

## Review

# Efficacy of the HPV Vaccine in the Secondary Prevention of Cervical Dysplasia in Patients Undergoing Surgery

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### Abstract

Chronic infection with human papillomavirus (HPV) is the leading cause of cervical cancer. Patients continue to suffer from relapse or residual disease despite major advancements in diagnostic and therapeutic procedures such as colposcopy, loop electrosurgical excision procedure, and surgical conization. The most effective way to prevent cervical cancer is to avoid HPV infection. There are no definitive data on the administration of an adjuvant HPV vaccine to patients with cervical intraepithelial neoplasia who have undergone local surgical procedures. In addition, it is believed that administering an adjuvant vaccine to this patient population might very well reduce the incidence of cervical cancer. Vaccines are believed to provide protection against reinfection or reactivation for seropositive individuals whose infection has been cleared. The use of adjuvant HPV vaccine in high-risk individuals with HPV infection and HPV-related lesions is not supported by strong evidence. In this systematic review, we sought to determine the effect of HPV vaccination on the risk of HPV infection and the recurrence of pre-invasive disease associated with HPV infection after local surgical intervention for cervical disease or other HPV-associated diseases.

**Keywords:** Cancer, cervical cancer, HPV, secondary prevention, vaccine

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Every year, cervical cancer affects around half a million women.<sup>[1]</sup> Chronic human papillomavirus (HPV) infection is the most frequent cause of cervical cancer.<sup>[2]</sup> The World Health Organization has called for the eradication of cervical cancer as a global epidemic by 2018. A triple intervention plan with specific global goals by 2030 has been established: 9/10 of girls should be completely immunized with the HPV vaccination by the age of 15; 7/10 of women must be tested twice with a high-performance test between the ages of 35 and 45 and 9/10 of women diagnosed with cervical cancer must get medical help.<sup>[3]</sup>

HPV is a viral family consisting of about 200 distinct non-enveloped double-stranded DNA viruses that might also infect mucosal and cutaneous epithelium. On the basis of

their oncogenic potential, they are categorized as high-risk or low-risk. Approximately 70% of persistent HPV infections are caused by types 16 and 18, while the remaining 19% are caused by types 31, 33, 45, 52, and 58.4-6 Up to 90% of HPV-induced changes will spontaneously reverse after 12–36 months of infection.<sup>7,8</sup> However, chronic infection plays a significant role in the development of invasive cervical cancer due to the formation of mutations in the transformation zone generated by HPV infection. An individual's genetic predisposition, such as p53 polymorphism, genetic diversity within the HPV type, coinfection with other HPV types, the frequency of re-infection, hormone levels, and the patient's immune system may all influence the progression and clearance of an infection.<sup>[2]</sup>

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Low-grade squamous intraepithelial lesions (LSILs) and high-grade squamous intraepithelial lesions (HSILs) are frequent in women and are often linked with cervical cancer. Despite major developments in diagnostic and treatment procedures such as colposcopy, the loop electrosurgical excision procedure (LEEP), and surgical conization, up to 6.6% of patients suffer recurrence or residual disease.<sup>[4]</sup> Geographic location has a significant impact on the prognosis of cervical cancer. Cervical cancer incidence has already been reduced by half as a result of the implementation of systematic screening programs, with the greatest reduction occurring in high-income countries. Cervical cancer, on the other hand, continues to be the main factor responsible for cancer-linked fatalities among African and Latin American women.<sup>[5]</sup>

In this systematic analysis, we sought to determine the impact of HPV vaccination on the risk of HPV infection and the recurrence of pre-invasive disease associated with HPV infection after local surgical intervention for cervical disease or other diseases associated with HPV infection.

### Primary Prevention of Cervical Cancer

The major method of preventing cervical cancer is avoiding HPV infection. HPV vaccine is the most effective technique, particularly for teenagers before their first sexual contact. Cervarix® (GlaxoSmithKline, Brentford, UK), Gardasil® (Merck, Kenilworth, NJ, USA), and Gardasil9® (Merck) are extensively used prophylactic HPV vaccines (Table 1).<sup>[9]</sup> The primary use of these vaccinations is to prevent cervical intraepithelial neoplasia (CIN), invasive squamous intraepithelial neoplasia (AIS), or invasive cervical cancer needing surgical or multimodal therapy.

