Systematic Review

Adjuvant Human Papillomavirus Vaccine to Reduce Recurrent Cervical Dysplasia in Unvaccinated Women

A Systematic Review and Meta-analysis

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OBJECTIVE: To perform a systematic review and meta-analysis evaluating the efficacy of adjuvant human papillomavirus (HPV) vaccination in preventing recurrent cervical intraepithelial neoplasia (CIN) 2 or greater after surgical excision.

DATA SOURCES: Electronic databases (Cochrane, PubMed, EMBASE, MEDLINE, Scopus, and ClinicalTrials.gov) were searched for studies comparing surgical excision alone to surgical excision with adjuvant HPV vaccination for CIN 2 or greater. Studies published from January 1990 to January 2019 were included.

METHODS: A total of 5,901 studies were reviewed. The primary outcomes evaluated included: recurrence of CIN 2 or greater, CIN 1 or greater, and HPV 16,18 associated CIN within 6–48 months. We used Covidence software to assist with screening, and meta-analysis was performed using Review Manager.

TABULATION, INTEGRATION, AND RESULTS: Six studies met inclusion criteria and were included in the final analysis. In total 2,984 women were included; 1,360 (45.6%) received adjuvant HPV vaccination after surgical excision, and 1,624 (54.4%) received either placebo or surgical management alone for CIN 2 or greater. Recurrence of CIN 2 or greater occurred within 6–48 months in 115 women (3.9%) overall; however, recurrence was significantly lower for vaccinated women: 26 of 1,360 women (1.9%) vs 89 of 1,624 unvaccinated women (5.9%) (relative risk [RR] 0.36 95% CI 0.23–0.55). The risk of CIN 1 or greater was also significantly lower with adjuvant HPV vaccination, occurring in 86 of 1,360 vaccinated women (6.3%) vs 157 of 1,624 unvaccinated women (9.7%) (RR 0.67 95% CI 0.52–0.85). Thirty-five women developed recurrent CIN 2 or greater lesions specific to HPV 16,18; nine received adjuvant vaccination (0.9%) vs 26 who were unvaccinated (2.0%) (RR 0.41 95% CI 0.20–0.85).

CONCLUSION: Adjuvant HPV vaccination in the setting of surgical excision for CIN 2 or greater is associated with a reduced risk of recurrent cervical dysplasia overall and a reduction in the risk of recurrent lesions caused by the most oncogenic strains (HPV 16,18). Human papillomavirus vaccination should therefore be considered for adjuvant treatment in patients undergoing surgical excision for CIN 2 or greater.

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Globally, cervical cancer is one of the most common cancers among women. Fifteen high-risk human papillomavirus (HPV) oncogenic types are known to cause cervical cancer.[1,2] However, persis-

tent infection with HPV types 16 or 18 accounts for approximately 70% of cases, and HPV types 31, 33, 45, 52 and 58 account for an additional 19% of cases.[3] Although the majority of HPV infections are transient and cleared within 2 years of exposure, 10–20% of infections will persist, leading to disease progression and, ultimately, invasive cancer.[4,5] The two major approaches for control of cervical cancer thus include primary prevention through HPV vaccination and secondary prevention by early detection and treatment of precancerous lesions.

Human papillomavirus vaccination has been shown to be both cost-effective and successful in preventing persistent HPV infection,[6] and there have been three FDA approved prophylactic HPV vaccines (bivalent, quadrivalent, nonavalent). The nonavalent HPV vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58) provides protection against approximately 90% of HPV-associated cancers and diseases, including not only cervical dysplasia but also vulvar dysplasia and genital warts.[7] Yet, even with the advent of effective vaccines, there remains a large population both in the United States and globally that remain unvaccinated. According to the Advisory Committee on Immunization Practices, as of 2018, only 51.1% of adolescents aged 13–17 years were up to date with the HPV vaccine series; 68.1% had received at least one dose of HPV vaccine in 2018.[8] Globally, the World Health Organization approximates only 51% of countries included the HPV vaccination in their national immunization program as of October 2019.[9] Therefore, screening remains a priority for cervical cancer prevention as it leads to the early detection and treatment of precursor lesions.[10]

The ASCCP has developed consensus management guidelines for the treatment of cervical dysplasia. For women younger than age 30 years with a histologic diagnosis of cervical intraepithelial neoplasia (CIN) 2 or greater, excision (eg, loop electrosurgical excision, cold knife conization), ablation (eg, cervical cryotherapy, laser ablation), or conservative management are acceptable treatment modalities; for women aged 30 years or older, either excision or ablation are recommended.[11] Among women with CIN 2 or greater, 6% will have recurrent CIN 3 or greater at 5 years, and 16.5% will have recurrent CIN 2 or greater at 5 years.[12] Although HPV vaccination is a well-recognized and accepted primary preventative measure, there is ongoing investigation of its benefit in the adjuvant setting to reduce the risk of dysplasia recurrence.

Recent studies suggest that adjuvant HPV vaccination may help to prevent recurrence of CIN 2 or greater, vulvar intraepithelial neoplasia (VIN), and genital warts. In a 2012 post hoc analysis of a randomized trial, Joura et al found that adjuvant HPV vaccination was associated with a 64.9% reduced risk of recurrent CIN 2 or greater, and a 46.2% reduction of all HPV-related disease.[13] Similarly, a 2018 prospective cohort study found that receipt of the quadrivalent HPV vaccine reduced the risk of recurrent high-grade CIN by 81.2%.[14] Nevertheless, there is currently no consensus on the benefit of HPV vaccination for adjuvant treatment of high-grade cervical dysplasia. Furthermore, even when this available evidence is used to make recommendations, it is often only the most privileged patients who are able to access vaccination by paying out of pocket. The objective of this study is to perform a systematic review and meta-analysis to evaluate the effect of adjuvant HPV vaccination after surgical excision for CIN 2 or greater compared with placebo or surgical procedure alone.

DATA SOURCES

With the assistance of a librarian, electronic databases including Cochrane, EMBASE, MEDLINE, Scopus, and ClinicalTrials.gov were searched from January 1, 1990, to January 1, 2019. Search terms used included: papillomavirus vaccines, HPV, human papillomavirus, Gardasil, Cervix, conization, loop electrical excision procedure, large loop excision of the transformation zone, excise, excision, and secondary prevention. Electronic searches were supplemented by reviewing reference lists of included studies and prior systematic reviews and contacting authors of included studies for any additional published or unpublished studies meeting review inclusion criteria. Published abstracts alone were excluded if a related article by the authors could not be obtained. For studies with more than one publication, data from the most recent complete report were used, and supplemented, if additional information was found.

This meta-analysis was conducted according to the methods described in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines for reporting systematic reviews and meta-analyses of randomized controlled trials.[15]

Details of the review protocol were registered on PROSPERO, an international database of prospectively registered systematic reviews, and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=135870. As a meta-analysis of existing data, our review was exempt from institutional review.

STUDY SELECTION

We searched for randomized controlled trials and cohort studies on HPV vaccination in the setting of treatment (loop electrosurgical excision procedure [LEEP], conization, and cryosurgery therapy) for CIN 2 or greater. We included studies in which women undergoing surgical treatment received at least one dose of an intradermal, intracervical, or intramuscular HPV-16,18 targeted vaccine, licensed to-date, within 48 months prior-to or after surgical treatment. All included studies had both treatment and control, or placebo groups, comparing the intervention. Exclusion criteria included studies in which participants had invasive disease, immunodeficiency, or autoimmune conditions; were on systemic corticosteroids other than inhaled corticosteroids or prednisone 10 mg or less (or equivalent); or were pregnant or less than 3 months postpartum or breastfeeding. Additionally, studies were excluded whose intervention included experimental vaccines, interleukins, interferons, growth factors, or intravenous immunoglobulin within 60 days before study entry.

