



Review

Prophylactic HPV vaccination after conization: A systematic review and meta-analysis

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ABSTRACT

Introduction: Human papillomavirus (HPV) vaccination is essential for cervical cancer prevention. However, the value of HPV vaccination in the context excisional treatment of high-grade cervical intraepithelial neoplasia (CIN 3) remains unclear.

Methods: In this meta-analysis, three retrospective and three prospective studies, three post-hoc analyses of RCTs and one cancer registry study analysing the effect of pre- or post-conization vaccination (bi- or quadrivalent vaccine) against HPV were included after a systematic review of literature. Random-effect models were prepared to evaluate the influence of vaccination on recurrent CIN 2+.

Results: Primary end point was CIN2+ in every study. The overall study population included 21,059 patients (3,939 vaccinations vs. 17,150 controls). The results showed a significant risk reduction for the development of new high-grade intraepithelial lesions after HPV vaccination (relative risk (RR) 0.41; 95% CI [0.27; 0.64]), independent from HPV type. Due to the heterogeneous study population multiple sub analyses regarding HPV type, age of patients, time of vaccination and follow-up were performed. Age-dependent analysis showed no differences between women under 25 years (RR 0.47 (95%-CI [0.28; 0.80]) and women of higher age (RR 0.52 (95%-CI [0.41; 0.65])). Results for HPV 16/18 positive CIN2+ showed a RR of 0.37 (95% CI [0.17; 0.80]). Overall, the number of women that would have to be vaccinated before or after conization to prevent one case of recurrent CIN 2+ (NNV) is 45.5.

Conclusion: Meta-analysis showed a significant risk reduction of developing recurrent cervical intraepithelial neoplasia after surgical excision and HPV vaccination compared to surgical excision only.

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1. Introduction

Since the development of human papillomavirus (HPV) vaccination in 2006 cervical cancer prevention programs have gone

through tremendous changes. Most European countries have implemented HPV testing in their screening algorithms. Germany started to offer co-testing of cytology and HPV for women at the age of 35 and above in three-yearly intervals in 2020 [1]. The primary goal of all cervical cancer screening programs is identification of women with high-grade cervical intraepithelial neoplasia (CIN) or high-grade squamous intraepithelial lesions (HSIL), the immediate precursor lesion of invasive cervical cancer.

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These women usually receive excisional surgery of their pre-neoplastic cervical lesions [2]. Most commonly, procedures like loop electrosurgical excision procedure (LEEP) or laser conization are performed. About 52,600 conizations are executed in Germany every year due to high grade CIN [3]. Side effects or future risks of these patients are for example shortening of cervical length with the risk of premature delivery in pregnancy [4]. Despite this preventive operation, up to 8% of women with conization due to high-grade CIN are affected by a relapse of the disease [5]. Not only the risk of developing a cervical or vaginal carcinoma, but also mortality is increased, as current studies show [6].

The prophylactic HPV vaccines have been developed from a bivalent (HPV 16, 18) or quadrivalent (HPV 6, 11, 16, 18) to a 9-valent vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58) which could prevent almost 90% of all cervical cancer cases [7]. The effectiveness of these vaccines is explained by the induction of neutralizing antibodies. These antibodies prevent the attachment of the virus to the basement membrane. The cell surface binding is stopped and the antibody-virus complex eliminated by neutrophils [8].

There is great variation of primary HPV vaccination coverage worldwide. While countries with school-based vaccination programs such as Australia or the UK reach relatively high vaccination rates (Australia 2015: 78% in females and 67% in males (three doses)[9]; England 2018/19: 83.9% (two doses) [10]), the rates in other countries are low, even in first world countries. In Germany, only 31% of the 15-year old girls (range 22 – 57% in different states) were completely vaccinated in 2015 [11]. Criticism about the effectiveness or safety of vaccines could not be reassured in several studies [12]. The vaccines reveal a high safety and low side effect profile.

There have been tremendous efforts during the last years in the research of therapeutic HPV vaccination to treat existing HPV-related disease [13]. However, it will take several more years until the introduction of the first therapeutic HPV vaccines. Besides that, there is a growing body of evidence that prophylactic vaccination in the context of excisional treatment of high-grade CIN can reduce the risk of recurrence.

A further preventive option for women already treated by conization could therefore be the HPV vaccination shortly before or after treatment. Immunologically, the surgical intervention seems to induce a major change in the local inflammatory response in the cervix [14] and reduce TNF α and other pro-inflammatory cytokines [15]. The resulting anti-inflammatory microenvironment disadvantages a persistent HPV infection. A vaccine being applied at this point could theoretically prevent new or recurrent infections similar to an HPV naïve environment. This systematic review of randomized controlled trials, cohort studies, post-hoc and retrospective comparative analyses was conducted to assess the influence of prophylactic HPV vaccination when applied shortly before or after cervical excisional surgery.

