Adjuvant VaccInation After Conization for the Treatment for CervicAL Dysplasia

Carlotta Caia[a], Francesca De Maria[a], Francesco Sopracordevole[b], Andrea Ciavattini[c], Jvan Casarin[d], Fabio Ghezzi[d], Giuseppe Vizzielli[e], Valentina Chiappa[a], Umberto Leone Roberti Maggiore[a], Camilla Valsecchi[a], Giovanni Scambia[f], Francesco Raspagliesi[a], Giovanni Corso[g,h] and Giorgio Bogani[a]

This study aimed to evaluate the role of adjuvant HPV vaccination in women undergoing conization for cervical intraepithelial neoplasia. This prospective study assessed factors influencing recurrence in patients undergoing conization for high-grade cervical dysplasia. After conization, patients were counseled on the potential benefits of vaccination. We compared outcomes between two groups: women who underwent conization with adjuvant human papillomavirus (HPV) vaccination and observation versus conization with observation only. Data from 281 patients were analyzed, comprising 168 (59.8%) patients in the conization-only group and 113 (40.2%) patients in the conization-plus vaccination group. Vaccinated patients were younger than nonvaccinated patients (38 vs. 45 years, $P < 0.001$). Positive surgical margins were more frequently observed in the vaccinated group compared with the nonvaccinated group (9.7 vs. 3.6%; $P = 0.038$). Median follow-up was shorter in the vaccinated group, although this difference was not statistically significant (24.9 vs. 27.8 months; $P = 0.395$). The risk of developing HPV-related lesions was similar between the vaccinated and nonvaccinated groups ($P = 0.594$, log-rank test). Likewise, the need for reconization did not differ significantly between the groups ($P = 0.593$, log-rank test). Multivariate analysis showed no significant impact of HPV vaccination on postoperative outcomes [hazard ratio (HR): 0.50, 95% confidence interval (CI): 0.15–1.68) for any lesion; HR: 0.90, 95% CI: 0.47–1.73 for reconization]. This study indicates that adjuvant HPV vaccination does not significantly affect short-term outcomes in women undergoing conization for cervical dysplasia. Ongoing randomized trials will provide more robust evidence to clarify the role of adjuvant vaccination in this setting. ***European Journal of Cancer Prevention*** **XXX: XXXX–XXXX**

European Journal of Cancer Prevention XXX, **XXX**:XXXX–XXXX

Keywords: adjuvant, cervix HPV, conization, vaccination

[a]Gynecologic Oncologic Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, [b]Gynecological Oncology Unit, Centro di Riferimento Oncologico-National Cancer Institute, Aviano, [c]Woman's Health Sciences Department, Gynecologic Section, Polytechnic University of Marche, Ancona, [d]Department of Obstetrics and Gynecology, 'Filippo Del Ponte' Hospital, University of Insubria, Varese, [e]Department of Medical Area (DAME), University of Udine, 'Santa Maria Della Misericordia' University Hospital, Azienda Sanitaria Universitaria Friuli Centrale, Clinic of Obstetrics and Gynecology, Udine, [f]Gynecologic Oncology Unit, Department of Women, Children and Public Health Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, [g]Department of Oncology and Hemato-Oncology, University of Milan. [h]Division of Breast Surgery, European Institute of Oncology (IEO), Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Milan, Italy

Correspondence to Carlotta Caia, MD, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Via Venezian 1, Milan 20133, Italy
Tel: +00 390223902392; fax: +00 390223902349;
e-mail: carlotta.caia@istitutotumori.mi.it

Received 26 February 2025 **Accepted** 19 March 2025.

Introduction

Human papillomavirus (HPV) infection is a significant risk factor for the development of cancer. Although the immune system spontaneously clears the majority of HPV infections, persistent infections can progress to preinvasive lesions and, eventually, invasive cancers (Kesic *et al*., 2023; McGee *et al*., 2023; Perkins *et al*.,2023). Virtually all cases of cervical cancer are caused by HPV. The implementation of both primary and secondary prevention strategies has demonstrated a substantial impact on reducing the burden of HPV-related diseases, including cervical cancer. However, despite these efforts, cervical cancer continues to pose a serious concern for public health systems worldwide (Kesic *et al*., 2023; McGee *et al*., 2023; Perkins *et al*., 2023).