All published studies that were deemed suitable were retrieved and reviewed using Covidence software. Two reviewers independently screened titles and abstracts. When discrepancies arose between reviewers, a third team member served as a third adjudicator and a final decision. Reviewers used a similar process for data extraction and to evaluate studies' risk of bias. Data were extracted and input into Covidence. In several cases, study authors were contacted to obtain, confirm, and clarify data. Additionally, Refworks was used throughout the review process for reference management.

Determination of whether to perform a meta-analysis was based on qualitative assessment of reasonably comparable study populations and interventions. We presumed that, if studies met our inclusion criteria, the outcome of recurrent cervical disease would be comparable across studies. Clinical, methodologic, and statistical evidence of heterogeneity was assessed and was considered in the assessment to do a meta-analysis. A pairwise meta-analysis was performed comparing adjuvant HPV vaccination compared with surgical excision alone. In deciding whether to present summary relative risk (RR) estimates, clinical and methodologic sources of heterogeneity across studies were considered. The Q statistic, the I^2 and the Tau-squared were used for statistical heterogeneity; for the Q statistic, a critical value of less than 0.1 was used; for the I^2 statistic, I^2 values of 25–50%, 51–75% and 76–100% signified low, moderate and high heterogeneity respectively.[16] The CIs of the risk estimates in the forest plots were assessed for overlap. Tau-squared was reported and used a critical value of less than 1.0. In case of statistically significant heterogeneity (P value for the Cochrane Q statistic less than 0.1), the random-effects model of DerSimonian and Laird was used to obtain the pooled RR estimate.

Study quality was evaluated using both the Cochrane Risk of Bias tool to evaluate randomized studies,[17] and the ROBINS-I (Risk of Bias in Nonrandomized Studies of Interventions) assessment tool.[18] The Cochrane tool evaluates each study's overall risk of bias through assessment of six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. We identified possible selection bias by evaluating investigators' description of random component of sequence generation (ie, random number table, random number generation, coin tossing.) Allocation concealment was evaluated based on whether study participants or investigators could foresee assignments of intervention compared with placebo or control. Bias stemming from blinding assessed the studies' blinding of participants, health care providers, and outcome assessors. Completeness of outcome data was evaluated based on attrition data or the percentage of participant withdrawal or drop-outs. If studies exceeded 20% loss of participants for short-term follow-up, or 30% for long-term follow-up, a high rate of attrition bias was designated to the study. Selective outcome reporting was determined based on the study's protocol, if it was available and all prespecified primary and secondary outcomes of interest had been reported. For studies without a published protocol or if there was a change in the measurement or analysis of the prespecified primary outcome then the risk of bias was determined to be high. Other bias was assessed based on the design on the study (post hoc analysis, subgroup analysis, nonrandomized case–control). Ultimately, the risk of bias in each category was categorized as low, high, or unclear.

The ROBINS-I tool includes seven domains broken into three parts: preintervention, at intervention, and postintervention. In the preintervention domain, bias owing to confounding and participant selection were evaluated. We identified possible preintervention confounding factors to include age, race, ethnicity, comorbidities, immune status, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), tobacco use, HPV strain (ie, 16,18), HPV vaccine type (bivalent,

quadrivalent, or nonavalent), and vaccine manufacturer. Bias "at intervention" stems from misclassification of interventions (surgery alone vs surgical therapy plus HPV vaccination). We also identified bias "at intervention" to include the time lapse from surgery to administration of the HPV vaccine, as well as time between vaccinations. Postintervention biases included: deviations from intended interventions, missing data, measurement of outcomes, selection of the reported result, time to follow-up, patients lost to follow-up, and process for monitoring recurrence of disease. In the end, the risk of bias in each category was categorized as low, high, or unclear.

The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) tool was used as a framework to assess quality of evidence presented in our study for each outcome. The quality of evidence was based on five factors: 1) limitations of detailed design and execution (risk of bias criteria), 2) inconsistency or heterogeneity between studies, 3) indirectness (Patient, Problem, or Population; Intervention; Comparison or Control; Outcome [PICO] and applicability),[19] 4) imprecision (number of events and CIs), and 5) publication bias. The evidence for each outcome was rated as high, moderate, low, or very low.[20]

The primary outcome of interest for this meta-analysis is the proportion of women who have recurrence of CIN 2 or greater within 6–48 months of treatment, irrespective of HPV type. We selected CIN 2 or greater as the primary outcome of interest, because CIN 2 or greater is widely accepted as a surrogate marker for vaccine efficacy in studies of prophylactic HPV vaccines against cervical cancer.[21]

Although both the ASCCP and the American College of Obstetricians and Gynecologists support the use of the LAST (Lower Anogenital Squamous Terminology) guidelines, the majority of studies included in this analysis used CIN terminology, and this was therefore used for consistency. For the purpose of this meta-analysis, studies reporting high-grade squamous intraepithelial lesions (HSIL) were categorized as CIN 2 or greater. Secondary outcomes included the incidence of low-grade intraepithelial lesion (CIN 1 or greater), incidence of recurrent CIN lesions associated with HPV16,18, clearance of HPV, VIN and vaginal intraepithelial neoplasia, and the development of HPV-related genital warts. Data for CIN 1 or greater included all cases reported to be of severity CIN 1 or greater, thus including low-grade squamous intraepithelial lesions, HSIL, CIN 2, and CIN 3.

RESULTS

Our initial search identified 5,928 bibliographic references stemming from the five electronic databases and Clinical Trails.gov. Subsequently, 1,220 duplicate articles were removed, for a total of 4,708. We further excluded 4,665 references through screening titles and abstracts. Four independent reviewers screened 37 full-text articles for eligibility into the systematic review and meta-analysis. After careful scrutiny, we further excluded 31 of these references as they did not fulfill the inclusion criteria. Nineteen studies were excluded as they reported on experimental HPV vaccines; an additional seven were review articles or editorial articles rather than primary research or were not addressing the specific review question. In two studies, women included were disease-free at the time of vaccination and thus these studies were not included in this review.[22,23] Two active trials were identified on ClinicaTrials.gov. One did not yet have reported results,[24] and the other began active recruitment in June 2019, with results expected in April 2020.[25] Finally, we excluded a conference abstract, because the full article could not be obtained (Museridze N, Kristesashvili J, Nadareishvili L, Goglidze M. Results of vaccination by "grandasil" after laser vaporization and conization in reproductive age patients with HSIL (open controlled trial) [abstract]. Int J Gynecol Cancer 2011;21:58). Ultimately, six studies meeting the inclusion criteria were included in our review (Fig. 1).

