Journal of Obstetrics, Gynecology and Cancer Research | ISSN: 2476-5848

Histopathological Spectrum of Cervical Intraepithelial Neoplasia in HPV-Vaccinated vs. Unvaccinated Women: A Retrospective Study in Southwest of Iran

Azar Ahmadzadeh[1], Samaneh Bahrami[1], Najmieh Saadati[1,2], Elham Farhadi[3], Nooshin Safikhani[1*]

1. *Department of Obstetrics and Gynecology, School of Medicine, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
2. *Fertility Infertility and Perinatology Research Center, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
3. *Department of Biostatistics, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*

Article Info

10.24200/jogcr.10.8.635

Received: 2025/04/05
Accepted: 2025/05/26
Published Online: 10 Jul. 2025

Corresponding Information:
Nooshin Safikhani,
Department of Obstetrics and Gynecology, School of Medicine, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Email: nooshin.safikhani@gmail.com

ABSTRACT

Background & Objective: HPV is a well-established risk factor for cervical cancer. Vaccination against HPV, particularly targeting high-risk viral strains, significantly reduce the incidence of cervical cancer. This study was conducted with aim to investigate the histopathological spectrum of Cervical Intraepithelial Neoplasia (CIN) in HPV-vaccinated versus unvaccinated women in southwest of Iran.

Materials & Methods: This descriptive-analytical, cross-sectional study was conducted at Imam Khomeini Hospital in Ahvaz, Iran, between 2020 and 2023. The study population consisted of women diagnosed with CIN based on cytology and confirmed by colposcopy and biopsy. Data collected included demographic characteristics, sexual history, contraceptive methods, menstrual status, smoking habits, history of genital warts, presence of immunodeficiency, cervical cytology results, histopathological findings, and HPV vaccination status. Statistical analysis of data was performed using Chi-square test for categorical variables and independent samples t-test for quantitative variables. $P<0.05$ was considered statistically significant.

Results: The mean age of patients was 38.79±8.08 years. Of the 384 patients, 7.81% had received the HPV vaccine. A statistically significant association was observed between HPV vaccination and genital wart type, with unvaccinated women showing a higher prevalence of malignant genital warts compared to vaccinated women ($P=0.04$). A significant association was also found between vaccination status and colposcopy results ($P=0.049$). The distribution of histopathological diagnoses showed no significant difference between the two groups ($P=0.28$), despite that a higher proportion of vaccinated women presented with normal histopathology.

Conclusion: HPV vaccination was associated with a reduction in malignant cases and shifts in clinical outcomes. While this study didn't show significant differences in certain histopathological outcomes, the overall reduction in HPV-related conditions among vaccinated individuals reinforces the critical role of HPV vaccination in disease prevention.

Keywords: Vaccination, Uterine cervical dysplasia, Pathology, Human papillomavirus

Copyright © 2025, This is an original open-access article distributed under the terms of the Creative Commons Attribution-noncommercial 4.0 International License which permits copy and redistribution of the material just in noncommercial usages with proper citation.

1. Introduction

Cervical Intraepithelial Neoplasia (CIN) represents a precancerous condition characterized by the abnormal proliferation of cells on the surface of the cervix, with the potential to progress to invasive cervical cancer. Specifically, CIN denotes the potentially premalignant transformation of cervical cells **(1,2)**. CIN typically arises at the squamocolumnar junction of the cervix, a transitional zone between the squamous epithelium of vagina and columnar epithelium of endocervix. It can also occur on the vaginal walls and vulvar epithelium. CIN is graded on a scale of 1 to 3, with CIN 3 representing the most severe abnormality **(1,3)**.

Human Papillomavirus (HPV) infection is a necessary precursor for development of CIN, but not all individuals infected with HPV will develop cervical cancer. Many women with HPV infection never progress to CIN or cervical cancer **(4)**. Typically, HPV infection is resolved spontaneously. However, those

with persistent HPV infection lasting more than one or two years are at a higher risk of developing higher-grade CIN **(5,6)**. HPV vaccines prevent the most common high-risk HPV types and are most effective when administered prior to initial HPV exposure, which is why vaccination is recommended before the onset of sexual activity, ideally between the ages of 9 and 13 years **(7,8)**.