In children and young adults, the introduction of HPV vaccination has altered the risk profile. They are developing HPV-related lesions, including cancers. Randomized-controlled trials have shown that HPV vaccination significantly reduces HPV infection rates, the occurrence of genital warts, and cervical lesions when compared with placebo. More importantly, the vaccines have been proven effective in lowering the incidence of cervical

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.eurjcancerprev.com).

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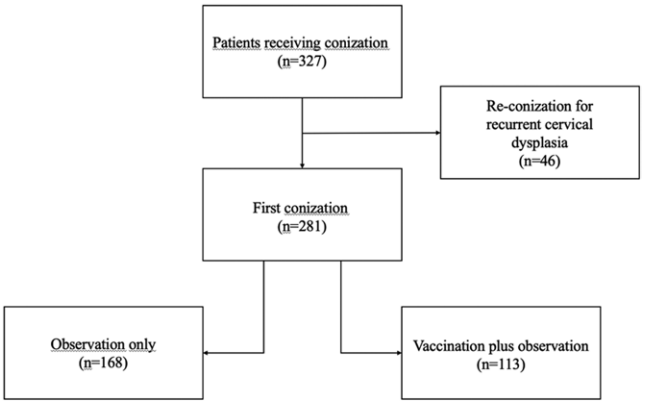
cancer itself. Accumulating evidence supports the widespread use of the HPV vaccine in both girls and boys aged between 11 and 26 years (Joura *et al*., 2012, 2015; Maldonado *et al*., 2022). The safety and immunogenicity of HPV vaccines have also been demonstrated in individuals up to 45 years old. Multiple studies have revealed a strong correlation between age and the effectiveness of HPV vaccination, with vaccines being most effective in younger populations, who are more likely to be naïve to HPV infections (Joura *et al*., 2012, 2015; Maldonado *et al*., 2022).

In recent years, increasing data has supported the use of HPV vaccination as an adjuvant therapy following surgical interventions like conization (Joura *et al*., 2012; Ghelardi *et al*., 2018; Bogani *et al*., 2020; Di Donato *et al*., 2021, 2022). Several retrospective studies have indicated that patients who received the HPV vaccine before or shortly after conization experienced a significantly lower risk of cervical dysplasia recurrence compared with those who underwent conization alone (Bogani *et al*., 2020; Di Donato *et al*., 2021, 2022).

The prospective SPERANZA study enrolled 172 women who underwent conization, followed by vaccination and conization alone, respectively (Ghelardi *et al*., 2018). Results indicated an 81.2% reduction in clinical disease recurrence among women who received the 4-valent HPV vaccine after conization, with two cases of recurrence in the vaccinated group compared to eleven cases in the unvaccinated group. Despite these promising findings, the definitive role of HPV vaccination in reducing recurrence remains a topic of ongoing investigation. In 2020, we initiated a prospective study aimed at identifying factors influencing the risk of cervical dysplasia recurrence. The present study seeks to specifically evaluate the role of HPV vaccination in women undergoing conization, contributing to the growing body of evidence on its potential benefits as an adjunct treatment to surgical procedures.

Fig. 1



Study design.

Methods

This prospective study was approved by the institutional review board (IRB) of the Fondazione IRCCS Istituto Nazionale dei Tumori (IRB-57/2020). The study was also registered on clinicaltrials.gov under the identification number NCT06611020 (VITAL Trial, 2024). The primary aim of this research is to identify predictive factors for 2-year recurrence in women undergoing treatment for HPV-related cervical disease. All participants provided written informed consent for research purposes. The inclusion criteria for the study were as follows: (a) a diagnosis of cervical dysplasia; (b) performance of a conization procedure; and (c) availability of follow-up data for at least 1 year. Exclusion criteria included (a) patients under the age of 18, (b) withdrawal of consent, (c) a preoperative diagnosis of cervical cancer, and (d) patients who underwent ablative procedures. Patients receiving conization between 1 January 2020 and 7 January 2023, were included in the present study. The primary outcome of this study was to assess the recurrence rate of cervical dysplasia in women treated with conization followed by HPV vaccination, compared with conization alone. Throughout the study period, no significant changes occurred in referral patterns. All patients were treated on an outpatient basis under local anesthesia, with conization performed under colposcopic guidance. Following Italian guidelines, all patients received counseling on the importance of HPV vaccination. Vaccination was recommended for all patients diagnosed with cervical intraepithelial neoplasia grade 2 and higher (CIN2+) lesions, irrespective of age. All vaccinated patients included in the study had nonvalent vaccination.