The main characteristics of the studies included in the review are summarized in Table 1. Of the studies included there was: one randomized controlled trial, two prospective case–control trial, one retrospective pooled analysis of two randomized controlled trials, one post hoc analysis of a prospective cohort, and one subgroup analysis of a community-based randomized trial. Studies included were conducted in Italy, Costa Rica, the United States, the Republic of Korea, and one was international, occurring in 14 different countries. All studies had both intervention (HPV vaccination) and comparison (placebo or hepatitis A vaccine) groups. Two studies vaccinated women with the bivalent HPV-16,18 AS04-adjuvanted vaccine (CervarixVR, GSK) Vaccines)[13,26] and the other four studies vaccinated women with the quadrivalent vaccine.[14,27–29]

Six studies reported on the incidence of CIN 2 or greater and CIN 1 or greater, comparing patients who underwent surgical resection with adjuvant HPV vaccination and those who underwent surgical resection plus placebo or hepatitis A vaccination, for a total of the 2,984 women. One randomized trial and one nonrandomized trial recorded events of CIN 3, and four studies specifically evaluated the recurrence of lesions that were positive for HPV 16,18 at the time of recurrence. Human papillomavirus testing for HPV

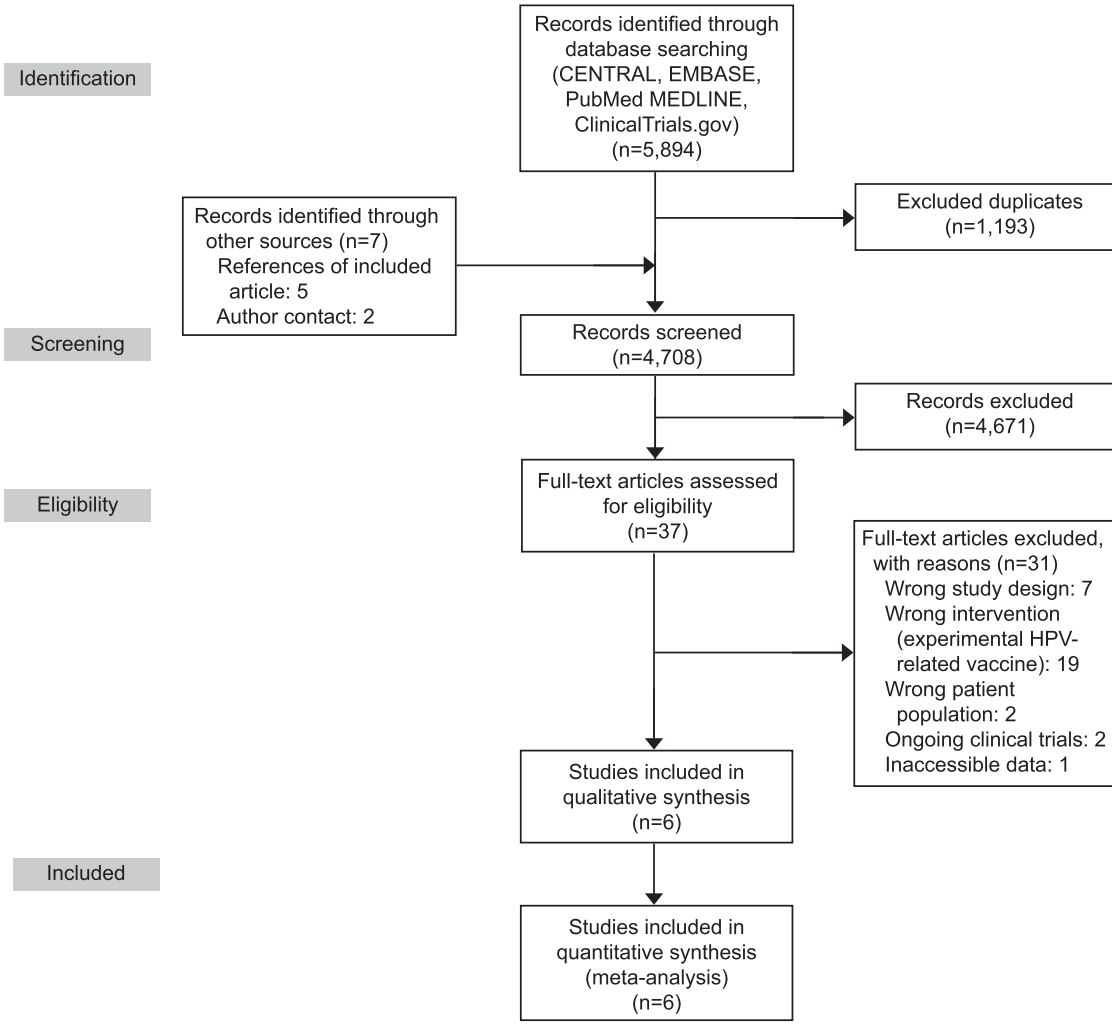

Fig. 1. Flow of identification, screening and eligibility, and inclusion. HPV, human papillomavirus.
Lichter. Human Papillomavirus Vaccine to Reduce Recurrent CIN. Obstet Gynecol 2020.

16,18 was performed in the research setting only to determine clearance of these specific HPV types. Of the four studies that evaluated recurrence of HPV 16,18 lesions, two studies vaccinated women with the quadrivalent vaccine,[15,29] and two vaccinated with the HPV-16,18 AS04-adjuvanted vaccines (Cervarix, GSK Vaccines).[28,30] Two of the six studies included in this review were supported by industry (one by Cervarix GlaxoSmithKline[28] and the other by Gardasil Merck&Co., Inc[13]).

Only a single study reported on incidence of VIN and genital warts.[13] In this study, VIN 2 or greater was reduced by 25% with HPV vaccination (RR 0. 75 95% CI 0.18–3.10). Vulvar intraepithelial neoplasia 2 or greater occurred in 3 of 474 (0.6%) women who received adjuvant HPV vaccination and in 5 of 589 (0.8%) who received placebo hepatitis A vaccination. Additionally, during the 4-year follow-up, VIN 1 or greater occurred in 12 of 474 (2.5%) patients receiving HPV vaccination vs 19 of 589 (3.2%) in the placebo arm (RR 0.78 95% CI 0.38–1.60). Genital warts were reduced by 60% with vaccination (RR 0.40 95% CI 0.17–0.92). Genital warts were identified in 7 of 474 (1.5%) patients receiving HPV vaccination and in 22 of 589 (3.7%) receiving placebo.

Two studies[14,26] reported on persistence, or clearance, of HPV. One study[14] tested for HPV at 6 months after surgery, and another[26] evaluated persistence of HPV during follow-up (median follow-up 27.3 months; interquartile range 15.3–39.6 months). This study found that HPV test of cure (TOC) rates at 6 months were 89.4% for the vaccinated group and 81.4% for the nonvaccinated group. In the vaccinated group 26 patients were found positive for HPV

positive at 6 months vs 32 in the nonvaccinated group. The other study[26] evaluated persistence of HPV infection defined as detection of type-specific HPV at two or more consecutive visits after treatment. The following HPV categories were assessed: HPV-16,18, HPV-31,33,45, and oncogenic types (presence of any of the 12 oncogenic HPV types). During the follow-up period HPV persistence in the vaccinated compared with the unvaccinated arm was: HPV16,18 –4 of 142 (2.8%) vs 6 of 169 (3.6%) (RR 0.79 95% CI 0.23–2.76); HPV-31,33,45–2 of 142 (1.4%) vs 8 of 169 (4.7%) (RR 0.30 95% CI 0.06–1.38); and all oncogenic types–22 of 142 (15.5%) vs 30 of 169 (17.8%) (RR 0.87 95% CI 0.53–1.44). Meta-analyses were not performed for incidence of genital warts, VIN and vaginal intraepithelial neoplasia, or clearance of HPV owing to limited and insufficient data.