All vaccines were created utilizing recombinant DNA technology. Vaccines were created using pure self-assembling L1 protein, which mimic virus-like particles.<sup>[10]</sup> Therefore, the vaccinations have a high immunogenic potential and are extremely successful in preventing HPV infection and disorders associated with HPV infection in prepubescent girls and boys; however, they do not eliminate the virus or diminish its persistence in women with chronic infections. Although the FDA has approved prophylactic HPV vaccination for individuals up to the age of 45.<sup>[11]</sup> The effectiveness

among such previously exposed, presently uninfected individuals (HPV IgG positive without accompanying DNA positivity) is little known.

### Secondary Prevention of Cervical Cancer

Recently, an update of the management guideline for Cervical Cancer Screening Tests and Premalignant Lesions has been published.<sup>[12]</sup> The consensus provides management and treatment guidelines for people with abnormal cervical cancer screening findings. The risk of developing CIN 3+ is calculated using the presence of cervical dysplasia, the patient’s age, pregnancy status, LSIL or HSIL lesion, and the patient’s history. A treatment recommendation is offered according to the calculated risk ratio. Conservative follow-up is considered to be a more appropriate approach for individuals under the age of 25. For these patients, follow-up with colposcopy, cytology, and HPV-based tests will usually be sufficient.<sup>[12]</sup> For surgical excisional therapy, many treatment techniques are available. LEEP, cold knife biopsy, and laser cone biopsy are the preferred surgical therapy techniques. In trials comparing these surgical treatment techniques, the advantage of one over the other has not been proven.<sup>[13]</sup> However, the risk of CIN 2+ recurrence after surgery is approximately 5–6%.<sup>[14]</sup> Failure to resection of the lesion, persistent infection in the tissues surrounding the resection areas, reactivation of a latent HPV infection, or reinfection with a different HPV type all increase the risk of CIN recurrence.<sup>[12,14,15]</sup> Age of the patient, body mass characteristics, size of the lesion, severity of the intraepithelial lesion, and total resection of the lesion have been identified as independent predisposing variables.<sup>[12,14,15]</sup> In addition, the prior treatment strategy, the presence of persistent HPV after local therapy, and the patient’s presence of other comorbidities may indeed influence the risk of CIN lesion development.<sup>[12]</sup>

There are no definitive data on the administration of an adjuvant HPV vaccine to patients treated with local surgical procedures for CIN. In addition, it is believed that the incidence of cervical cancer might decrease if this patient group is administered an adjuvant vaccine. It is known that patients with high-grade CIN are vulnerable to HPV infection. These patients may become re-infected with HPV following local treatment, and re-infection may increase the risk of developing cervical cancer.<sup>[11,16]</sup> After HPV infection, the risk of intraepithelial neoplasia and invasive malignancy is greater in these patients than in the general population.<sup>[17-19]</sup> However, adjuvant vaccine therapy is not recommended as standard in this patient population, and additional prospective research is required in this field.

The HPV vaccine that will be administered after surgical

**Table 1.** Information about HPV vaccines

Commercial name	HPV genotypes	Administration schedule	Valency
Cervarix	16, 18	0, 1, 6 months	Bivalent
Gardasil	6, 11, 16, 18	0, 2, 6 months	Quadrivalent
Gardasil 9	6, 11, 16, 18, 31, 33, 45, 52, 58	0, 2, 6 months	Ninevalent

treatment might well prevent the patient from contracting the same or different varieties of HPV infection. However, this vaccine is not expected to eradicate the patient's existing HPV infection. A previous studies shown that HPV vaccinations are far more immunogenic than the disease itself.<sup>20</sup> Vaccines are believed to give protection against reinfection or reactivation for seropositive people with a previously cleared infection.<sup>[21,22]</sup>

Repeated conizations are known to be related with negative reproductive consequences.<sup>[23-26]</sup> There are contradictory findings regarding the efficacy of HPV vaccination during conization procedures. A post hoc analysis of controlled studies revealed indirect evidence of decreased recurrence of high-grade CIN particularly in comparison to placebo.<sup>[27,28]</sup> While some observational studies have found a reduction of up to 80% in the recurrence of high-grade CIN in women vaccinated during treatment, other studies have contradicted these findings and found no effect.<sup>[29,30]</sup> In addition, two randomized controlled trials reported a reduction in CIN relapse; however, both studies were severely understaffed and enrolled fewer than 250 patients each.<sup>[30,31]</sup>