2. Material and Methods

A systematic database research was performed for reports and trials comparing the relapse or recurrence rate after excisional therapy of high-grade CIN among women of any age with and without pre- or postoperative vaccination against HPV. Studies were included regardless of the type of vaccine used in the trials. Prospective (randomized) trials were included as well as observational and retrospective studies with adequate intervention and control groups. Post-hoc analyses of the large FUTURE and PATRICIA trials and cancer registry evaluations were also included in the meta-analysis. Only comparative studies with complete publication of all results in English or German were considered because congress abstracts often contain preliminary or incomplete data.

If possible, the authors of studies that were only published as congress abstracts were tried to be contacted via email and asked to provide their data. No restrictions were made regarding publication date.

Three databases (Embase and MEDLINE via Embase; Cochrane Central Register of Controlled Trials (CENTRAL)) were accessed using the search algorithms presented in the supplementary items. Study selection was done independently by JK and MJ. In case of conflicting opinions PH decided about inclusion or exclusion. The reasons for exclusion are mentioned in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (Fig. 1). A complete list of all search results can be found in the supplementary items.

Data extraction from each included study was done on the basis of study characteristics and outcome variables that were defined beforehand (see Table 1). The following items were extracted from each study for further analysis: study endpoint, type of vaccine (bivalent or tetravalent; studies using the 9-valent vaccine are still ongoing), cases of recurrent high-grade CIN in the vaccination and control group with and without regard to vaccine-related HPV genotypes (effectiveness), study population (age), time of vaccination (before or after conization) and duration of follow-up. To assess the clinical value of vaccination the total number of cases of recurrent CIN 2+ in the vaccine group and in the control group and the corresponding relative risks were calculated. The updated Cochrane risk of bias tool 2 (RoB 2) was used to assess the scientific quality of the included studies (Fig. 2) [14]. Inter-study heterogeneity was assessed using the maximum likelihood estimator with calculation of τ^2 and its corresponding p-value. This p-value indicates the probability that deviation from inter-study homogeneity can be explained by chance with a lower p-value implying significant heterogeneity.

All studies were evaluated regarding potential conflicts of interest on the basis of the available information on this matter. Statistical analysis was conducted by random-effect models due to significant inter-study heterogeneity. Analysis was by intention to treat.

Due to the heterogeneous study population, multiple subgroup analyses regarding the HPV type, age of patients, time of vaccination and duration of follow-up were performed. Several studies did not report separate results for specific age groups. Therefore the aspect of age was evaluated comparing studies on very young women (Joura (15–26 years), Garland (15–25 years), Sand (only the young cohort up to 25 years)) with studies on women of higher age (Petrillo (32–47 years), Del Pino (26–64 years), Sand (second and third cohort from 26 to 35 years and > 36 years). All calculations were done using R statistics (<https://www.r-project.org>).

3. Results

Included studies, characteristics, risk of bias

Numerous cases of women vaccinated against HPV after surgical treatment are described in pro- and retrospective studies. In total, 212 studies fulfilled the primary search criteria. Ten of the studies (Table 1), which involve 21,059 patients in total, were included after considering the inclusion and exclusion criteria. Three studies were performed prospectively (Pieralli [16] (randomized), Ghelardi [17] (non-randomized), Del Pino [18] (non-randomized)) and three retrospectively (Kang [19], Petrillo [20] and Ortega-Quifonero [21]). Three studies (Hildesheim [22], Garland [23], Joura [24]) are post-hoc sub analyses of an originally prospective study design. One study (Sand [25]) was a prospective population-based cohort study from the Danish pathology database. Studies were published from 2012 to 2020. Women were 65 years of age maximum; maximum follow-up time was 10 years