Using the Cochrane Risk of Bias tool, the randomized trials were found to have an overall high risk of bias (Fig. 2). The studies were determined to have a high risk of selection bias because randomization occurred at entry into the main trial and not at the time of LEEP. Both studies were assessed to have appropriate concealment and blinding of participants and personnel. The studies were determined to have high rates of reporting bias owing to deviations from prespecified outcomes in the protocol. Lastly, other bias was determined based on the design of the study–one was a post hoc analysis and the other a subgroup analysis. We deemed these to have a higher risk of bias owing to the fact that these analyses were not prespecified at the time of the original randomized trial.

Using the ROBINS-I tool,[18] studies were found to have an overall high risk of bias (Fig. 3). Regarding the risk for confounding, studies were all noted to have a high risk of bias as confounders were not controlled with randomization. In regard to bias stemming from the measurement of the intervention, all studies had a low risk of bias as all were dichotomous interventions. For studies without a protocol, the bias owing to deviations from intended interventions was unclear.

In total, six studies were included in the meta-analysis for a pooled total of 2,984 women. The women included in the studies were between the ages of 15 and 45. Of all women included, 1,360 (45.6%) received adjuvant HPV vaccination and 1,624 (54.4%) received either a placebo hepatitis A vaccine 806 (59.3%), or surgical management alone 554 (40.7%). The summary of evidence for each outcome of interest and the magnitude of effect is summarized in Table 2.

All six studies reported on recurrence of cervical CIN 2 or greater within 6–48 months after treatment. Of the 2,984 women included in the pooled analysis, CIN 2 or greater occurred in 115 women (3.9%) total. In the vaccinated group, CIN 2 or greater recurrence occurred in 26 women (1.9%); in the unvaccinated group, CIN 2 or greater recurrence occurred in 89 women (5.5%) (RR 0.36 95% CI 0.23–0.55)–Figure 4. Three studies reported a significant risk reduction of CIN 2 or greater, and another two studies reported a nonsignificant risk reduction among women treated with adjuvant vaccination. One study reported a higher risk of recurrence.[27]

On examining the incidence of CIN 1 or greater within 6–48 months among women who received adjuvant vaccination compared with those who underwent surgery alone, (plus placebo hepatitis A vaccine), a reduction in recurrent CIN 1 or greater was also noted for those who underwent surgery with adjuvant vaccination. There was a pooled total of 243 events of CIN 1 or greater, with 86 in the patients who received adjuvant vaccination (6.3%) and 157 in the patients who did not receive adjuvant HPV vaccination (9.7%). Overall, adjuvant vaccination was associated with a 33% reduction in the risk of CIN 1 or greater in the vaccinated group (RR 0.67 95% CI 0.52–0.85)–Figure 5. All six studies reported on the risk of recurrent CIN 1 or greater in HPV vaccinated and unvaccinated patients; three studies reported a significant risk reduction of CIN 1 or greater, and another two studies reported a nonsignificant risk reduction among women treated with adjuvant vaccination. One study reported a higher risk of recurrence.[27]

Two studies recorded events of CIN 3 within 6–48 months after surgical treatment. Among the 1,137 women followed in these two studies, 496 women were vaccinated and 641 received a control or placebo. There were 17 total events (1.5%) of subsequent CIN 3 across both studies. There were three events (0.6%) in the vaccinated group, and 14 events (2.2%) in the unvaccinated cohort. Overall, there was a 68% reduction of CIN 3 in the vaccinated group (RR 0.32 95% CI 0.10–1.02)–Figure 6.

Four studies specifically evaluated the recurrence of lesions that were positive for HPV 16,18 at the time of recurrence. There was a pooled total of 35 events of HPV 16,18 CIN 2 or greater. Nine occurred in women who received adjuvant vaccination (0.9%) and 26 occurred in those who did not receive the vaccine (2.0%). There was a statistically significantly reduction in recurrence of HPV 16,18 related CIN 2 or greater (RR 0.41 95% CI 0.20–0.85)

Table 1. Studies Included in the Meta-analysis and Systematic Review

Study	Country	Duration	Design	Intervention	Control	Treatment
Garland et al[28]	14 countries in Asia Pacific, Europe, Latin America, and North America	2004–2007	Post hoc analysis of a prospective cohort study (PATRICIA)[24]	HPV-16,18 AS04-adjuvanted vaccine at 0, 1, and 6 mo at the time of study enrollment	Hepatitis A vaccine	LEEP, conization
Ghelardi et al[14]	Italy	2013–2017	Prospective case–control study (SPERANZA project)	Quadrivalent HPV vaccine (types 6, 11, 16, 18 L1 VLP vaccine Gardasil, Merck, Whitehouse station) given at 30 d and 6 mo after surgery	No HPV vaccination; normal follow-up after treatment	LEEP
Hildesheim et al[30]	Costa Rica	2004–2010	Subgroup analysis of a community-based randomized trial[29]	AS04-adjuvanted HPV-16,18 VLP vaccine given in 3 doses in the 6 mo at the time of study enrollment	Hepatitis A vaccine	LEEP
Joura et al[13]	United States	2001–2003	Retrospective pooled analysis of 2 randomized controlled trials (FUTURE I and FUTURE II)[5,30]	3 doses of quadrivalent HPV vaccine at day 1, month 2, and month 6 at the time of study enrollment	225 g aluminum hydroxy-phosphate sulfate	LEEP (84.7%), cervical conization (12.5%), cryotherapy (0.7%), and other* (2.1%)
Kang et al[27]	Republic of Korea	2007–2010	Randomized controlled trial	HPV quadrivalent vaccination given 1 dose at week 1 and 2 doses at month 6 after surgery	No HPV vaccination	
Grześ et al[29]	Poland	2009	Prospective case–control	3 doses of quadrivalent HPV vaccination	No HPV vaccination	LEEP

HPV, human papillomavirus; LEEP, loop electrosurgical excision procedure; CIN, cervical intraepithelial neoplasia; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; VLP, virus-like particles; IQR, interquartile range; VIN, vulvar intraepithelial neoplasia.

* Other is not defined by the study.

† Number of women with at least one follow-up visit for the respective endpoint after surgery. A woman is counted only once for each endpoint (that is, once in each row) but may have developed more than one endpoint (and so may appear in more than one row).

(Fig. 7). There were 49 events of HPV 16,18 related CIN 1 or greater; 11 in those vaccinated (1.1%) 38 in those unvaccinated (3.1%). There was also a statistically significant reduction in recurrence of HPV 16,18 related CIN 1 or greater (RR 0.35 95% CI 0.18–0.67) (Fig. 8).

