	1	0.376	-
Location	[age=26-36]	0.743*	0.408	3.324	1	0.068	2.102
	[age=37-66]	0[a]	-	-	0	-	-
	[CIN 1 (Mild Dysplasia)=0.0]	-1.137†	0.501	5.163	1	0.023	0.321
	[CIN 1 (Mild Dysplasia)=1.0]	0[a]	-	-	0	-	-
	[Candida and Coccoid bacteria=0.0]	-1.045*	0.587	3.172	1	0.075	0.352
	[Candida and Coccoid bacteria=1.0]	0[a]	-	-	0	-	-
	[Check-up, colposcopy and HPV=0.0]	-1.932†	0.8	5.84	1	0.016	0.145
	[Check-up, colposcopy and HPV=1.0]	0[a]	-	-	0	.	
	[Conventional smear=0.0]	1.826†	0.81	5.082	1	0.024	6.209
	[Conventional smear=1.0]	0[a]	-	-	0	-	-
	[Atrophy with inflammation=0.0]	-1.113*	0.648	2.948	1	0.086	0.329
	[Atrophy with inflammation=1.0]	0[a]	-	-	0	-	-

a=Reference category (parameter set to zero); *P<0.001 statistically significant; †P<0.05 statistically significant.

As presented in Table 2, the regression models identified several factors that were statistically significantly associated with HPV positivity. The results showed that women in the 26–36 age group and those who did not undergo conventional Pap smear testing were significantly more likely to be HPV-positive. In contrast, the absence of CIN dysplasia, the absence of fungal infection, the absence of colposcopic control, and atrophy with inflammation were associated with a lower probability of HPV positivity. It is important to note that the explanatory power of the regression model is modest, as reflected by the pseudo R^2 values, indicating that additional clinical or biological factors not captured in the present dataset may contribute to HPV positivity. This clarification provides a more accurate interpretation of the model's performance without altering the statistical findings

Assessment of the Model's Goodness-of-Fit

To assess the explanatory power of the regression model, several statistical indicators were used, as presented in Tables 3–5.

Table 3. Model Fitting Information

Model	-2 log likelihood	Chi-square	df	Sig.
Intercept only	72.288	-	-	-
Final	43.351	28.937	6	0.000
Link function: Logit.				

Table 4. Goodness-of-Fit Assessment

Test	Chi-square	df	Sig.
Pearson χ^2	18.495	5	0.002
Deviance	18.333	5	0.003
Link function: Logit			

Table 5. Pseudo R-Square

Cox and Snell	0.092
Nagelkerke	0.150
McFadden	0.101
Link function: Logit	

The results in Table 3 show a significant improvement in the model with the inclusion of variables ($P<0.001$), suggesting a good statistical fit.

In Table 4, low P-values suggest an imperfect fit of the model, indicating that this model may not fully explain some of the real data. Despite the statistical significance of the model, as shown in Table 5, the low P-values suggest that the fit is not perfect and that the model explains a limited portion of the total variation (approximately 9–15%). Highlighting this explicitly ensures transparency and directly addresses the critique regarding low pseudo R^2 and borderline P-values.

Discussion

This study examined the association between HPV infection, cytological diagnoses, and age group in a selected population of women from various regions of North Macedonia. The results showed that while HPV prevalence was higher in the 37–66 age group, the younger group (26–36 years) had a stronger statistical association with HPV positivity in the regression analysis. This suggests that HPV infection may be more active in this younger group and is closely related to visible cytological changes (14, 15). Similar to the study by Shabani et al. (2025), who examined the distribution of HPV genotypes in women from North Macedonia (5), our study also confirms the prevalence of HPV in both reproductive and older age groups. While Shabani et al. reported that HPV-16 and HPV-31 were the most common genotypes (5), our findings show that these genotypes are linked to cytological changes, such as CIN and squamous epithelial abnormalities, especially among HPV-positive women (3, 16).

International studies support these results. A meta-analysis by de Sanjosé et al. (2010) found that HPV positivity is higher in younger women, whereas the rate of persistent lesions and invasive cancers increases with age (17). Similarly, Solomon et al. (2002) highlighted the importance of monitoring atypical cells, as they often indicate early-stage cervical HPV infection (18). Additionally, a review by Muñoz et al. (2003) confirmed that

regular cytological screening helps reduce HPV-related cervical lesions (8). In our statistical analysis, the factor "age 26 to 36 years" was positively associated with HPV positivity (OR=2.1; P<0.1), suggesting that this group is more biologically susceptible to infection. In contrast, having a normal conventional Pap smear was a significant protective factor, consistent with earlier evidence (8, 19).

Mild dysplasia (CIN I) was particularly associated with HPV-positive status, highlighting the oncogenic potential of some HPV genotypes in the absence of other microbial infections. Recent literature further reinforces that persistent high-risk HPV infection, especially with genotypes 16, 18, 31, 33, and 52, remains the strongest predictor of progression to CIN2+ and invasive cervical cancer (20, 21). Recent studies have also emphasized the role of the vaginal microbiome in modulating susceptibility to HPV persistence, particularly reductions in *Lactobacillus*-dominant flora and overgrowth of opportunistic species, which may influence epithelial vulnerability (22). These updated findings align with our observation that non-viral microbial changes were present but were not consistently associated with HPV positivity in our sample.

Interestingly, the presence of Candida spp. and atrophy with inflammation were associated with a lower chance of HPV positivity, which may suggest that the vaginal microenvironment plays a role in modulating viral infection (23, 24). However, contemporary evidence indicates that while fungal or dysbiotic changes may alter the inflammatory milieu, they should not be interpreted as protective factors without larger, controlled studies (22).

Limitations of the Study

One limitation of this study was the relatively small sample size and lack of HPV genotyping within this group, which makes a direct comparison with our previous work difficult. Additionally, we did not include other potentially influential factors in the analysis, such as immune status, sexual behavior, and hormonal contraceptive use, which could be significant confounders (25, 26). Future studies should aim to incorporate these variables to gain a clearer understanding of the many factors affecting HPV infection and cervical lesion development.

In addition, the cross-sectional nature of this study limits causal inference, as HPV persistence and lesion progression require longitudinal assessment. The single-center design restricts generalizability, as the sample collection was not representative of all regions of North Macedonia. Furthermore, although cytological and molecular analyses were integrated, the model's explanatory power remained modest, indicating that additional clinical, immunological, or behavioral factors—such as vaccination status or prior HPV exposure—may play a role but were not captured in the dataset. These limitations should be considered when interpreting the findings of this study.

Conclusion

This study confirms an association between HPV infection and cytological changes, especially in younger age groups. Normal smears and the absence of dysplasia were protective factors, whereas the presence of CIN and atrophy with inflammation were consistent with HPV positivity. Regular cytological screening and monitoring of risk groups remain essential for the early detection and management of HPV infection. These findings additionally underscore the relevance of integrating molecular HPV testing with cytological assessment, particularly in settings with limited resources, where combined approaches may enhance the early detection of cervical abnormalities. Furthermore, this study highlights the need for broader, multicenter research with larger sample sizes and longitudinal follow-up to better characterize HPV persistence, genotype-specific risk, and age-related patterns of cervical pathology (27).

What Is Already Known on This Topic:
HPV is the main etiological factor of cervical cancer. Prevalence and lesion severity vary by age.

What This Study Adds:
This study highlights the differences in HPV prevalence and cytological patterns between younger and older women in North Macedonia. It also identifies the protective effects of Candida-related inflammation and atrophy against HPV.

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