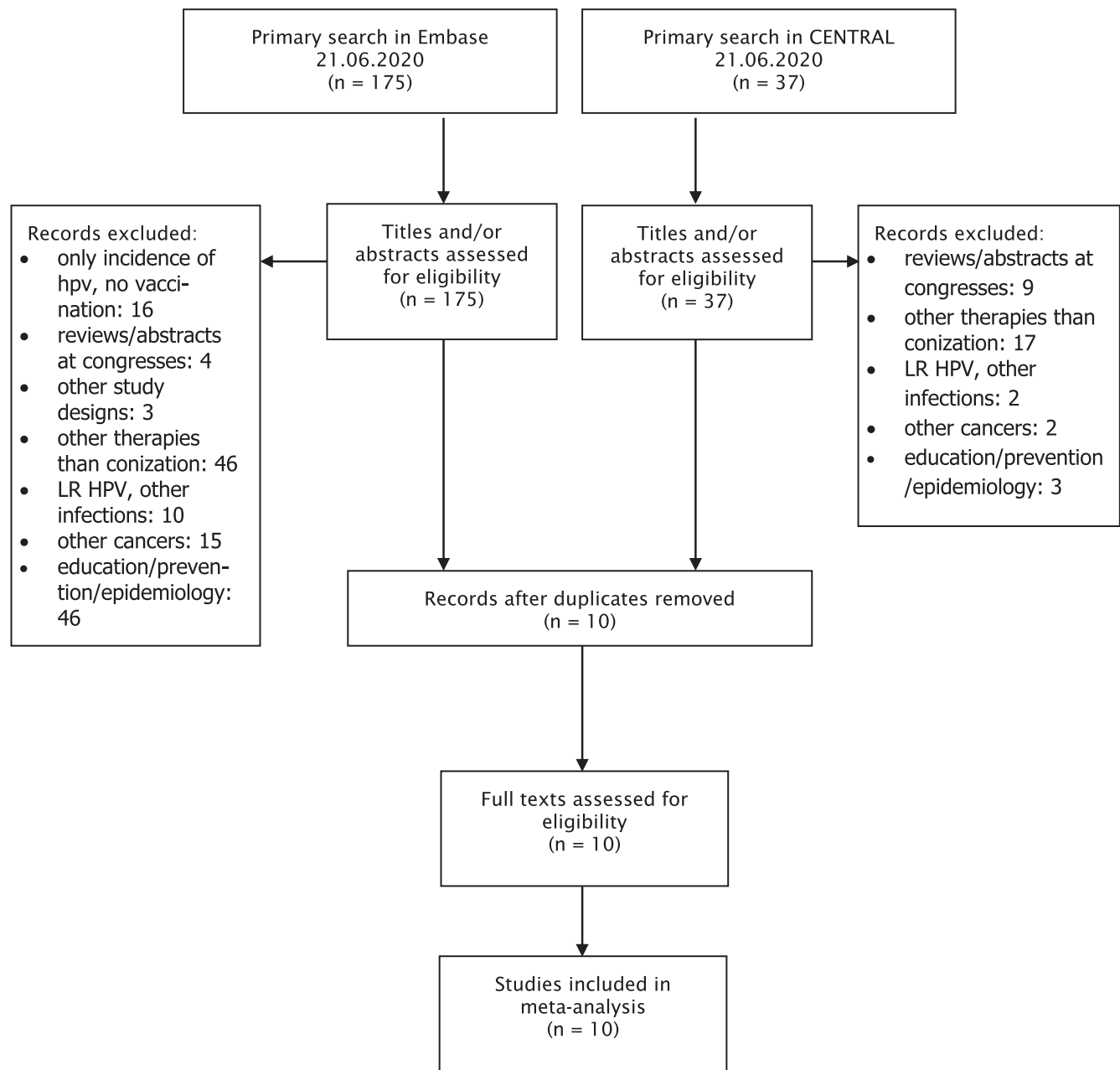


Fig. 1. PRISMA Flow chart.

after treatment. HPV vaccination was performed after operative treatment in six studies, and before in two studies (Joura, Garland), as well as before or after surgery in two studies (Sand, Ortega-Quinero), respectively. The vaccine applied was quadrivalent in four (Joura, Kang, Ghelardi, Pieralli) and bivalent in two studies (Hildesheim, Garland). In another four studies both vaccines (bivalent and quadrivalent) were used (Sand, Petrillo, Ortega-Quinero, Del Pino). Primary end point was HSIL or CIN2+ in every study.

Considerable heterogeneity between the included studies was assumed (Chi-squared test for heterogeneity: $\tau^2 = 0.1980$, $p = 0.03$). Therefore, the results from the random-effect analyses were used for meta-analysis.

The risk of bias assessment revealed a large overall risk of bias since the included studies were either post-hoc analyses of trials

designed to measure other outcomes than recurrent CIN after cervical surgery or studies were not randomized or studies were not prospective. Furthermore, studies had different inclusion criteria such as negative/ positive HPV status and cytology before vaccination. It has to be assumed that there is a relevant risk of publication bias since there were five trials that were only published as congress abstracts without complete data available and one trial from Poland without complete report in English [26].

All included studies were assessed regarding potential conflicts of interest. In nine studies all authors have completed the ICMJE uniform disclosure form. In five of the studies (Garland, Hildesheim, Joura, Sand, Del Pino), connections to and support by the vaccine manufacturer (GlaxoSmithKline Group and/or Merck & Co. Inc.) were indicated. One study (Ortega-Quinero) did not publish the ICMJE uniform disclosure form in its paper.

Table 1
Included studies (n.a. = not available).