The I^2 statistic, which showed the inter-study heterogeneity as a proportion of the total heterogeneity, ranged

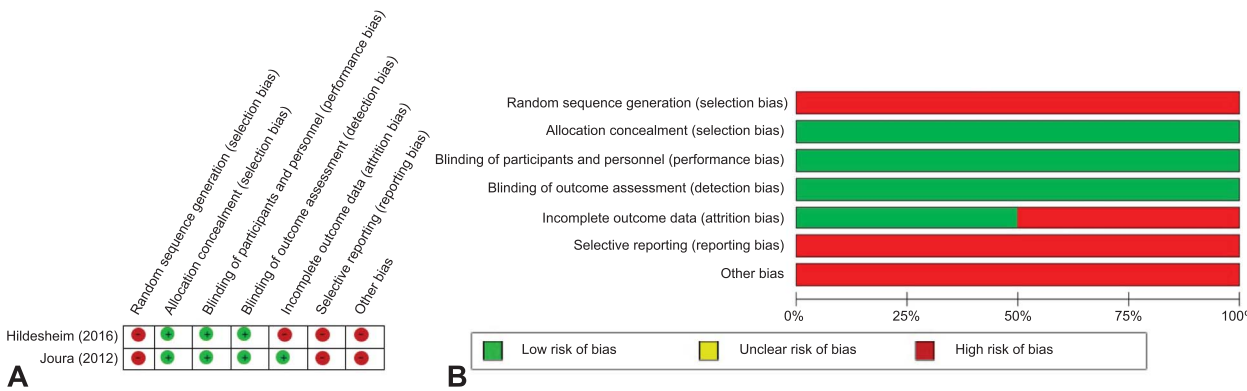

Fig. 2. A. Cochrane risk of bias summary: review authors' judgments about each risk of bias item for each included randomized study. **B**. Cochrane risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Lichter. Human Papillomavirus Vaccine to Reduce Recurrent CIN. Obstet Gynecol 2020.

Follow-up	Participants Receiving HPV Vaccination	Participants Without HPV Vaccination	Age of Participants (y)	Outcomes
Monthly follow-up starting 60 d after surgery for 4 y	190	264	15–25 (mean age of women with subsequent recurrence was 18.7±3.3 y)	Subsequent CIN 2 or greater, CIN 1 or greater; LSIL, HSIL for lesions with HPV-16,18 and for lesion irrespective of HPV DNA type more than 60 d after treatment for a first cervical lesion
Patients were followed with HPV test, colposcopy, and Pap test every 6 mo in the first 2 y and then annually until the 4th year posttreatment	172	172	18–45	Clinical recurrence of disease (disease relapse, histologically confirmed CIN 2 or greater during the 4 y follow-up period) and HPV test of cure at 6 mo after surgery
Median follow-up 27.3 mo; IQR 15.3–39.8) as part of their participation in the larger trial	142	169	18–25	CIN 1 or greater, CIN 2 or greater, LSIL or greater, HSIL or greater, HPV infection, persistent HPV for HPV DNA types 16, 68, 39, 52, 68.
4 y	474*	592†	15–26 y	CIN 2 or greater, CIN 1 or greater, genital warts, VIN or VAIN 2 or greater, VIN or VAIN 1, and any HPV-related disease for HPV types 6, 11, 16, or 18
Postconization follow-up was performed at 3, 6, 12, 18, and 24 mo during the first 2 y and yearly thereafter	360	377	20–45 (mean age of recurrence was 36.29±6.35 y)	Recurrence by patient characteristics: age, initial cytology, CIN at LEEP (2 and 3), cone margin, endocervical cytology, vaccination
Follow-up at 12 and 18 mo	22	50	Unknown	Presence of CIN and HPV DNA

between 0% and 46% which indicates a low level of heterogeneity between the studies in each of the meta-analyses.

DISCUSSION

This meta-analysis summarizes the currently available data on the efficacy of HPV vaccination as an adjuvant treatment to surgery for CIN 2 or greater. Our review of the available data demonstrates that adjuvant HPV vaccination in women ages 15–45 is associated with a significantly reduced risk of recurrence of CIN 2 or greater by 64% as well as CIN 1 or greater by 33% in the first 6–48 months after treatment. Given that CIN 1 and CIN 2 or greater are both caused by HPV and both require

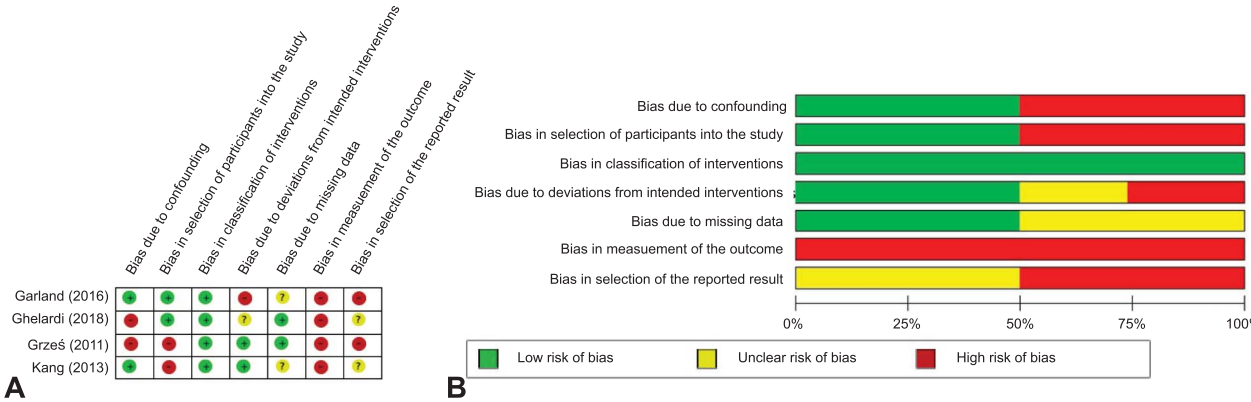

Fig. 3. A. Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) risk of bias summary: review authors' judgments about each risk of bias item for each included nonrandomized study. **B**. ROBINS-I risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Lichter. Human Papillomavirus Vaccine to Reduce Recurrent CIN. Obstet Gynecol 2020.

Table 2. Summary of Findings: Efficacy of Adjuvant Human Papillomavirus Vaccination vs Placebo or Control for Prevention of Recurrent High-Grade Cervical Intraepithelial Neoplasia After Surgical Excision*

Outcomes	No. of Studies Reporting Outcome	Pooled Intervention Group (Placebo or Control Group)	Total Events Intervention Group (Pooled Number of Events in Control or Placebo Group)	Relative Effect [RR (95% CI)]	Absolute Risk Difference/ 100 People	NNTb	Quality of the Evidence (GRADE)†
CIN 2 or greater (irrespective of HPV type)	6	1,360 (1,624)	26 (89)	0.36 (0.23–0.55)	3.6	28	⊕⊕⊕⊖ Moderate
CIN 1 or greater (irrespective of HPV type)	6	1,360 (1,624)	86 (157)	0.67 (0.52–0.85)	3.3	30	⊕⊕⊕⊖ Moderate
CIN 3 (irrespective of HPV type)	2	496 (641)	3 (14)	0.32 (0.10–1.02)	1.6	63	⊕⊕⊖⊖ Low
CIN 2 or greater (HPV 16,18)	4	1,004 (1,237)	9 (26)	0.41 (0.2–0.85)	1.2	83	⊕⊕⊕⊖ Moderate
CIN 1 or greater (16,18)	4	1,004 (1,237)	11 (38)	0.35 (0.18–0.67)	2.0	51	⊕⊕⊕⊖ Moderate
VIN 1 or greater (irrespective of HPV type)	1	474 (589)	12 (19)	0.78 (0.38–1.60)	0.7	144	⊕⊖⊖⊖ Very low
VIN 2 or greater (irrespective of HPV type)	1	474 (589)	3 (5)	0.75 (0.18–3.10)	0.7	463	⊕⊖⊖⊖ Very low
VIN 1 or greater (HPV 16,18)	1	474 (589)	2 (6)	0.41 (0.08–2.04)	0.6	168	⊕⊖⊖⊖ Very low
VIN 2 or greater (HPV 16,18)	1	474 (589)	1 (3)	0.41 (0.04–3.97)	0.3	335	⊕⊖⊖⊖ Very low
Genital warts (irrespective of HPV type)	1	474 (589)	7 (22)	0.40 (0.17–0.92)	2.3	44	⊕⊖⊖⊖ Very low
Genital warts (HPV 16,18)	1	474 (589)	2 (6)	0.41 (0.08–2.04)	0.6	168	⊕⊖⊖⊖ Very low
HPV persistence, 6 months	1	29 (39)	26 (32)	1.09 (0.90–1.32)	8.6	12	⊕⊖⊖⊖ Very low
HPV persistence during follow-up	1 (median follow-up 27.3 mo; interquartile range 15.3–39.6 mo)	HPV 16,18—142 (169) HPV 31,33,45—142 (169) All oncogenic HPV types—142 (169)	HPV 16,18—4 (6) HPV 31,33,45—2 (8) All oncogenic HPV types—22 (30)	HPV 16,18—0.79 (0.23–2.76) HPV 31,33,45—0.30 (0.06–1.38) All oncogenic HPV types—0.87 (0.53–1.44)	HPV 16,18—0.7 HPV 31,33,45—3.3 All oncogenic HPV types—22 (30)—2.3	HPV 16,18—136 HPV 31,33,45—30 All oncogenic HPV types—44	⊕⊖⊖⊖ Very low

