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Research Report

# An investigation into human papillomavirus (HPV) vaccination for patients undergoing surgery for high-grade cervical or vulvar dysplasia

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ABSTRACT

*Introduction:* Eligibility for the human papillomavirus (HPV) vaccine now includes adults 27 through 45 years. It has not been reported how providers are addressing HPV vaccination in patients with existing preinvasive disease. Our objectives were to determine the rates at which vaccination is offered to and received by patients undergoing surgery for high-grade cervical or vulvar dysplasia.

*Materials and Methods:* This was a single-institution retrospective cohort study including patients ages 18 through 45 years undergoing surgery for high-grade cervical or vulvar dysplasia from 10/2018 to 2/2020. Our primary outcome was the rate at which HPV vaccination was discussed at the pre- and/or post-operative visits. The secondary outcome was the rate of vaccine uptake in these individuals. Characteristics of those offered HPV vaccination were compared to those not offered vaccination.

*Results:* Of the 115 patients included, 36 (31.3%) had HPV vaccination addressed in the perioperative setting. Thirty-two of these patients had never been vaccinated, and 21 of these (65.6%) went on to receive partial or complete HPV vaccination. Those in whom HPV vaccination was addressed were more likely to be under 27 years (RR 3.2; 95% CI 2.1–4.8) and less likely to be smokers (RR 0.5; 95% CI 0.2–0.9) or have prior excisional procedures (RR 0.3; 95% CI 0.1–0.9). The absolute rate of discussing HPV vaccination with patients improved from 26.0% within six months of vaccine age eligibility expansion, to 35.4% after six months ($P = 0.32$).

*Conclusions:* Providers did not consistently address HPV vaccination among patients being treated for high-grade cervical or vulvar dysplasia despite the potential benefits. However, a high proportion of these patients are amenable to vaccination. Quality improvement initiatives are warranted to increase the rate of HPV vaccine counseling in this context.

## 1. Introduction

Human papillomavirus (HPV) is a common infection responsible for a large burden of cervical, anogenital, and oropharyngeal cancers worldwide. Greater than 90% of cervical cancers are due to persistent infection by high-risk (HR) HPV subtypes. (de Martel et al., 2017) In recent decades, HPV vaccination has made strides in preventing HPV-associated disease, most notably precancerous high-grade cervical lesions. (Garland et al., 2007; Group FIS, 2007) The vaccine is also highly effective in preventing vulvar and vaginal lesions produced by high-risk HPV strains. (Joura et al., 2007) Among HPV 16- and 18-naïve populations, vaccine efficacy is estimated to be 98–100% at these disease sites. (Garland et al., 2007; Group FIS, 2007; Joura et al., 2007).

While vaccination prior to onset of sexual activity is most effective, vaccination after HPV exposure or even development of cellular dysplasia also appears to have benefit. (Joura et al., 2007; Joura et al., 2012) These findings pertain to many people in the United States considering that in 2018 the estimated proportion of adults ages 18–26 years who had completed the HPV vaccination series was only 21.5%. (Boersma and Black, 2020) Vaccination has been shown to prevent high-grade lesions caused by new high-risk HPV subtypes in patients with existing HPV infection (Group FIS, 2007; Joura et al., 2007), and there is mounting evidence supporting its use as adjuvant treatment to prevent recurrent dysplasia. (Joura et al., 2012; Lichter et al., 2020; Di Donato

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et al., 2021; Ghelardi et al., 2018).

On October 5, 2018 the U.S. Food and Drug Administration (FDA) approved expansion of the Gardasil-9 vaccine to include adults ages 27 through 45 years (previously 9 through 26 years) irrespective of HPV status. (FDA, 2018) This change has the opportunity to affect many patients with existing HPV-associated disease. It has not been reported how providers are addressing the option for HPV vaccination with such patients who are newly eligible. Our study aimed to determine the rate at which gynecologic surgeons (gynecologists and gynecologic oncologists) address and/or offer HPV vaccination to patients undergoing surgery for high-grade cervical or vulvar dysplasia, rates of vaccine uptake among these individuals, and factors which may influence these practices.

## 2. Materials and methods

This was a single-institution retrospective cohort study evaluating HPV vaccination among patients undergoing excisional procedures for high-grade cervical or vulvar dysplasia. All surgeries were performed by faculty within the Department of Obstetrics and Gynecology at a tertiary academic medical center from October 5, 2018 to February 28, 2020. This study was approved by The Ohio State University Office of Responsible Research Practices (IRB #2020H0088). Surgery logs were manually reviewed by one author (G.P.B.) to identify cases of cervical cold knife conization (CKC) or loop electrosurgical excision procedure (LEEP) or simple partial vulvectomy (SPV), also termed wide local excision (WLE) of the vulva. Patients were included if they were 18 through 45 years old (HPV vaccine-eligible) and had cervical intraepithelial neoplasia (CIN) 2–3, cervical carcinoma in situ (CIS), or adenocarcinoma in situ (AIS), or vulvar intraepithelial neoplasia (VIN) 2–3.