Demographic data, HPV genotyping results before treatment, and treatment details were prospectively entered into a dedicated database. HPV types were classified as high-risk based on data from the International Agency for Research on Cancer (Schiffman *et al*., 2009). The goal of conization was to remove a cone-shaped section of the cervix that encompassed the endocervical canal, including the entire transformation zone. All patients had conization via loop electrosurgical excision procedure (LEEP). Specific techniques for conization have been described in detail in previous publications (Bogani *et al*., 2020). The follow-up schedule and examinations adhered to conventional clinical protocols and have also been detailed in earlier publications (Bogani *et al*., 2020). According to institutional standards, patients underwent colposcopic evaluation in the outpatient clinic at 3 months postconization (for positive margins) or 6 months (for negative margins). Follow-up included a pap smear, colposcopy, and, if clinically indicated, colposcopically guided biopsy every 6 months for the first

2 years, followed by annual examinations for up to 5 years. A specialized team of gynecologists conducted all gynecological and colposcopic assessments. HPV testing was typically performed during the first postconization follow-up examination in patients with prior HPV infections. Persistence of HPV infection was defined as the detection of the same HPV type at the first clinical follow-up after conization (usually at 6 months). Persistence or recurrence following conization was defined as a diagnosis of a new high-grade squamous intraepithelial lesion (HSIL)/CIN2+ lesion requiring secondary conization or hysterectomy. Patients who did not undergo secondary conization were considered free of recurrence. Recurrences of both low-grade [low-grade squamous intraepithelial lesion (LSIL)/CIN1] and high-grade (HSIL/CIN2+) cervical lesions were recorded. Detection of HPV postconization without accompanying cytological or histological abnormalities was not considered a recurrent disease.

Basic descriptive statistics were used. Differences in categorical variables were analyzed using the chi-square or Fisher exact tests when appropriate. The Mann–Whitney test was used to compare continuous variables. Recurrence-free survival was estimated using the Kaplan–Meier model, and the log-rank trend test was used to test any trends in the survival curves. Recurrence-free survival time was defined from the conization to the recurrence for low-grade or high-grade cervical lesions or any other recurrence. The Cox proportional hazard model was used to estimate hazard ratio (HR) and 95% confidence intervals (95% CIs) for recurrence-free survival for both multivariate and univariate models. *P* values less than 0.05 were considered statistically significant. Statistical analysis was performed with Statistical Analysis System Software (Release SAS: 9.04; SAS Institute, Cary, North Carolina, USA).

Results

Overall, 327 patients had conization during the study period. After excluding 46 patients who had conization for recurrent cervical dysplasia (they already had at least one conization), 281 patients were available for the analysis. The study population included 168 (59.8%) and 113 (40.2%) patients with conization alone and conization followed by vaccination, respectively. Fig. 1 shows details of the study design. Vaccination rate increased over the study period from 31.8% in 2020 to 42.1% in 2022 (*P*-for-trend < 0.001). Baseline characteristics of the two groups of patients are reported in Table 1. Patients who received vaccination after conization were younger than patients who did not (38 vs. 45 years, $P < 0.001$). Patients in the vaccination group were slightly (not statistically significant) less likely to receive conization because of persistent low-grade cervical dysplasia than patients who did not receive vaccination (19.6 vs. 24.8%; $P = 0.305$). Positive surgical margins at conization were more frequently observed in the vaccination and in the no-vaccination group (9.7 vs. 3.6%; $P = 0.038$). No differences between the two groups were observed for the HPV status at conization ($P = 0.8989$), histological findings ($P = 0.1376$), cytology at 6 months ($P = 0.2692$), HPV status at 6 months ($P = 0.6619$), and reconization ($P = 0.8462$).