RR, relative risk; NNTb, number needed to treat for benefit; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; VIN, vulvar intraepithelial neoplasia.

* Patient or population: females aged 15–45 years undergoing surgical excision for CIN 2 or greater; intervention: HPV vaccination; comparison: control or placebo.

† GRADE Working Group grades of evidence:

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important effect on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

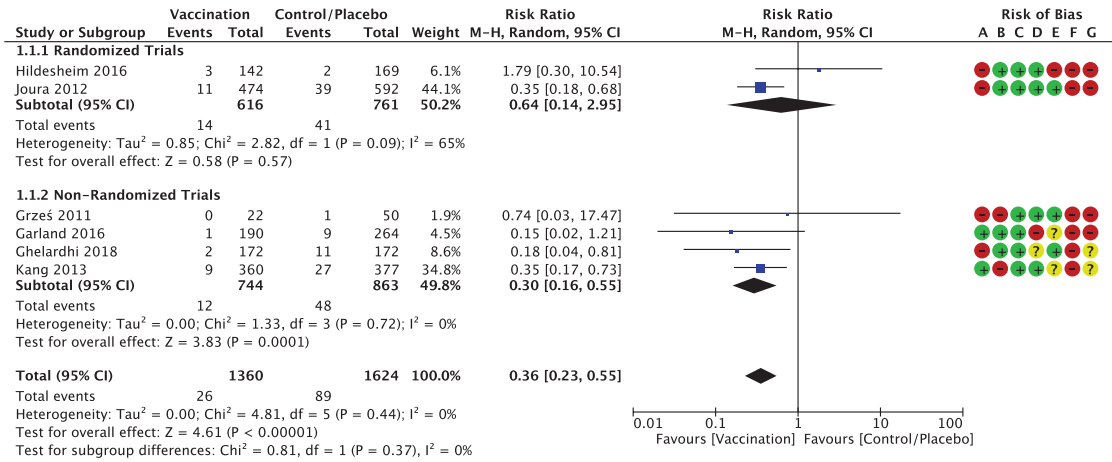

Fig. 4. Forest plot of the risk of cervical intraepithelial neoplasia 2 or greater recurrence with comparison of human papillomavirus (HPV) vaccination vs control (irrespective of HPV type). I^2 statistic represents the interstudy heterogeneity as a proportion of the total heterogeneity. I^2 values of 25–50%, 51–75%, and 76–100% signified low, moderate, and high heterogeneity, respectively. Risk of bias for randomized trials: *A* indicates random sequence generation (selection bias), *B* indicates allocation concealment (selection bias), *C* indicates blinding of outcome assessment (performance bias), *D* indicates blinding of outcome assessment (detection bias), *E* indicates incomplete outcome data (attrition bias), *F* indicates selective reporting (reporting bias), and *G* indicates other bias. Risk of bias for nonrandomized trials: *A* indicates bias due to confounding, *B* indicates biases in selection of participants into the study, *C* indicates bias in classification of interventions, *D* indicates bias due to deviations from intended interventions, *E* indicates bias due to missing data, *F* indicates bias in measurement of the outcome, and *G* bias in selection of the reported results. M-H, Mantel-Haenszel.

Lichter. Human Papillomavirus Vaccine to Reduce Recurrent CIN. Obstet Gynecol 2020.

close clinical follow-up, which is burdensome to patients, these findings may have significant clinical effects. Furthermore, adjuvant vaccination was also associated with a reduced subsequent CIN 2 or greater recurrence, irrespective of HPV type, as well as lesions that were specifically found to be positive for HPV 16,18. Although

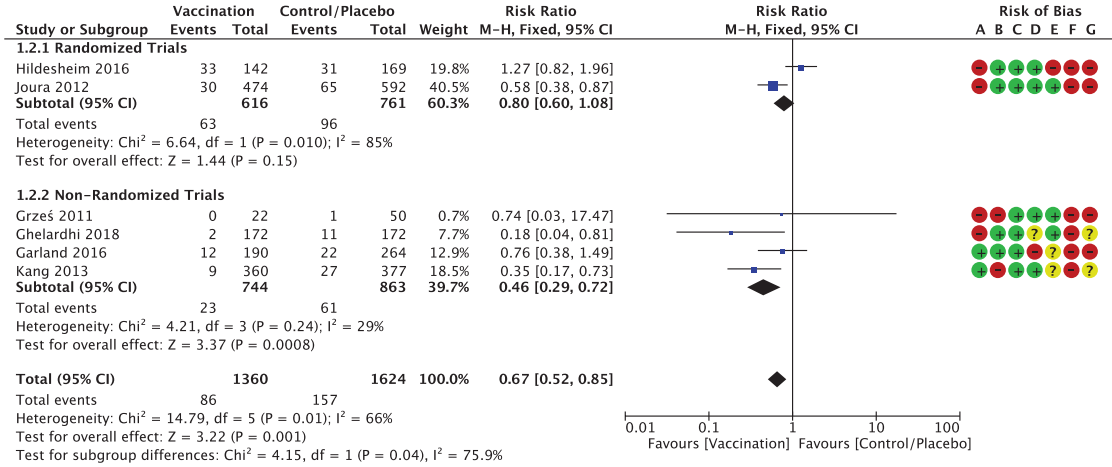

Fig. 5. Forest plot of the risk of cervical intraepithelial neoplasia 1 or greater recurrence with comparison of human papillomavirus (HPV) vaccination vs control (irrespective of HPV type). I^2 statistic represents the interstudy heterogeneity as a proportion of the total heterogeneity. I^2 values of 25–50%, 51–75%, and 76–100% signified low, moderate, and high heterogeneity, respectively. Risk of bias for randomized trials: *A* indicates random sequence generation (selection bias), *B* indicates allocation concealment (selection bias), *C* indicates blinding of outcome assessment (performance bias), *D* indicates blinding of outcome assessment (detection bias), *E* indicates incomplete outcome data (attrition bias), *F* indicates selective reporting (reporting bias), and *G* indicates other bias. Risk of bias for nonrandomized trials: *A* indicates bias due to confounding, *B* indicates biases in selection of participants into the study, *C* indicates bias in classification of interventions, *D* indicates bias due to deviations from intended interventions, *E* indicates bias due to missing data, *F* indicates bias in measurement of the outcome, and G bias in selection of the reported results. M-H, Mantel-Haenszel.