Three authors (G.P.B., J.B., R.P.) abstracted information from the electronic medical record into an encrypted database per IRB protocol. Key variables included demographics (age, race and ethnicity, marital status, tobacco use), relevant medical characteristics (HIV status, immunosuppressive conditions or medications, history of organ transplantation, etc.), provider characteristics (surgeon division, faculty versus resident clinic), and factors related to HPV vaccination (discussion of vaccination at pre- or post-operative visits, receipt of vaccination, etc.). Vaccination status was cross-checked with a state-wide vaccination registry.

The primary outcome was the rate at which providers offered HPV vaccination to patients in the preoperative and/or postoperative setting. The secondary outcome was the rate at which these patients completed all or part of the recommended adult HPV series. Logistic regression was performed to determine variables associated with a greater or lower likelihood of providers initiating discussion of HPV vaccination. Fisher exact tests and chi-squared tests were used to compare categorical variables and independent student *t* tests were used for continuous variables, as appropriate, and relative risk ratios were generated. Two-tailed 95% confidence intervals and *P* values were reported with $P < 0.05$ representing statistical significance. Statistical analyses were completed using JMP Pro 16.0.0 (SAS Institute, Cary, NC, USA).

## 3. Results

One-hundred fifteen patients met inclusion criteria. There were 96 patients who underwent either CKC (n = 76) or LEEP (n = 20) for high-grade cervical dysplasia and 19 patients who underwent SPV/WLE for high-grade vulvar lesions. As seen in Table 1, the mean age of patients in our cohort was 34.7 years (range 21.6–45.1). Most patients were White (77.4%), non-Hispanic (94.8%), and unmarried (63.5%). Forty patients (34.8%) were current smokers and an additional 33 (28.7%) were former smokers, six of whom had quit within the past year. With respect to medical comorbidities, 48.7% of patients were obese, 9.6% were on chronic immunosuppressive agents, 6.1% had diabetes, 3.5% had HIV infection, and two patients (1.7%) were organ transplant recipients.

**Table 1**
Patient demographics and other clinical characteristics according to whether vaccination was addressed perioperatively.

| Variable | Vaccination addressed (n = 36) | Vaccination not addressed (n = 79) | *P* |
|---|---|---|---|
| Age (years) | 31.9 +/- 6.0 | 36.0 +/- 4.8 | <0.01 |
| Age < 27 yr | 9 (25.0) | 2 (2.5) | <0.01 |
| Age 27–45 yr | 27 (75.0) | 77 (97.5) | |
| Race | | | 0.06 |
| White | 23 (63.9) | 66 (83.5) | |
| Black | 7 (19.4) | 8 (10.1) | |
| Asian | 3 (8.3) | 1 (1.3) | |
| Other | 3 (8.3) | 4 (4.3) | |
| Ethnicity | | | 0.37 |
| Non-Hispanic | 33 (91.7) | 76 (96.2) | |
| Hispanic | 3 (8.3) | 3 (3.8) | |
| Marital status | | | 0.41 |
| Single | 25 (69.4) | 48 (60.8) | |
| Married | 11 (30.6) | 31 (39.2) | |
| Tobacco use | | | 0.02 |
| Current | 7 (19.4) | 33 (41.8) | |
| Non-smoker | 29 (80.6) | 46 (58.2) | |
| Obesity (BMI > 30) | 16 (44.4) | 40 (50.6) | 0.55 |
| Comorbidities | | | 1.00 |
| Diabetes | 2 (5.6) | 5 (6.3) | |
| HIV | 2 (5.6) | 2 (2.5) | 0.59 |
| Immunosuppressive medications | 2 (5.6) | 9 (11.4) | 0.50 |
| Organ transplant | 1 (2.8) | 1 (1.3) | 0.53 |
| Division | | | 0.21 |
| OB/GYN | 20 (55.6) | 54 (68.4) | |
| Gynecologic oncology | 16 (44.4) | 25 (31.6) | |
| Clinic type | | | 0.84 |
| Resident | 15 (41.7) | 31 (39.2) | |
| Faculty | 21 (58.3) | 48 (60.8) | |

Data are presented as count (percentage) or mean +/- standard deviation.
BMI, Body mass index.