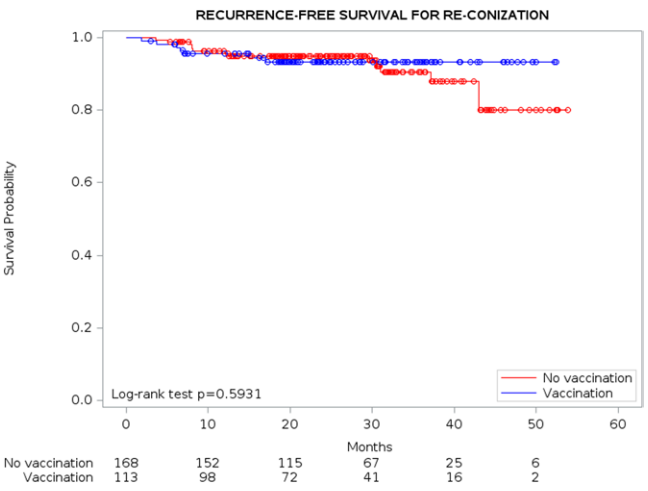
The median follow-up was shorter in the vaccination group than in the no-vaccination group, though the difference was not statistically significant (24.9 vs. 27.8 months; $P = 0.395$). The risk of developing any HPV-related abnormality over time was similar between groups; Fig. 2 compared the recurrence-free survival for reconization and showed no significant differences ($P = 0.593$, log-rank test). Similarly, patients receiving vaccination experienced a similar risk (over time) of having

Table 1 Study population

	Total	No vaccination	Vaccination	
	N = 281	*N* = 168	*N* = 113	*P* value
Age, median (IQR)	40 (32–48)	45 (33–52)	38 (31–42)	**<0.0001**
Smoking history, *n* (%)				
No	180 (64.1)	107 (63.7)	73 (64.6)	0.876
Yes	101 (35.9)	61 (36.3)	40 (35.4)	
HPV status at conization, *n* (%)				
Negative	195 (69.4)	118 (70.2)	77 (68.1)	0.8989
Positive	2 (0.7)	1 (0.6)	1 (0.9)	
Unknown	84 (29.9)	49 (29.2)	35 (31)	
Surgical indication, *n* (%)				
LSIL	61 (21.7)	33 (19.6)	28 (24.8)	0.3058
HSIL	220 (78.3)	135 (80.4)	85 (75.2)	
Histological findings, *n* (%)				
Negative	29 (10.3)	17 (10.1)	12 (10.6)	0.1376
CIN1	19 (6.8)	12 (7.1)	7 (6.2)	
CIN2	119 (42.3)	77 (45.8)	42 (37.2)	
CIN3	100 (35.6)	58 (34.5)	42 (37.2)	
Carcinoma	14 (5)	4 (2.4)	10 (8.8)	
Positive margins, *n* (%)				
No	264 (94)	162 (96.4)	102 (90.3)	**0.0336**
Yes	17 (6)	6 (3.6)	11 (9.7)	
Positive ectocervical margins, *n* (%)				
No	277 (98.6)	166 (98.8)	111 (98.2)	–
Yes	4 (1.4)	2 (1.2)	2 (1.8)	
Positive endocervical margins, *n* (%)				
No	268 (95.4)	164 (97.6)	104 (92)	**0.048**
Yes	13 (4.6)	4 (2.4)	9 (8)	
Cytology 6 months, *n* (%)				
Negative	203 (72.2)	127 (75.6)	76 (67.3)	0.2692
Positive	59 (21)	32 (19)	27 (23.9)	
Unknown	19 (6.8)	9 (5.4)	10 (8.8)	
HPV positivity at 6 months, *n* (%)				
No	151 (53.7)	94 (56)	57 (50.4)	0.6619
Yes	79 (28.1)	45 (26.8)	34 (30.1)	
Unknown	51 (18.1)	29 (17.3)	22 (19.5)	
Reconization, *n* (%)	19 (6.8)	11 (6.5)	8 (7.1)	0.8462
Year of conization, *n* (%)[a]				
2020	66 (23.5)	45 (68.2)	21 (31.8)	0.2446
2021	93 (33.1)	53 (57.0)	40 (43.0)	
2022	121 (43.1)	70 (57.9)	51 (42.1)	
2023	1 (0.4)	0	1 (100)	
Follow-up, median (IQR)	26.6 (19.3–**36.1**)	27.8 (19.5–**36.4**)	24.9 (19.0–**35.5**)	**0.3958**