HPV infection is a well-established risk factor for certain malignancies, most notably cervical cancer. Vaccination against HPV, particularly targeting high-risk viral strains, has demonstrated the potential to significantly reduce the incidence of these malignancies, especially cervical cancer **(9)**. Therefore, the present study was conducted with aim to characterize and compare the histopathological features of CIN in women with a documented history of HPV vaccination versus those without vaccination to determine if HPV vaccination is associated with differences in histological severity, lesion type, or presence of specific HPV subtypes within CIN lesions.

2. Materials and Methods

This retrospective, descriptive-analytical, cross-sectional study was conducted at Imam Khomeini Hospital, affiliated with Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, between 2020 and 2023. The study population consisted of women who were referred to the clinic of Imam Khomeini hospital and diagnosed with CIN based on cytology and confirmed through colposcopy and biopsy. Patients were selected via convenience sampling. Eligible patients were categorized into two groups based on HPV vaccination status: those with a documented history of HPV vaccination and those without. Patients were excluded from the study if they met any of the following criteria: presence of severe or untreated psychiatric disorders, presence of severe neurological disorders or dementia, history of radiotherapy or total hysterectomy for CIN, incomplete medical records and pregnancy.

The sample size was calculated based on a previous study by Drolet et al., **(10)** with a Z-score of 1.96 for a 95% confidence interval, alleviate the incidence of CIN II and III in patients who were vaccinated (p) of 0.5, and a margin of error (d) of 0.05, the required sample size was determined to be 384 participants.

The study protocol was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethical code: IR.AJUMS.HGOLESTAN.REC.1403.117). Data were collected using a researcher-developed checklist including the following information: demographic characteristics (age, marital status, education level), sexual history (number of sexual partners, age at first sexual intercourse), contraceptive methods, menstrual status, tobacco and hookah smoking habits, history of genital warts, presence of immunodeficiency, cervical cytology results, and histopathological findings from colposcopic biopsies. Data were extracted from patient medical records.

Colposcopy-directed biopsy results were classified according to the following categories: normal, CIN 1, CIN 2, CIN 3, and cervical carcinoma. Cervical cytology results (Pap smear) were categorized as: Normal, ASC-US (Atypical Squamous Cells of Undetermined Significance), LSIL (Low-grade Squamous Intraepithelial Lesion), ASC-H (Atypical Squamous Cells - cannot exclude HSIL), HSIL (High-grade Squamous Intraepithelial Lesion). Histopathological assessment was performed by experienced pathologists who were blinded to the patients' vaccination status.

Data was analyzed using SPSS (version 27). Quantitative variables were presented as means and standard deviations and qualitative variables were reported as frequencies and percentages. The Shapiro-Wilk test assessed normality. Associations between categorical variables were analyzed using the Chi-square test or Fisher's exact test when appropriate. The independent samples t-test was used for comparison of quantitative variables between the two groups. $P<0.05$ was considered statistically significant. All analyses were performed using SPSS version 27.

3. Results

Out of 384 investigated patients, 30 (7.81%) had received the HPV vaccine. Among 30 individuals who received the HPV vaccine, 17 (56.7%) received the bivalent vaccine, 10 (33.3%) received the quadrivalent vaccine, and 3 (10%) received the 9-valent vaccine. Table 1 presents the relationship between HPV vaccination and demographic and reproductive variables. A statistically significant association was observed between HPV vaccination status and education level (P=0.046). Specifically, the group without HPV vaccination had lower education levels (illiterate, primary School) compared to the vaccinated group. There were no statistically significant associations between HPV vaccination status and marital status (P=0.36), number of sexual partners (P=0.15), gestational number (P=0.48), prevention method (P=0.27), or presence of genital warts in the husband (P=0.84). Additionally, no significant differences were found between the vaccinated and unvaccinated groups in the mean age (P=0.48) and mean sexual maturity onset age (P=0.43). None of the women reported smoking or having sexual partners other than their husbands.

Detailed distribution of HPV vaccination doses in the vaccinated group showed that 26.67% received one dose, 40% two doses and 33.33% three doses. The mean time from HPV vaccination to CIN diagnosis was 3.67±1.29 years. The study also found a statistically significant difference in the prevalence of malignant genital wards (20% in vaccinated vs. 39.27% in

Table 1. The relationship between HPV vaccination and demographic and reproductive variables