Reference	Endpoint	Vaccine type	No. of recurrent CIN cases		Risk reduction (%) [95% CI] or study results as reported	Study population	Study design
			Vaccinated cohort 2/4v vaccine n/N (%)	Control group n/N (%)			
Joura et al.	CIN2+ (HPV-type independent)	Quadri-valent	8/474 (1.7)	26/592 (4.4)	64.9 [20.1–86.3]	Age 15–26 years Vaccination before surgery	Post-hoc-analysis (FUTURE I and II) Follow-up 2.5 years (median) retrospectively
	CIN2+ (HPV 16, 18)	Quadri-valent	1/474 (0.2)	3/592 (0.51)	61.3 [–382.4 to 99.3]		
Garland et al.	CIN2+ (HPV-type independent)	Bivalent	1/190 (0.53)	9/264 (3.41)	88.2 [14.8–99.7]	Age 15–25 years Vaccination before surgery	Post-hoc analysis PATRICIA prospective randomization Follow-up 4 years
	CIN 2+ (HPV 16, 18)	Bivalent	0/190 (0)	4/265 (1.51)	100 (–63.1–100)		
Kang et al.	CIN2+ (HPV-type independent)	Quadri-valent	9/360 (2.5)	27/377 (7.2)	65.1 (p < 0.05)	Age 20–45 years Vaccination after surgery	Retrospective Follow-up 3.5 years (median)
	CIN2+ (HPV16, 18)	Quadri-valent	5/197 (2.5)	18/211 (8.5)	70.2 (p < 0.01)		
Ghelardi et al.	CIN2+ (HPV-type independent)	Quadri-valent	2/172 (1.2)	11/172 (6.4)	81.2 [34.3–95.7]	Age 18–45 years Vaccination after surgery	Prospective, non-randomized Follow-up 36 years (median)
Hildesheim et al.	CIN2+ (HPV-type independent)	Bivalent	3/142 (2.11)	2/169 (1.18)	“No significant effect”	Age 18–25 years Vaccination after surgery	Randomized double blind clinical trial of 7466 Costa Rican women (NCI)
	CIN 2+ (HPV 16,18)	Bivalent	3/142 (2.11)	1/169 (0.59)	n.a.		Follow-up 57 mo. (HPV +), 27 mo. (LEEP)
Pieralli et al.	CIN 2+ (HPV-type independent)	Quadri-valent	0/89 (0)	4/89 (4.49)	n.a. for CIN 2+	Age < 45 years Vaccination after surgery	Prospective, randomized Not blinded Follow-up 3 years
	LSIL	Quadri-valent	3/89 (3.37)	8/89 (8.99)	3.4% vs. 13.5% Recurrence (p = 0.0147) NNT 10 HR 0.86 [0.67–1.09]		
Sand et al.	CIN 2+ (HPV type independent)	Bi-/Quadri-valent	82/2074 (3.95) 14/399 (3.51) (before LEEP) 68/1675 (4.06) (after LEEP)	777/15054 (5.16)		Age 17–51 years Vaccination before (0–3 months) or after (0–12 months) surgery	Prospective, cohort study (nationwide registry)
Petrillo et al.	CIN 2+ (HPV independent)	Bi-/Quadri-valent	6/182 (3.29)	14/182 (7.69)	3.3% vacc vs. 13.6% non-vacc = HR 0.24	Age 32–47 Vaccination after (0–1 month) after surgery	Retrospective Follow-up 2 years
	CIN 1+	Bi-/Quadri-valent	13/182 (7.14)	17/103 (16.50)	7.1% vacc vs. 16.5% non-vacc = HR 0.43		
Ortega-Quinonero et al.	CIN 2+ (HPV independent)	Bi-/Quadri-valent	5/103 (4.85)	22/139 (15.83)	4.8% vacc vs. 15.8% non vacc = HR 0.3	Age 18–65 Vaccination before or after (0–1 month) surgery	Retrospective Follow-up 2 years
	CIN 2 + (HPV 16,18)	Bi-/Quadri-valent	3/51 (5.88)	15/69 (21.74)	5.8% vacc vs. 21.7% non vacc = HR 0.27		
Del Pino et al.	CIN 2+ (HPV independent)	Bi-/Quadri-valent	5/153 (3.27)	12/112 (10.71)	3.3% vacc vs. 10.7% non vacc = HR 0.31	Age 26–64 Vaccination after (0–12 months) surgery	Prospective Follow up 22.4 months median

	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall		
Joura et al.	+	+	+	+	?	!	+	Low risk
Garland et al.	+	+	+	+	?	!	?	Some concerns
Kang et al.	–	+	+	+	–	–	–	High risk
Ghelardi et al.	–	+	+	+	+	–		
Hildesheim et al.	+	+	+	+	–	–		
Pieralli et al.	+	+	+	+	+	+		
Sand et al.	–	–	+	–	–	–		
Petrillo et al.	–	+	+	–	+	–		
Ortega-Quinonero	–	–	+	+	+	–		
Del Pino et al.	–	+	+	+	+	–		

Fig. 2. Overall risk of bias.