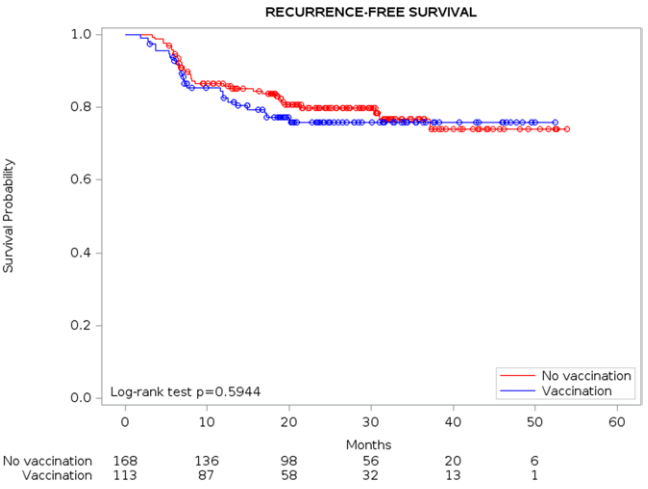
HPV vaccination following conization.
CIN, cervical intraepithelial neoplasia grade; HPV, human papilloma virus; HSIL, high-grade squamous intraepithelial lesion; IQR, interquartile range, LSIL, low-grade squamous intraepithelial lesion.
[a]For this variable we have reported the row percentages.
Statistically significant P-values are indicated in bold.

Fig. 2



Risk of reconization stratified for those who received vaccination or not.

Fig. 3



Recurrence-free survival stratified for those who received vaccination or not.

another HPV-related lesion than those without (Fig. 3; P = 0.594, log-rank test). In Supplementary Material 1, Supplemental Digital Content 1, *http://links.lww.com/EJCP/A550*, we stratified the Kaplan–Meier curves for the risk of developing low-grade (LSIL/CIN1) (panel A) and high-grade (HSIL/CIN2+) (panel B) lesions. There were no differences for both outcomes (P = 0.520 for LSIL/CIN1; P = 0.531 for HSIL/CIN2+). In our series, the administration of vaccination after conization did not reduce the risk of developing HPV-related lesions and reconization rates even in the subset of patients undergoing conization because of high-risk cervical dysplasia and in those with negative margins and without HPV persistence (data not shown). Similar results (Supplemental Material 2, Supplemental Digital Content 2, *http://links.lww.com/EJCP/A551*) were observed, focusing only on patients with longer follow-ups. No differences were observed in the two recurrence outcomes between patients treated between 2020 and 2021 in those who received and who did not receive vaccination (P = 0.592 for reconization and P = 0.382 for any HPV-related abnormality). Table 2 shows the uni- and multivariate Cox proportional hazard model analyses regarding factors predicting HPV-related lesions and reconization risk. In the multivariate analysis, HPV persistence at 6 months (HR: 14.69, 95% CI: 3.04–70.87, P = 0.0008), and smoking history (HR: 3.55, 95% CI: 1.15–10.92, P = 0.027) were the only variable that impacted on the risk of having a new conization. Via multivariate analysis both smoking history (HR: 2.99, 95% CI: 1.64–5.40, P = 0.0004) and HPV persistence at 6 months (HR: 6.15, 95% CI: 3.09–12.26, P < 0.0001) impacted on the risk of developing any HPV-related lesion. The execution of HPV vaccination after conization did not impact postoperative outcomes (HR: 0.50, 95% CI: 0.15–1.68 and HR: 0.90, 95% CI: 0.47–1.73 for any lesion and reconization, respectively).

Discussion

This study evaluated the impact of HPV vaccination in women undergoing conization and revealed several notable findings. First, 6-month HPV persistence and a history of smoking were the only factors significantly influencing the risk of developing HPV-related lesions and the need for reconization. Second, only 40% of the patients received HPV vaccination postconization. Third, in our cohort, HPV vaccination did not appear to reduce the risk of developing HPV-related lesions or the need for reconization. Fourth, we noted that smoking history is one of the main factors associated with cervical dysplasia recurrence. Smoking cessation should be advocated.

Although HPV vaccination is undoubtedly valuable in the target population, solid evidence is lacking to support its use as an adjuvant treatment postsurgery. Data from randomized trials on vaccination suggest that HPV vaccines do not impact the clearance of existing HPV infections. However, vaccination may protect against new HPV infections, the risk of having subsequent conization, and the (indirect) risk of preterm delivery in women having two or more conization (Bevis and Biggio, 2011; Athanasiou *et al.*, 2022). Interestingly, a cost-effective analysis testing the integration of nonavalent adjuvant vaccination in women having conization supported the economic value of adding HPV vaccines in preventing subsequent HPV-attributable diseases in patients surgically treated for CIN2+ (Cherif *et al.*, 2024). Indeed, several retrospective and prospective studies have reported encouraging outcomes in women vaccinated after conization. Specifically, the prospective SPERANZA trial found that the HPV vaccine provided 81.2% clinical effectiveness in preventing disease relapse postconization