Because HPV persistence is the single most significant and controllable risk factor for the development of CIN lesions to high-grade cervical dysplasia and cancer, patients who have been treated for high-grade cervical dysplasia should get an adjuvant vaccination. Because no vaccine has yet been authorized for therapeutic use in HSIL patients, efforts have been undertaken to establish the efficacy of HPV preventive immunization in avoiding HSIL recurrence and cervical cancer. To date, several studies have been undertaken, but few are prospective. In Table 2, we have included the most recent prospective research on preventive HPV vaccination in patients with CIN who had undergone surgical treatment.<sup>[29-37]</sup>

Adjuvant HPV vaccination is a hot topic, and there are some recent prospective studies on this subject. In most of the studies, the adjuvant HPV vaccine has been shown to reduce the recurrence of CIN1/2 lesions. Approximately 20,000 patients were included in the prospective study published by Sand et al. All of these patients were diagnosed with CIN3+, and 17,000 were followed up without vaccination, and 2000 patients were followed up with adjuvant HPV vaccination.<sup>[32]</sup> All of the vaccinated patients were vaccinated within the 1st year, while 400 patients were vaccinated in the first 3 months. The result of this study, which included a large number of patients, is perhaps the biggest supporter of the recommendation for the use of adjuvant HPV vaccine. As a result of the study, the risk of CIN2+ was reduced by 23% in patients who were vac-

inated in the first 3 months after conization compared to those who were not vaccinated. There was a 13% reduction in the risk of developing CIN2+ when the patients who were vaccinated in the 1<sup>st</sup> year were compared with those who were not. In a Spanish study, in 2022, HPV vaccine was recommended to 398 patients who underwent conization, and the vaccine was administered to 306 patients who accepted it.<sup>[35]</sup> At the first control examination after conization, the prevalence of HSIL in vaccinated patients was found to be lower (2.6% [3/115] vs. 10.5% [4/38];  $p=0.043$ ). Del Pino et al. conducted another important study with 265 patients with CIN2-3+ after conization.<sup>[33]</sup> A total of 153 patients had HPV vaccination, and the HSIL rates of these patients and those who did not receive the vaccine were compared. Most of the patients were vaccinated after conization (93.5%) and the majority of them had only a single dose of vaccination (77%). In the first controls after conization, there was no difference between the vaccinated and non-vaccinated patients in terms of HSIL prevalence ( $p=0.58$ ). When the rates of HSIL detection after a mean follow-up of 22.4 months were compared, it was found that the rate of HSIL in the vaccinated patient was statistically lower ( $p=0.015$ ). Another prospective randomized study evaluating secondary prophylaxis was published in 2018.<sup>30</sup> In this study conducted in Italy, patients were randomized in a 1:1 ratio as HPV vaccinated and unvaccinated patients. In this study, which included a total of 178 patients, disease-free survival was found to be higher in the vaccinated arm ( $p=0.01$ ). In another randomized controlled trial, the efficacy of adjuvant HPV vaccine was tested in stage 1A1 cervical cancer patients treated with conization.<sup>[29]</sup> While the recurrence rate was 1.2% in the HPV vaccine group after conization, this rate was 5 times higher in the unvaccinated arm ( $p=0.01$ ). Grzes et al. observed that none of the 25 vaccinated women who had had surgery for CIN 1-2-3 or carcinoma in situ experienced disease recurrence over the period of follow-up.<sup>[34]</sup> Firnhaber et al. performed a research including 180 HIV-positive individuals with CIN 2-3.<sup>[36]</sup> Their procedure had quite differences. The aim of the research was HIV-positive women who were pathologically diagnosed with HSIL during regular cancer screening. During the initial visit, the quadrivalent vaccination is administered. At week 4, participants got LEEP treatment. At weeks 26 and 52, women were evaluated, histological samples were taken, and colposcopy was performed if a lesion was detected. They found that HPV vaccination had no influence on reducing recurrent HSILs following LEEP in HIV-positive participants. There is one study research on bivalent vaccine.<sup>[33]</sup> After surgical treatment, Zhao et al. randomized 87 vaccinated and 81 non-vaccinated women.<sup>[37]</sup> The median duration of follow-up for treated women