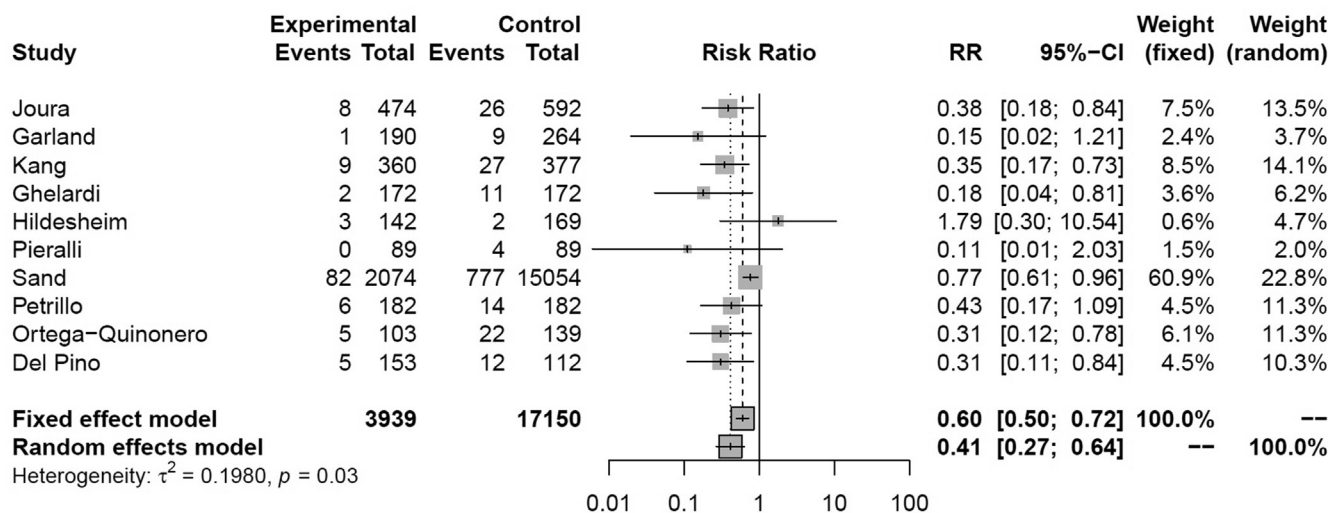


Fig. 3. Meta-analysis of all included studies, HPV independent.

Meta-analysis

Over all studies, the risk of recurrent CIN2+ after conization was 3.1% (121/3,939) with HPV vaccination and 5.3% (904/17,150) without. Random-effects *meta*-analysis showed a significant reduction of CIN2 + recurrence after vaccination with

a relative risk (RR) of 0.41 (95%–CI [0.27; 0.64]) (Fig. 3), independent from HPV type. The reduction of risk is therefore 59% after pre- or postoperative vaccination. Age-dependent analysis showed no differences between women under 25 years (RR 0.47 (95%–CI [0.28; 0.80]) and women of higher age (RR 0.52 (95%–CI

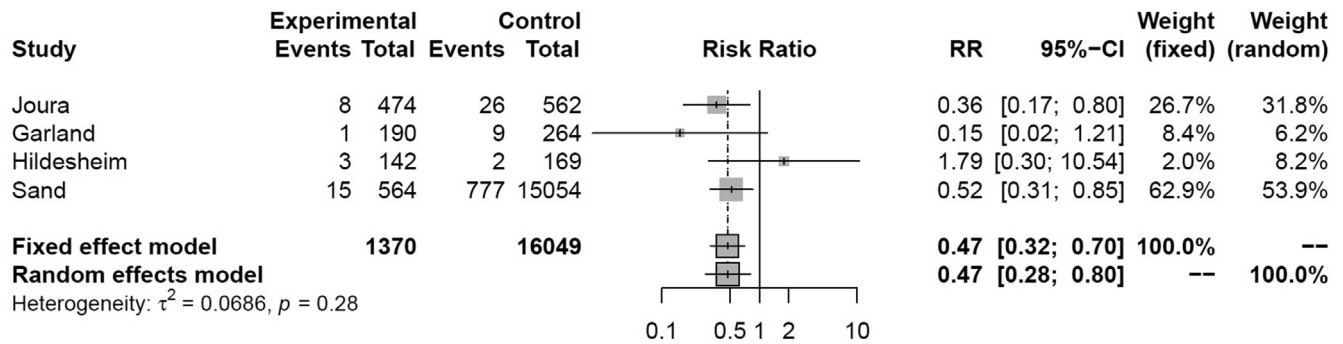


Fig. 4. Supplemental material: Age under 26, HPV independent.