Table 2 Prognostic factor for redeveloping any lesion for human papilloma virus and developing a new conization

	Risk of developing a new conization				Risk of redeveloping any lesion for HPV			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.01 (0.97–1.05)	0.6479	0.97 (0.92–1.03)	0.3225	1.02 (0.99–1.04)	0.1653	0.99 (0.96–1.03)	0.6064
Vaccination at 12 years								
No	Ref		Ref		Ref		Ref	
Yes	10.24 (1.34–78.00)	**0.0248**	3.76 (0.34–41.23)	0.2789	2.68 (0.37–19.43)	0.329	1.24 (0.15–10.34)	0.8447
Adjuvant vaccination								
No	Ref		Ref		Ref		Ref	
Yes	0.78 (0.32–1.94)	0.5942	0.50 (0.15–1.68)	0.2611	1.15 (0.69–1.93)	0.5948	0.90 (0.47–1.73)	0.7507
Smoking history								
No	Ref		Ref		Ref		Ref	
Yes	3.52 (1.42–8.73)	**0.0067**	3.55 (1.15–10.92)	**0.0271**	3.65 (2.14–6.23)	**<0.0001**	2.99 (1.64–5.49)	**0.0004**
Surgical indication								
LSIL	Ref		Ref		Ref		Ref	
HSIL	1.84 (0.54–6.28)	0.3288	2.27 (0.55–9.43)	0.2582	1.22 (0.63–2.34)	0.5585	1.14 (0.57–2.29)	0.7063
Positive ectocervical margins								
No	Ref		Ref		Ref		Ref	
Yes	4.27 (0.57–32.13)	0.1585	–	–	2.55 (0.62–10.46)	0.1939	1.01 (0.14–7.62)	0.9905
Positive endocervical margins								
No	Ref		Ref		Ref		Ref	
Yes	8.36 (3.06–22.84)	**<0.0001**	20.33 (4.39–94.13)	0.0001	2.22 (0.89–5.54)	0.0887	2.84 (0.84–9.60)	0.094
HPV positivity at 6 months								
No	Ref		Ref		Ref		Ref	
Yes	11.14 (2.52–**49.32**)	**0.0015**	14.69 (3.04–**70.87**)	**0.0008**	6.26 (3.26–**12.04**)	**<0.0001**	**6.15 (3.09–12.26)**	**<0.0001**

HPV vaccination following conization.

CI, confidence interval; HPV, human papilloma virus; HR, hazard ratio; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion. Statistically significant P-values are indicated in bold.

(Ghelardi *et al*., 2018). At a 4-year follow-up, this study reported two recurrences among 172 patients who underwent conization with vaccination and surveillance, versus 11 recurrences among 172 patients who received conization with surveillance alone. However, it is essential to note that the SPERANZA trial has some limitations, including a lack of randomization, a high rate of positive margins in both groups, the inclusion of microinvasive disease, and a significant rate of patients lost to follow-up. Consequently, the SPERANZA trial results should be interpreted cautiously (Ghelardi *et al*., 2018).

The results of the present study questioned the efficacy of HPV vaccination after conization. It highlights the importance of focusing HPV vaccination efforts on the target population (individuals aged 11–12 years) to optimize the use of resources and achieve maximum preventive benefits (Center of Disease Control, 2024).