**Table 2.** Prospective research on preventive HPV vaccination in patients with CIN

	<b>Study design</b>	<b>Study population</b>	<b>Age</b>	<b>Inclusion criteria</b>	<b>Surgical method</b>	<b>Vaccination type</b>	<b>Vaccination time</b>
Pieralli et al.	Randomized controlled trial	178 patients	Under 45	Negative HPV test, cytology and colposcopy 3 months after surgical treatment for CIN	Conization, other n.a.	Quadrivalent	3, 5, and 9 months after surgical treatment
Sand et al.	Prospective population-based cohort study	17,128 patients	17–51	CIN 2–3, carcinoma in situ	Conization	Quadrivalent	3 months before or 12 months after surgery
Del Pino et al.	Prospective	265 patients	Mean age 39	CIN 2–3	Conization	Bivalent, quadrivalent and ninevalent	Bivalent at 0, 1, and 6 months Quadrivalent at 0, 2, and 6 months Nonavalent at 0, 2 and 6 months
Ghelardi et al.	Prospective case control	536 patients	18–45	CIN 2+ lesions and stage IA1 cervical cancer	LEEP	Quadrivalent	30 days after LEEP and at 2 and 6 months after 1st dose
Grzes et al.	Prospective case control	75 patients	N.A.	CIN 1-2-3 and carcinoma in situ	LEEP and conization	Quadrivalent	N.A.
Henere et al.	Prospective	398 patients	Mean age 39	HSIL	LEEP	Ninevalent	Before or after treatment, at 2 and 6 months
Firnhaber et al.	Randomized, double-blind, placebo-controlled prospective clinical trial	180 patients	Median 40	CIN 2–3	LEEP	Quadrivalent	Baseline, at 4 and 26 weeks
Zhao et al.	Randomized, double-blind prospective clinical trial	168 patients	18–25	LSIL + and CIN 2–3	LEEP	Bivalent	Baseline, at 1 and 4 weeks
Karimi et al.	Randomized controlled prospective clinical trial	312 patients	28–36	CIN 1-2-3	LEEP and conization	Quadrivalent	Baseline, at 2 and 6 months

was 46 months. Regardless of HPV DNA types, the vaccination effectiveness for the incidence of LSIL+ was 55.3% (95% Confidence Intervals [CI], 12.1–82.2%). No significant difference observed between the two groups ( $p=0.088$ ). In this study, immunization had no impact on viral clearance or on the persistence of HPV infection. Karimi-Zarchi et al. followed 312 patients with CIN-1, CIN-2, or CIN-3 who were vaccinated with two or three doses.<sup>[31]</sup> Two and three doses of HPV vaccination were 38.6% and 63.1% effective in treating CIN 1 and 50 and 72.2% effective in treating CIN 2, respectively. All women with CIN 3 got three doses of the vaccine, and the researchers discovered that the effectiveness of the vaccine in women who received three doses was superior to that of those who received two doses; both of these groups were superior than the control group.

Data on adjuvant HPV vaccine were evaluated in PATRICIA, FUTURE I, and FUTURE II clinical trials.<sup>[28,38]</sup> Nevertheless, the clinical characteristics of the patients included in these studies were different. FUTURE I and II included patients with genital warts, vulvar/vaginal intraepithelial neoplasia, or who had undergone cervical surgery.<sup>20</sup> In the PATRICIA study, the bivalent vaccine was administered to patients infected with other carcinogenic HPV types (ie HPV-31, 33, 45, and 51) that the vaccine did not target.<sup>[38]</sup> In this study, it was evaluated whether cross immunization, which will develop with the effect of vaccine, will reduce the development of neoplasia. In the vaccination group, none of the patients with cervical lesions detected and treated developed HPV-16 and/or HPV-18-related CIN2+ after vaccination. In addition, when all HPV types are considered, no CIN2+ cases were detected in 88% of the patients after vaccination. Regardless of the HPV type, the preventive effect of the vaccine against the subsequent CIN1 could not be demonstrated. In addition, CIN1 associated with targeted HPV types showed efficacy in lesion development. According to both studies, patients who underwent surgery for cervical neoplasia after vaccination had a lower risk of developing new or recurrent CIN 2+.

## Conclusion

There is no strong evidence for the use of adjuvant HPV vaccine in high-risk individuals with HPV infection and HPV-related lesions. However, a recent meta-analysis compared the vaccinated and unvaccinated groups and recommended HPV vaccine for patients with cervical precancerous lesions.<sup>[39]</sup> They reported recurrence risk and calculated pooled estimated odds ratio was 0.33 (95% CI 0.20–0.52;  $p<0.0001$ ) for CIN 2+ and 0.45 (95% CI 0.7–0.73;  $p=0.001$ ) for CIN 1+ lesions. There is a need for prospective, randomized, phase 3 clinical trials examining the effect of preventive vaccinations on relapsed and/or recurring CIN to re-

solve these contradictory problems. For clinicians to have a clearer understanding of secondary vaccination, its timing, and its cost-effectiveness, there must be a clear worldwide guideline.

## Disclosures

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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