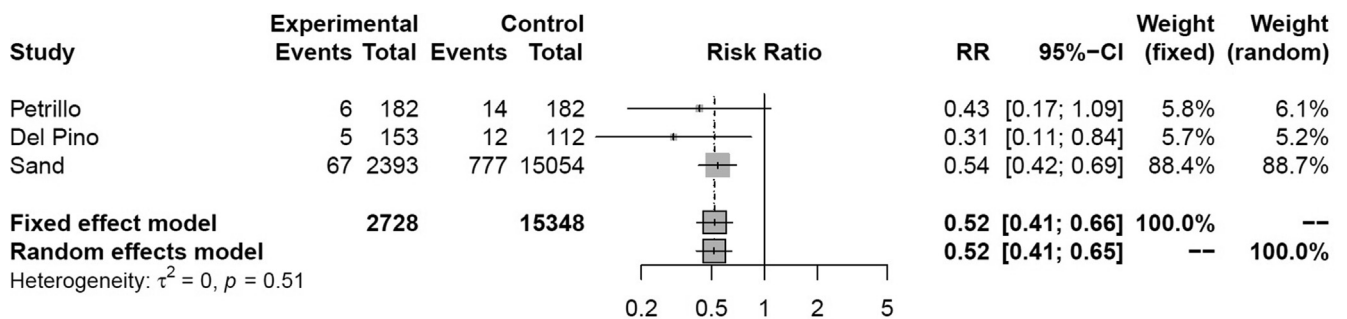


Fig. 5. Supplemental material: Age 26 and older, HPV independent.

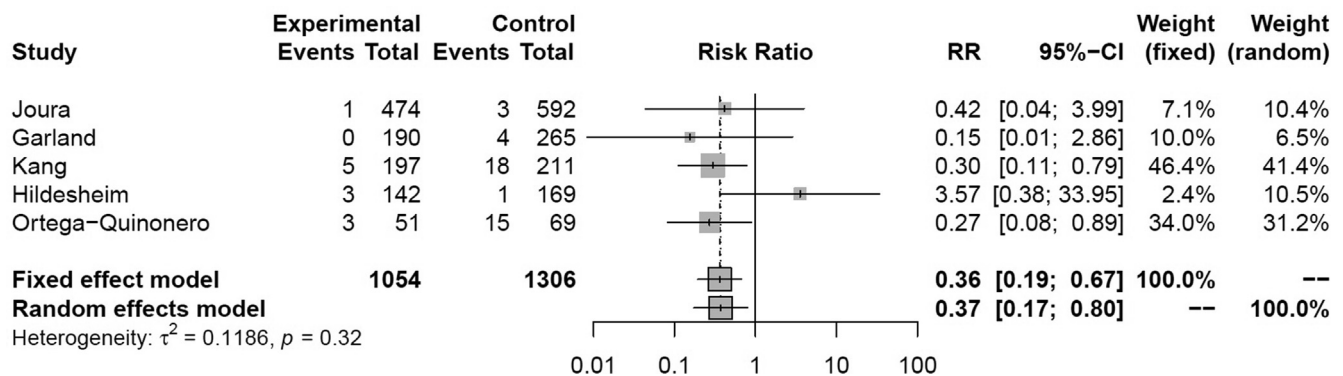


Fig. 6. Supplemental material: HPV 16 and 18.

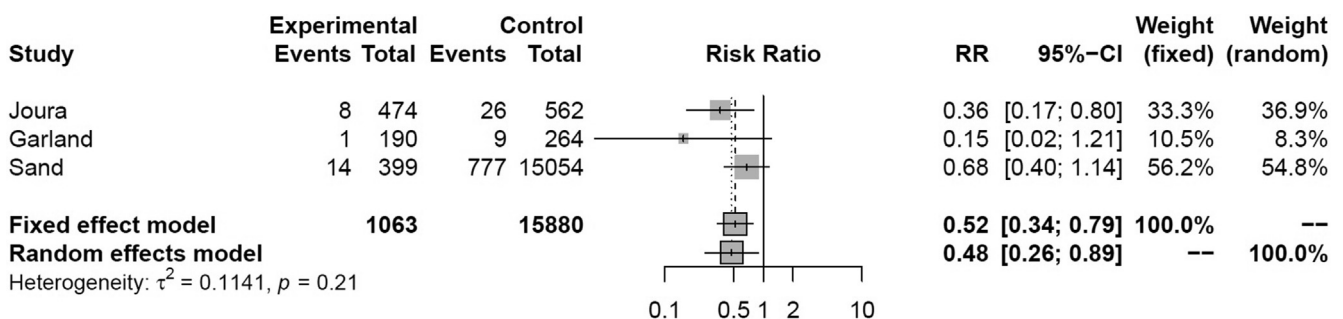


Fig. 7. Supplemental material: Vaccination before conization.

[0.41; 0.65]) (Figs. 4 and 5, supplemental material). Results for HPV 16/18 positive CIN2+ showed a RR of 0.37 (95% CI [0.17; 0.80]) (Fig. 6, supplemental material). Evaluation of time of vaccination and duration of follow-up did not reveal any significant

differences (Figs. 7–10, supplemental material). Overall, the results show that the number of women that would have to be vaccinated before or after conization to prevent one case of recurrent CIN 2+ (NNV) is 45.5.