Lichter. Human Papillomavirus Vaccine to Reduce Recurrent CIN. Obstet Gynecol 2020.

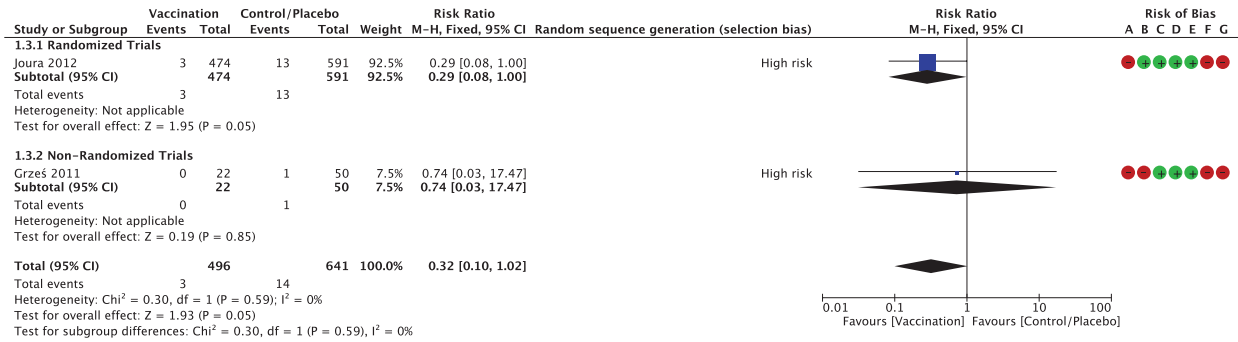

Fig. 6. Forest plot of the risk of cervical intraepithelial neoplasia 3 recurrence with comparison of human papillomavirus (HPV) vaccination vs control (irrespective of HPV type). I^2 statistic represents the interstudy heterogeneity as a proportion of the total heterogeneity. I^2 values of 25–50%, 51–75%, and 76–100% signified low, moderate, and high heterogeneity, respectively. Risk of bias for randomized trials: *A* indicates random sequence generation (selection bias), *B* indicates allocation concealment (selection bias), *C* indicates blinding of outcome assessment (performance bias), *D* indicates blinding of outcome assessment (detection bias), *E* indicates incomplete outcome data (attrition bias), *F* indicates selective reporting (reporting bias), and *G* indicates other bias. Risk of bias for nonrandomized trials: *A* indicates bias due to confounding, *B* indicates biases in selection of participants into the study, *C* indicates bias in classification of interventions, *D* indicates bias due to deviations from intended interventions, *E* indicates bias due to missing data, *F* indicates bias in measurement of the outcome, and *G* bias in selection of the reported results. M-H, Mantel-Haenszel.

Lichter. Human Papillomavirus Vaccine to Reduce Recurrent CIN. Obstet Gynecol 2020.

the post hoc analysis of a large randomized controlled trial included in this meta-analysis exemplified this significant risk reduction,[28] the current data have not yet sufficiently driven practice guidelines. Thus, although some clinicians may recognize these early findings and recommend vaccination in this setting, insurance companies often do not cover the cost of vaccination. Therefore, even when currently recommended, access to this intervention may be limited to only those patients who can afford to pay for it.

The mechanism explaining the efficacy of HPV vaccination as an adjuvant therapy to reduce recurrence is not well understood, as it was engineered to be a primary preventive vaccine. Current HPV vaccines

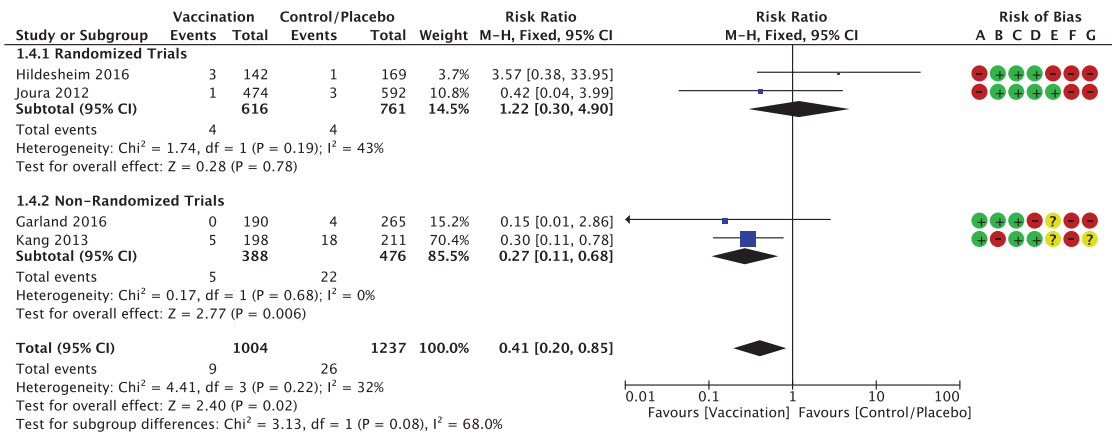

Fig. 7. Forest plot of the risk of cervical intraepithelial neoplasia 2 or greater recurrence with comparison of human papillomavirus (HPV) vaccination vs control (HPV 16,18). I^2 statistic represents the interstudy heterogeneity as a proportion of the total heterogeneity. I^2 values of 25–50%, 51–75%, and 76–100% signified low, moderate, and high heterogeneity, respectively. Risk of bias for randomized trials: *A* indicates random sequence generation (selection bias), *B* indicates allocation concealment (selection bias), *C* indicates blinding of outcome assessment (performance bias), *D* indicates blinding of outcome assessment (detection bias), *E* indicates incomplete outcome data (attrition bias), *F* indicates selective reporting (reporting bias), and *G* indicates other bias. Risk of bias for nonrandomized trials: *A* indicates bias due to confounding, *B* indicates biases in selection of participants into the study, *C* indicates bias in classification of interventions, *D* indicates bias due to deviations from intended interventions, *E* indicates bias due to missing data, *F* indicates bias in measurement of the outcome, and *G* bias in selection of the reported results. M-H, Mantel-Haenszel.

Lichter. Human Papillomavirus Vaccine to Reduce Recurrent CIN. Obstet Gynecol 2020.