Currently, three randomized trials are assessing the role of adjuvant HPV vaccination: the VACCIN trial (Trial-Registration-NL7938) (van de Laar *et al*., 2020), the NOVEL trial (evaluating the nonavalent HPV vaccine Gardasil 9 after conservative treatment for cervical intraepithelial neoplasia) (NOVEL Trial, 2019), and the HOPE9 Trial studying the HPV vaccination's effect on disease relapse in women treated with LEEP for cervical intraepithelial neoplasia (HOPE9 Study, 2024). Preliminary randomized data from the NOVEL trial (showed at the 26th European Society of Gynecologic Oncology Congress in Rome) indicate that HPV vaccination after conization does not significantly reduce the 24-month risk of recurrence. The findings suggest that HPV vaccination should not be routinely recommended after conization because of the lack of evidence supporting its efficacy. This agrees with another (randomized) preliminary data from the Netherlands. Specifically, in October 2024, van de Laar presented findings from the randomized VACCIN trial at the IGCS 2024 meeting. In this trial, 402 women received the HPV vaccine, and 407 received a placebo. After that, the outcomes will be assessed; 24 months of follow-up, there were 23 cases of CINII and III recurrence in the vaccinated group (5.7%) vs. 34 cases in the placebo group (8.3%) (relative risk: 0.67, 95% CI: 0.40–1.11, $P = 0.11$). HPV positivity during follow-up was noted in 127 (31.6%) of the vaccinated group and 148 (36.4%) of the placebo group ($P = 0.12$). Although the follow-up period was short, the authors concluded that HPV vaccination should not be recommended after conization (van de Laar *et al*., 2020). Interestingly, in our study, we also found that HPV vaccination did not significantly reduce the risk of developing subsequent HPV-related lesions. While the results of ongoing randomized trials are awaited to clarify the role of adjuvant HPV vaccination, further studies are needed to identify which populations may benefit most from HPV vaccination and to define the optimal surveillance strategy. Additional research is also required to investigate biological mechanisms through which vaccination may enhance the immune response in non-HPV-naive patients.

A key strength of our study is its prospective, real-world approach. However, several limitations impact

the interpretation of our findings. First, the short-term follow-up period is a limitation. Because available data suggest that HPV vaccination does not affect current infections but may prevent subsequent infections, a longer follow-up (at least 5–10 years) would be necessary to assess the occurrence of new, nonpersistent lesions (Woodman *et al*., 2007). Second, the populations were not homogeneous. This is not a randomized trial. Although we attempted to mitigate allocation bias through multivariable analysis, we are comparing two groups with differing baseline characteristics and risk factors, such as age, surgical indications, pathology findings, and margin status. These differences could influence our results. Third, only 40% of the total population chose vaccination, mainly in the later years of the study, which affects the results' interpretation. Fourth, because this study did not include a placebo, it is possible that vaccinated women did not take protective measures against risky behaviors, which may have influenced the outcomes. Fifth, the timing of adjuvant vaccination could impact HPV vaccine effectiveness (Di Donato *et al*., 2021, 2022); however, we do not have specific data on timing in this study. Other limitations include missing data on confounding variables, possible treatments received at other centers, and the absence of information on the types of HPV involved in cervical dysplasia and recurrent disease. Therefore, our findings should be interpreted with caution. Another interesting point that should discussed is the median age of women included in our study (40 years). Several data suggest that vaccination is more effective in very young individuals (those more likely to be naïve from HPV) (Joura *et al*., 2012, 2015; Maldonado *et al*., 2022; Perkins *et al*., 2023; McGee *et al*., 2023; Kesic *et al*., 2023). Recently, Krog *et al*. (2024) reported data from a population-based cohort study in Denmark assessing the risk of progression of CIN2+ in HPV-vaccinated ($n = 3867$) and unvaccinated ($n = 4037$) women. They observed that vaccination reduces the risk of progression in CIN2+ only if the vaccine is administered by the age of 20 years (Krog *et al*., 2024).

In conclusion, HPV vaccines have a proven value in the target population (boys and girls <25 years) (Joura *et al*., 2015). However, no data from randomized trials supported the value of adjuvant HPV vaccines. This study raises questions about the short-term benefits of implementing HPV vaccination in women undergoing conization. Vigilant surveillance remains essential, even after vaccination. These data are valuable for counseling patients on their short-term outcomes. Because we can postulate that adjuvant vaccination reduces the risk of new HPV infections after surgery, the risk of developing subsequent lesions (related to these new infections), and the time needed for developing a new cervical lesion, a longer follow-up is required to assess the actual value of vaccination after conization. Indeed, long-term follow-up data are necessary to determine the actual value of vaccination in this at-risk population. Similarly, the results of randomized trials will provide a clearer understanding of the pros and cons of adjuvant HPV vaccination. On the basis of the current state of knowledge, women should be informed about the available data on HPV vaccination at the time of treatment, and the decision should remain a personal choice.

Acknowledgements

Conceptualization: C.C. and GB. Methodology, data extraction, writing – original draft, and writing – review & editing: all authors. Project administration: G.B. Supervision: G.S. and F.R.

Conflicts of interest

There are no conflicts of interest.

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