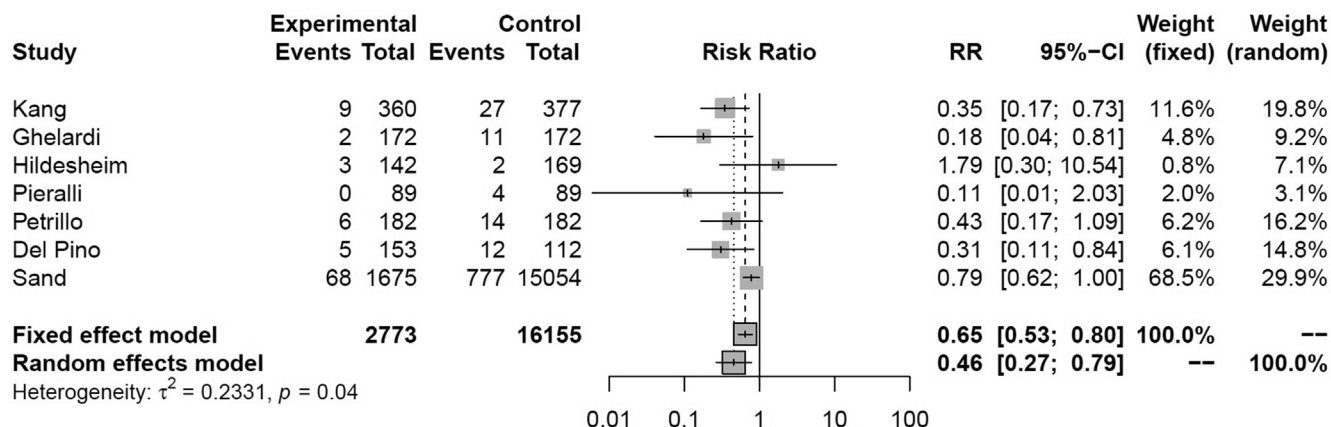


Fig. 8. Supplemental material: Vaccination after conization.

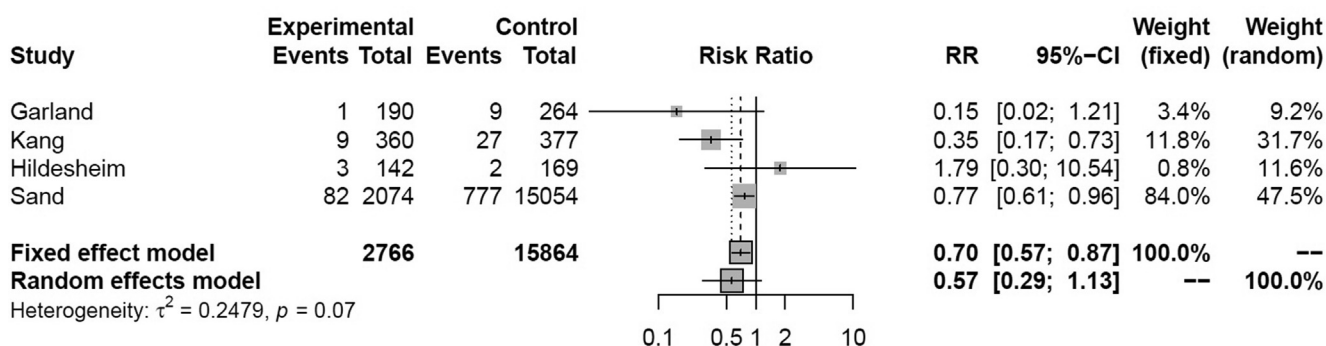


Fig. 9. Supplemental material: Follow-up > 3 years.

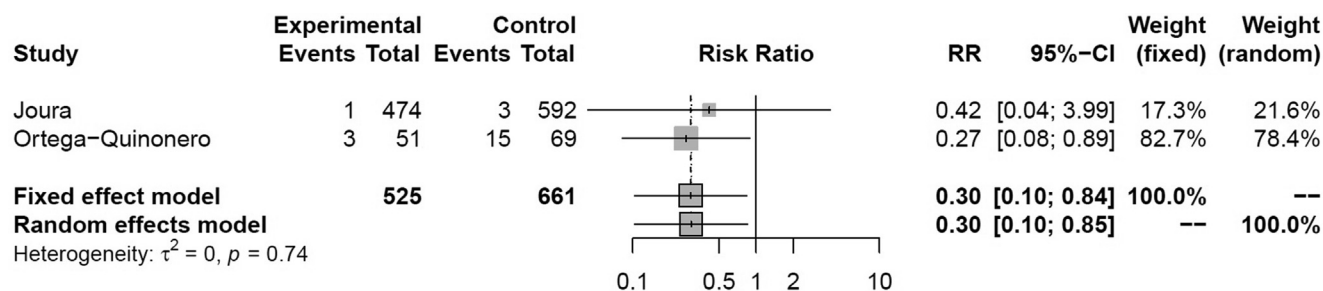


Fig. 10. Supplemental material: Follow-up < 3 years.

4. Discussion

To prevent relapse of cervical intraepithelial neoplasia in the high-risk population of HPV positive women treated with conization, the prophylactic vaccination in the context of surgical treatment could be an additional simple and effective method. The individual benefit of vaccination after primary infection and operative treatment is fairly understood. To clarify the possible gains of vaccination, this *meta-analysis* was performed. Our *meta-analysis* shows an overall risk reduction of developing a new or persisting CIN2 + after conization of 59%.