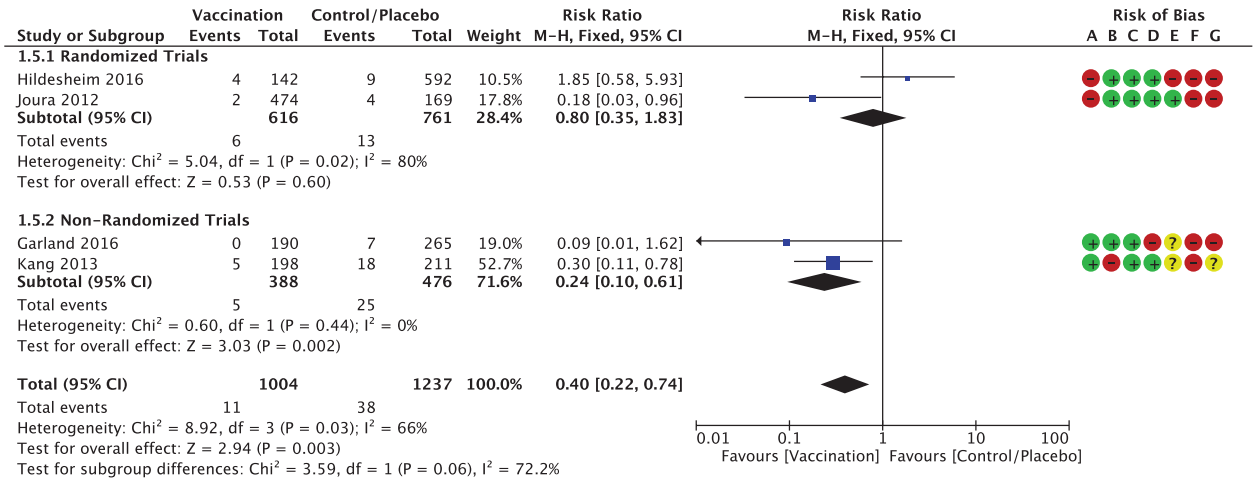

Fig. 8. Forest plot of the risk of cervical intraepithelial neoplasia 1 or greater recurrence with comparison of human papillomavirus (HPV) vaccination vs control (HPV 16,18). I^2 statistic represents the interstudy heterogeneity as a proportion of the total heterogeneity. I^2 values of 25–50%, 51–75%, and 76–100% signified low, moderate, and high heterogeneity, respectively. Risk of bias for randomized trials: *A* indicates random sequence generation (selection bias), *B* indicates allocation concealment (selection bias), *C* indicates blinding of outcome assessment (performance bias), *D* indicates blinding of outcome assessment (detection bias), *E* indicates incomplete outcome data (attrition bias), *F* indicates selective reporting (reporting bias), and *G* indicates other bias. Risk of bias for nonrandomized trials: *A* indicates bias due to confounding, *B* indicates biases in selection of participants into the study, *C* indicates bias in classification of interventions, *D* indicates bias due to deviations from intended interventions, *E* indicates bias due to missing data, *F* indicates bias in measurement of the outcome, and *G* bias in selection of the reported results. M-H, Mantel-Haenszel.

Lichter. Human Papillomavirus Vaccine to Reduce Recurrent CIN. Obstet Gynecol 2020.

prevent infection by producing virus-like particles, which elicit production of neutralizing antibodies and memory B-cells to these virus-like particles and block entrance into host cells. However, these vaccines are not effective in eliminating pre-existing infections because the target antigens (L1 capsid proteins) identified by the immune system after vaccination are not expressed in infected basal epithelial cells. Therefore, it is not effective at clearing virus in the large number of individuals who have already acquired HPV.[27] Nevertheless, our review of the available data suggests patients previously infected may still gain benefit from vaccine and have a decreased risk of recurrent disease.

Several hypotheses for its efficacy have been proposed.[15] First, vaccination may provide cross protection against HPV strains to which patients were not previously exposed. Current HPV vaccines do not provide protection against all HPV strains associated with cervical cancers. Thus, vaccination may provide protection from exposure to new HPV infections after treatment. For example, Hildesheim et al[30] found that six of nine women in their placebo group with disease recurrence were infected with a different HPV strain than was detected in the original surgical specimen. Furthermore, studies have shown that vaccination with the HPV 16,18 vaccine has cross protection against other HPV strains (ie, HPV 31 and HPV 45).[31–35]

A second hypothesis for the efficacy of adjuvant HPV vaccination is that the change in the immune microenvironment induced by surgery may create a new background, similar to the unexposed patient, in which prophylactic vaccine is efficacious. This proposed theory is supported by immunologic trials as well. Excision of primary HPV-related lesions causes a modulation in the inflammatory mucosal environment. Although patients with persistent HPV infection display increased levels of tumor necrosis factor-alpha in tissues,[36] patients treated with excision have significantly decreased tumor necrosis factor-alpha levels, comparable with levels of untreated control patients. The removal of the primary lesion therefore causes a change in the local inflammatory response. The surgical treatment of infected tissues may offer a new mucosal immune status of the cervix, similar to the noninfected, HPV naïve microenvironment. This introduces the opportunity for postsurgical prevention with HPV vaccine as an adjuvant therapy, as proposed by Gheladi et al.[15] Data from our meta-analysis further support this functionality.

The strengths of this study include that this meta-analysis comprehensively evaluates all the data from the available evidence to provide a large sample size to investigate the utility of adjuvant HPV vaccination after surgical excision for CIN 2 or greater compared

with placebo or surgical procedure alone. Additionally, the strength of the methodology used (Q statistic, the I^2 and the Tau-squared), as well as strict criteria of inclusion, specifically studies that compared adjuvant HPV vaccination after surgical excision for CIN 2 or greater compared with placebo or surgical procedure alone, ultimately allowed us to focus and more definitively answer the proposed question.

There are several limitations of this study. First, a small number of studies were included in the final analysis, and two of the studies accounted for nearly 60% of patients, potentially skewing the data in favor of those studies' findings. Second, because not all studies included were randomized, our results may not be generalized to all patients in this setting. We ultimately decided to include both randomized and nonrandomized studies in the final analysis as published literature on this subject is limited. By pooling the data, we can begin to investigate and make associations of reduced recurrence rates with adjuvant HPV vaccination in this setting. Third, each study vaccinated women at different time points before and after surgery and also there were different periods of follow-up among included studies. Finally, the time span among the included studies might introduce bias because of changes in the staging system, terminology, and definition over time. The included studies were published over a long period, and included populations using both the Bethesda and recent ASCCP terminology that have evolved over time.

The quality of our evidence for the primary outcome of interest, CIN 2 or greater, is moderate. Secondary outcomes of interest ranged from moderate to very low. In several analyses, the summary estimate of effect is statistically significant ($P<.01$), with narrow CIs suggesting a strong evidence in support of HPV vaccination; however, there was inconsistency between study designs and inconsistent results across studies. This limits the interpretation of our findings. Although the conclusion of almost all studies included in this systematic review and meta-analysis was that adjuvant vaccination was associated with decreased recurrence of cervical dysplasia, the conclusion from Hildesheim et al showed an increased risk of recurrence. The analysis from this article is a subgroup of the cohort that underwent a LEEP, and those patients included were not separately randomized; this study was therefore likely underpowered to detect a difference and may also have introduced bias.[30] For this reason, a meta-analysis of this type is critical to best understand and interpret the extent of available data in context. Further adequately powered, multi-centered randomized controlled trials answering this question are warranted to allow for appropriate pooling of the data.

Our analysis excluded studies that were conducted to test newly developed HPV vaccines that have not been FDA approved. These vaccines include VGX-3100 and pNGVL4a-Sig/E7(detox)/HSP70.[37–39] Because the efficacy of these vaccines has not been thoroughly tested, we anticipated that the effect of these vaccines would be heterogenous from those FDA approved vaccines. The clinical implication of our review is therefore not applicable to these new vaccines. However, these trials may help to better inform the effect of HPV vaccination on preventing CIN 2 or greater recurrence and may be considered further in the future.

In conclusion, this meta-analysis demonstrates that treatment with adjuvant HPV vaccination in women undergoing primary surgical excision of CIN 2 or greater is associated with a decreased risk of recurrent disease on the order of 66%. Additionally, considering the burden of HPV-related disease over the next few decades will be greatest among women who have not been vaccinated, the development of effective therapies targeting persistent infection remains imperative. These data advocate for further investigation with large randomized controlled trials to continue to prove the utility of the HPV vaccine as adjuvant therapy as well as its critical role in primary prevention.

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