Variable		HPV Vaccination		P-value
		Yes n(%)	No n(%)	
Marital status	Married	28(93.33)	340(96.05)	0.36
	Divorce or dead husband	2(6.67)	14(3.95)	
Education	Illiterate	0	52(14.69)	0.046
	Primary school	5(16.67)	90(25.42)	
	Guidance school	6(20.0)	77(21.75)	
	High school	14(46.67)	101(28.53)	
	Academic	5(16.67)	34(9.60)	
Number of partners	0	2(6.67)	7(1.98)	0.15
	1	28(93.33)	347(98.02)	
Gestational number	0	5(16.67)	35(9.89)	0.48
	1-2	9(30.0)	123(34.75)	
	3 or more	16(53.33)	196(55.37)	
Contraceptive method	Natural	15(53.57)	130(42.48)	0.27
	Condom	10(35.71)	108(35.29)	
	Tablet	1(3.57)	45(14.71)	
	IUD	2(7.14)	11(3.59)	
	Ampulla	0	12(3.92)	
Genital warts in husband	Yes	7(25.0)	91(26.76)	0.84
	No	21(75.0)	249(73.24)	
Age, mean (SD)		39.8(8.92)	38.71(8.01)	0.48
Sexual maturity onset age, mean (SD)		20.17(3.54)	19.68(3.23)	0.43

unvaccinated group, P=0.04) and colposcopy results, especially CIN 1 (80.0% in vaccinated vs. 59.04% in unvaccinated group, P=0.049). The histopathology analysis compared the distribution of diagnoses between the HPV-vaccinated and unvaccinated groups, revealing that in the vaccinated group, 23.33% presented with ASCUS, 3.33% with HSIL, 20.0% with LSIL, and 53.33% with normal histopathology; however, in the unvaccinated group, 31.07% presented with ASCUS, 10.73% with HSIL, 22.03% with LSIL, and 36.16% with normal histopathology. Moreover, no significant differences were observed between the two groups in histopathology results (P=0.28) (Table 2).

Table 2. The relationship between HPV vaccination status and genital ward type, colposcopy results, and histopathology findings

Variable		HPV Vaccination		P-value
		Yes	No	
Genital ward type	Malignant	6(20.00)	139(39.27)	0.04
	Benign	24(80.00)	215(60.73)	
Colposcopy result	CIN 1	24(80.0)	209(59.04)	0.049
	CIN 2	5(16.67)	122(34.46)	
	CIN 3	0	19(5.37)	
	Cervical carcinoma	1(3.33)	4(1.13)	
Histopathology results	ASCUS	7(23.33)	110(31.07)	0.28
	HSIL	1(3.33)	38(10.73)	
	LSIL	6(20.0)	78(22.03)	
	Normal	16(53.33)	128(36.16)	

4. Discussion

The purpose of the present study was to investigate the histopathological spectrum of CIN in HPV-vaccinated versus unvaccinated women. The main findings revealed a statistically significant association between HPV vaccination and genital wart type, with unvaccinated women showing a higher prevalence of malignant genital warts compared to vaccinated women. Additionally, a significant association was observed between vaccination status and colposcopy results, particularly CIN 1. While a higher proportion of vaccinated women presented with normal histopathology, no statistically significant differences were observed between the two groups in the overall distribution of histopathological diagnoses.

Several studies demonstrated the protective effect of HPV vaccination, indicating that vaccinated women experience a significant reduction in high-grade CIN lesions and a decrease in cervical dysplasia incidence **(11,12)**. Moreover, Ikeda et al., (2021) **(13)** support these findings by observing a significant reduction in abnormal cytology and CIN among vaccinated women in Japan **(13)**. These insights also align with Lei et al., findings, which emphasized a dramatic reduction in invasive cervical cancer risk among vaccinated girls and women in Sweden **(14)**. Additionally, other researchers provided evidence that HPV vaccination can reduce the likelihood of CIN recurrence after local surgical interventions **(15,16)**.

Considering the expected benefits of vaccination, our study contrary to many previous studies did not show a significant reduction in≥CIN2 lesions among vaccinated women. However, in line with expected protective effects, we found fewer malignant cases in the vaccinated group. Nevertheless, our findings suggest that while vaccination may reduce the risk of malignant conditions, vaccinated women in the present study exhibited a significantly higher prevalence of benign genital warts (20%) and low-grade CIN1 lesions on colposcopy (80.0%) than unvaccinated women. Furthermore, while the distribution of histopathological diagnoses (including ASCUS, HSIL, LSIL, and normal) showed no significant difference between the two groups (P=0.28), specific distributions was observed in the vaccinated group, including 23.33% with ASCUS, 3.33% with HSIL, 20.0% with LSIL, and 53.33% with normal histopathology.