Seventy-four surgeries (64.4%) were done by the division of general gynecology (GYN) compared to 41 surgeries (35.6%) by the division of gynecologic oncology (GO). Most patients (60.0%), and all within the GO division, were considered "faculty patients" while 40.0% belonged to "resident clinics." In resident clinics, resident physicians were primarily responsible for outpatient counseling under the oversight of attending faculty. Eleven patients (9.6%) had their surgery under age 27 years, within the age range initially recommended for HPV vaccination (9 to 26 years). Sixty-five patients (56.5%) underwent surgery greater than six months from the time that Gardasil-9 gained FDA approval for adults through 45 years. Final pathology specimens were as follows: CIN 1 (n = 14, 12.2%), CIN 2 (n = 13, 11.3%), CIN 3 (n = 59, 51.3%), AIS (n = 9, 7.8%), foci of invasive carcinoma (n = 1, 0.9%), VIN 2 (n = 4, 3.5%), and VIN 3 (n = 15, 13.0%). Twenty-eight (24.4%) specimens had positive margins. Of the 96 cervical specimens, HPV strains isolated were as follows: HPV-16 (n = 25, 26.0%), HPV-18 (n = 3, 3.1%), HPV-HR other (n = 4, 4.2%), multiple HR strains (n = 9, 9.4%), and HR non-genotyped (n = 24, 25.0%). HPV testing was not completed or unavailable in 27 cases (28.2%) and was negative in four (4.2%). Of the 19 vulvar specimens, one lesion underwent HPV testing; this was positive for high-risk HPV but was not genotyped.

Six patients (5.2%) had received HPV vaccination at some point prior to their surgery (though unlikely prior to HPV infection) while the vast majority (93.9%) were previously unvaccinated. Twenty of 115 patients (17.4%) were counseled on HPV vaccination at a preoperative visit. Twenty-eight of 115 patients (24.4%) were counseled postoperatively within 6 months of surgery. Twelve patients (10.4%) were offered vaccination in both settings. The primary outcome—the overall rate at which HPV vaccination was addressed—was 31.3% (n = 36). Before and after 6 months following the change in vaccine-eligible age groups, these

rates were 26.0% and 35.4%, respectively. Following surgery, 21 of the 32 patients (65.6%) who had not previously been vaccinated received either partial (n = 7) or complete (n = 14) HPV vaccination, consisting of three doses at 0-, 2-, and 6-months. Vaccine uptake was similar between faculty (9/17) and resident (12/15) patients (52.9% v 80.0%; $P = 0.11$).

Demographics and other patient and surgeon-related characteristics were compared between those who did have HPV vaccination addressed (n = 36) and those who did not (n = 79) [Tables 1 and 2]. Patients who were offered vaccination were more likely to be younger (mean age 31.9 vs 36.0 years, $P < 0.01$), and, specifically, were more likely to be under 27 years old (25.0% vs 2.5%; RR 3.2, 95% CI 2.1–4.8). They were less likely to be current smokers (19.4% vs 41.8%; RR 0.5, 95% CI 0.2–0.9). The remainder of demographics and other select clinical characteristics including surgeon division and clinic type were similar between groups ($P = 0.06–1.00$) [Table 1]. A history of a prior excisional procedure was associated with decreased likelihood of having vaccination addressed (11.1% vs 35.4%; RR 0.3, 95% CI 0.1–0.9). The distributions of disease site and procedure, time from Gardasil expansion, margin status, and the HPV subtype(s) implicated were similar between groups ($P = 0.11–1.00$) [Table 2].

## 4. Discussion

There is a growing body of evidence supporting vaccination as an adjuvant measure to prevent recurrence of HPV-related disease. For example, a post hoc analysis (n = 1350) of the FUTURE I and II randomized controlled trials showed vaccination led to reductions of 64.9% in recurrent CIN 2–3 and 46.2% in any HPV-related lesion when also including those with genital warts, VIN, or VaIN. (Joura et al., 2012). In a subsequent meta-analysis (n = 2984), Lichter et al report that after cervical surgery for CIN 2–3, recurrence of CIN 1 or CIN 2+ were both significantly lower (RR 0.67 and 0.36, respectively) in patients who received adjuvant vaccination. (Lichter et al., 2020) In the prospective setting, the SPERANZA project (n = 350) demonstrated an 80% reduction in recurrent high-grade cervical disease in their case-control study of patients undergoing cervical LEEP. (Ghelardi et al., 2018) Given the magnitude of potential benefits and demonstrated safety profile of HPV vaccination—the most common adverse reaction is injection site pain (Garland et al., 2007)—a balanced discussion of the risks and benefits of HPV vaccination in this context should be offered to patients.

Of the 115 patients with high-grade cervical or vulvar dysplasia included in this study, only 36 (31.3%) had HPV vaccination addressed in the perioperative setting. Younger age had a significant association with being offered HPV vaccination ($P < 0.01$). Among patients under 27 years old, the likelihood of having vaccination addressed was three-times greater (RR 3.2) compared to older patients. We hypothesize that providers were more likely to address HPV vaccination in this age group because these patients met the previously standing FDA eligibility criteria. We predict that the number of patients aged 27 through 45 years who are offered vaccination will continue to increase as providers gain familiarity with the recent eligibility changes. (FDA, 2018) There was no formal initiative by our department to promote vaccination in this specific population, but we believe such efforts are warranted and should include enhancing provider education. Our rate of discussing HPV vaccination did improve from 26.0% within six months of the FDA expansion, to 35.4% after six months ($P = 0.32$), a difference which was not statistically significant likely due to the small sample size and limited follow-up time. Further research should be done to characterize how this trend evolves over time.