Compared to other studies, these differences may be because HPV vaccination in our study was not associated with a reduction in≥CIN2 rates. The American study also showed that, overall, vaccinated women have a lower chance of contracting any type of HPV **(17)**. This divergence may be due to several factors: our study used a retrospective design, while other studies used prospective designs or meta-analyses, the difference in methodology can lead to various biases in data collection and interpretation on the other hand, genetic differences, cultural factors, and access to healthcare in these two populations can influence the results. The patients in the present study may have received different type of vaccines or followed different vaccination schedules. These differences in vaccine type and vaccination schedule can affect the vaccine's effectiveness against various HPV types. It is important to note that the higher prevalence of benign genital warts and CIN1 colposcopy results observed in the vaccinated group does not necessarily mean complete vaccine failure. This finding could indicate partial protection against all oncogenic HPV types or possibly increased sensitivity to types not covered by the vaccine. There is also a possibility that women in this group were previously infected with HPV or, for example, did not regularly participate in cervical cancer screening programs. If women have a history of HPV infection, the vaccine may be less effective compared to those who have never been infected. Since our study relies on retrospective data, we cannot assess who was previously infected with HPV. Additionally, the increase in CIN1 and genital warts may indicate diagnostic bias, meaning that vaccinated women, feeling protected against cervical cancer, are more likely to undergo screening, leading to increased detection of mild abnormalities. Furthermore, from a public health perspective in Iran, HPV vaccination has been shown to be a cost-effective strategy for cervical cancer prevention **(18)**.

Several limitations should be considered when interpreting the findings of this study. First, retrospective design inherently limits the ability to establish causal relationships and is susceptible to data collection biases, including incomplete medical records. Second, the use of convenience sampling at a single institution may restrict the generalizability of the results to broader populations. The relatively small sample size, particularly within the vaccinated group, reduces the statistical power to detect subtle differences between the groups. Finally, despite controlling for some potential confounders, residual confounding factors due to unmeasured or unknown variables cannot be entirely ruled out.

5. Conclusion

HPV vaccination was associated with reduced malignant cases and shifts in clinical outcomes. While this study did not observe significant differences in certain histopathological outcomes, the overall reduction in HPV-related conditions among vaccinated individuals reinforces the critical role of HPV vaccination in disease prevention.

6. Declarations

Acknowledgments

The authors would like to express sincere gratitude to the Deputy of Research and Technology at Ahvaz

Jundishapur University of Medical Sciences for providing the necessary ethical approval for this study.

Ethical Considerations

The study protocol was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethical code: IR.AJUMS.HGOLESTAN.REC.1403.117).

Authors' Contributions

Azar Ahmadzadeh contributed to study design, patient recruitment, and data collection; Samaneh Bahrami participated in data acquisition and manuscript preparation; Najmieh Saadati assisted with study coordination, data interpretation, and manuscript editing; Elham Farhadi performed statistical analysis and contributed to data interpretation; and Nooshin Safikhani contributed to study design and data interpretation and critically revised the manuscript. All authors reviewed and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

Fund or Financial Support

Ahvaz Jundishapur University of Medical Sciences.