Interestingly, smoking or having a prior excisional procedure (involving the cervix or vulva) were associated with lower likelihoods (RR 0.5 and 0.3, respectively) of having HPV vaccination addressed. This observation may highlight implicit biases among providers in selecting who they believe are likely to accept or benefit from HPV vaccination. Given the synergistic effects between smoking and HPV on cervical dysplasia and cancer, (Plummer et al., 2003; Deacon et al., 2000; Olsen et al., 1998) this group is especially important to counsel on the potential benefits of vaccination. Larger studies will allow for a more robust investigation of risk and protective factors within this population.

Of the 32 previously unvaccinated patients who were offered HPV vaccination in our cohort, 21 of these patients (65.6%) went on to receive partial or complete HPV vaccination. This rate of uptake compares very favorably with that of the general population in the United States; for example, in 2016 the rate of annual HPV vaccine uptake in adolescent females was only 19.7%. (Prabhu et al., 2021) We acknowledge the limitation of our small sample size in determining this rate. Nonetheless, our findings do suggest that increasing awareness of the potential benefits of HPV vaccination in patients with high-grade dysplasia is a viable strategy. This does not detract from ongoing public health efforts to promote HPV vaccination as primary prevention.

Little is known about real-world clinical practices surrounding HPV vaccination in patients with high-grade dysplasia and vaccine uptake among these individuals. This study helps close these knowledge gaps and provides hypothesis-generating material for future work on this subject. A particular strength of our study is its relevance across multiple disciplines including gynecology, gynecologic oncology, and primary care. Additionally, our manual chart review and cross reference to a state-wide vaccination registry limit the possibilities of exposure or outcome misclassification compared to relying on diagnosis codes or other administrative metrics. Weaknesses of this study include the small sample size from a single academic institution; our results may not necessarily be generalizable to other regions or to community-based practice. Patients with vulvar dysplasia may be underrepresented due to the age exclusion criteria. Finally, this study relied on accurate and comprehensive documentation by providers, which may have underestimated the rate of vaccination counseling.

Moving forward, quality improvement initiatives are needed to increase the frequency with which providers discuss potential benefits of vaccination with patients with HPV-related disease. Attention should be paid to ensuring that patient education is inclusive and free from bias. We look forward with anticipation to results from randomized, prospective trials evaluating the impact of vaccination on anal and vulvar HPV dysplasia recurrence. (Stankiewicz Karita et al., 2019) Finally, as additional data emerge on HPV vaccination in the adjuvant setting, we

**Table 2**
Surgery and pathology-related characteristics according to whether vaccination was addressed.

| Variable | Vaccination addressed (n = 36) | Vaccination not addressed (n = 79) | *P* |
|---|---|---|---|
| Surgery/disease site | | | 0.11 |
| Cervical cold knife cone | 22 (61.1) | 54 (68.3) | |
| Cervical LEEP | 10 (27.8) | 10 (12.7) | |
| Simple partial vulvectomy | 4 (11.1) | 15 (19.0) | |
| Prior excisional procedure(s) | 4 (11.1) | 28 (35.4) | <0.01 |
| Months from FDA expansion | | | 0.32 |
| <6 | 13 (36.1) | 37 (46.8) | |
| >6 | 23 (63.9) | 42 (53.2) | |
| Positive margins | 9 (25.0) | 19 (24.1) | 1.00 |
| HPV subtype* | | | 0.29 |
| 16 | 9 (25.0) | 16 (20.3) | |
| 18 | 2 (5.6) | 1 (1.3) | |
| HR other | 1 (2.8) | 3 (3.8) | |
| Multiple HR types | 5 (13.9) | 4 (5.1) | |

Data are presented as count (percentage).
LEEP, Loop electrosurgical excision procedure; HR, high-risk.
*Cases in which HPV testing was non-genotyped, not indicated (e.g., vulvar dysplasia), or unavailable are excluded from this table.

look to our governing bodies such as ACOG and SGO for clinical practice guidance statements on this topic.

*CRediT authorship contribution statement*

**Glenn P. Boyles:** Project administration, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Jae Baek:** Investigation, Writing – original draft. **Radhika Pandit:** Investigation. **Casey M. Cosgrove:** Supervision, Writing – review & editing. **Kristin L. Bixel:** Conceptualization, Supervision, Writing – review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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