References

1. Mitra A, Tzafetas M, Lyons D, Fotopoulou C, Paraskevaidis E, Kyrgiou M. Cervical intraepithelial neoplasia: screening and management. Br J Hosp Med (Lond). 2016;77(8):C118-23. [DOI:10.12968/hmed.2016.77.8.c118]
2. Petry KU. Management options for cervical intraepithelial neoplasia. Best Pract Res Clin Obstet Gynaecol. 2011;25(5):641-51. [DOI:10.1016/j.bpobgyn.2011.04.007]
3. Loopik DL, Bentley HA, Eijgenraam MN, IntHout J, Bekkers RL, Bentley JR. The natural history of cervical intraepithelial neoplasia grades 1, 2, and 3: a systematic review and meta-analysis. J Low Genit Tract Dis. 2021;25(3):221-31. [DOI:10.1097/LGT.0000000000000604]
4. Insinga RP, Perez G, Wheeler CM, Koutsky LA, Garland SM, Leodolter S, et al. Incident cervical HPV infections in young women: transition probabilities for CIN and infection clearance. Cancer Epidemiol Biomarkers Prev. 2011;20(2):287-96. [DOI:10.1158/1055-9965.EPI-10-0791]
5. Loopik DL, Bentley HA, Eijgenraam MN, IntHout J, Bekkers RL, Bentley JR. The natural history of cervical intraepithelial neoplasia grades 1, 2, and 3: a systematic review and meta-analysis. J Low Genit Tract Dis. 2021;25(3):221-31. [DOI:10.1097/LGT.0000000000000604]
6. Guo HY, Guo YL, You K, Geng L. Twelve-month follow-up detection of high-risk human papillomavirus (HPV) DNA for 93 cases with cervical intraepithelial neoplasia grade 2 or 3 (CIN 2-3) after a loop electrosurgical excisional procedure (LEEP). Eur J Gynaec Oncol. 2011 32(2):164-7. [PMID]
7. Athanasiou A, Bowden S, Paraskevaidi M, Fotopoulou C, Martin-Hirsch P, Paraskevaidis E, et al. HPV vaccination and cancer prevention. Best Pract Res Clin Obstet Gynaecol. 2020;65:109-24. [DOI:10.1016/j.bpobgyn.2020.02.009]
8. Lowy DR. HPV vaccination to prevent cervical cancer and other HPV-associated disease: from basic science to effective interventions. J Clin Invest. 2016;126(1):5-11.
9. Lowy DR. HPV vaccination to prevent cervical cancer and other HPV-associated disease: from basic science to effective interventions. J Clin Invest. 2016;126(1):5-11.
10. Drolet M, Bénard É, Pérez N, Brisson M, Ali H, Boily MC, et al. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet. 2019 394(10197):497-509. [DOI:10.1016/S0140-6736(19)30298-3]
11. Shiravani Z, Nazari Z, Yazdani F, Najib FS, Jahromi MA, Momtahan M, et al. Evaluation of the therapeutic effect of quadrivalent human papillomavirus (HPV) vaccination on cervical intraepithelial neoplasia lesions. Indian J Surg Oncol. 2023;14(2):504-9. [DOI:10.1007/s13193-022-01657-w]

12. Racey CS, Albert A, Donken R, Smith L, Spinelli JJ, Pedersen H, et al. Cervical intraepithelial neoplasia rates in British Columbia women: A population-level data linkage evaluation of the school-based HPV immunization program. J Infect Dis. 2020;221(1):81-90. [DOI:10.1093/infdis/jiz422]
13. Ikeda S, Ueda Y, Hara M, Yagi A, Kitamura T, Kitamura Y, et al. Human papillomavirus vaccine to prevent cervical intraepithelial neoplasia in Japan: a nationwide case-control study. Cancer Sci. 2021;112(2):839-46. [DOI:10.1111/cas.14682]
14. Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, et al. HPV vaccination and the risk of invasive cervical cancer. N Engl J Med. 2020;383(14):1340-8. [DOI:10.1056/NEJMoa1917338]
15. Kechagias KS, Kalliala I, Bowden SJ, Athanasiou A, Paraskevaidi M, Paraskevaidis E, et al. Role of human papillomavirus (HPV) vaccination on HPV infection and recurrence of HPV related disease after local surgical treatment: systematic review and meta-analysis. BMJ. 2022;378:e070135. [DOI:10.1136/bmj-2022-070135]
16. Lichter K, Krause D, Xu J, Tsai SHL, Hage C, Weston E, et al. Adjuvant human papillomavirus vaccine to reduce recurrent cervical dysplasia in unvaccinated women: a systematic review and meta-analysis. Obstet Gynecol. 2020;135(5):1070-83. [DOI:10.1097/AOG.0000000000003833]
17. Wright Jr TC, Parvu V, Stoler MH, Kodsi S, Eckert K, Yanson K, et al. HPV infections and cytologic abnormalities in vaccinated women 21–34 years of age: Results from the baseline phase of the Onclarity trial. Gynecol Oncol. 2019;153(2):259-65. [DOI:10.1016/j.ygyno.2019.02.016]
18. Yousefi M, Hasanzadeh M, Rostaminezhad V, Gaffarean M, Mousavi AS. Human Papillomavirus Vaccination: Is it Cost-Effective in Iran? J Obstet Gynecol Cancer Res. 2022;2(1):e10218. [DOI:10.5812/jogcr.10218]

How to Cite This Article:

Ahmadzadeh, A., Bahrami, S., Saadati, N., Farhadi, E., Safikhani, N. Histopathological Spectrum of Cervical Intraepithelial Neoplasia in HPV-Vaccinated vs. Unvaccinated Women: A Retrospective Study in Southwest of Iran. J Obstet Gynecol Cancer Res. 2025;10(8):635-40.

Download citation: RIS | EndNote | Mendeley | BibTeX |