When looking at the numbers in Germany with about 52,600 conizations per year [24] and the calculated recurrence rate of 5.3% we would expect about 2,790 cases of recurrent high-grade CIN. With an additional prophylactic vaccination after conization this number could be lowered to about 1,630 cases. This would

help about 1,160 women per year to avoid prolonged visits for colposcopies, psychological distress [27] and maybe even prevent cases of invasive cancer after conization.

This protective effect is most pronounced when restricting the analysis to the targeted HPV vaccine genotypes 16 and 18 with a risk reduction of 63%. Besides that the existing data does not reveal any other significant influence on the recurrence rate among the possible cofactors patient age, time of vaccination and duration of follow-up.

Strengths of our analysis include the large size of the cohort (21,059 patients), as well as the prospective study designs in three studies and long follow-up times. On the other hand it has to be kept in mind that there was only one true randomized controlled trial with acceptable quality (Pieralli et al.) designed to measure the outcome of recurrent CIN after conization with only 89 patients in each group. All other studies were either not designed to answer this question or they were not randomized or retrospective studies.

There were also substantial differences regarding inclusion criteria and methodology (e.g. time of vaccination) resulting in significant heterogeneity between studies.

There have been two other *meta*-analyses on the same topic published recently. The *meta*-analysis by Lichter et al. included six studies with a total population of 2,984 women [28]. Five of these are also included in our *meta*-analysis while the trial by Grześ et al. [26] was not included because there was no report available in English. The studies by Del Pino, Ortega-Quinero, Petrillo, Pieralli and Sand were not included in the Lichter analysis. Lichter et al. calculated a relative risk for recurrent CIN 2+ of 0.36 (95%-CI [0.23–0.55]).

The work by Bartels et al. included five studies with 3,562 women which were all also part of our analysis [29]. Again, the studies by Del Pino, Ortega-Quinero, Petrillo, Pieralli and Sand were not included and neither the study by Grześ. The Bartels analysis reported an odds ratio in the favor of vaccination of 0.51 (95%-CI [0.35–0.74]) and a NNV of 43.

The main reason why our systematic review included more studies is the time restriction until January 1, 2019 (Lichter) and June 2019 (Bartels) as the studies by Del Pino, Petrillo and Sand were published in late 2019 and early 2020. Nevertheless, both works by Bartels and Lichter have comparable results to our *meta*-analysis.

5. Conclusion

This *meta*-analysis of ten studies shows a significant reduction of risk for the development of new high-grade cervical intraepithelial lesions after excisional treatment and HPV vaccination with a RR of 0.41 (95%-CI [0.27; 0.64]). The number needed to vaccinate is 45.5.

Further prospective studies are needed to confirm these data and to determine the optimal point of time for vaccination – just before or shortly after vaccination. Our CENTRAL search revealed that there are at least three randomized controlled trials ongoing on this topic: the NOVEL trial in the UK (<https://clinicaltrials.gov/show/NCT03979014>), the VACCINstudy in the Netherlands (<https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-002764-94/NL>) and the COVENANT trial in South Africa (HPV vaccination among HIV-positive women at a see-and-treat program for cervical precancer; <https://clinicaltrials.gov/show/NCT03284866>). All three trials started in 2019 and are using the nonavalent vaccine.

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.

References

- [1] Hillemanns P, Frieze K, Dannecker C, et al. Prevention of Cervical Cancer: Guideline of the DGGG and the DKG (S3 Level, AWMF Register Number 015/0270L, December 2017) - Part 1 with Introduction, Screening and the Pathology of Cervical Dysplasia. *Geburtshilfe Frauenheilkd* 2019;79(2):148–59.
- [2] Hillemanns P, Frieze K, Dannecker C, et al. Prevention of Cervical Cancer: Guideline of the DGGG and the DKG (S3 Level, AWMF Register Number 015/0270L, December 2017) - Part 2 on Triage, Treatment and Follow-up. *Geburtshilfe Frauenheilkd* 2019;79(2):160–76.
- [3] Soergel P, Makowski L, Schippert C, et al. The cost efficiency of HPV vaccines is significantly underestimated due to omission of conisation-associated prematurity with neonatal mortality and morbidity. *Human Vacc Immunotherapeut* 2012;8(2):243–51.
- [4] Kyrgiou M, Koliopoulos G, Martin-Hirsch P, et al. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet* 2006;367(9509):489–98.
- [5] Arbyn M, Ronco G, Anttila A, et al. Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. *Vaccine* 2012;30(Suppl 5):F88–99.
- [6] Strander, B., J. Hällgren, and P. Sparén, Effect of ageing on cervical or vaginal cancer in Swedish women previously treated for cervical intraepithelial neoplasia grade 3: population based cohort study of long term incidence and mortality. *BMJ (Clinical research ed.)*, 2014. 348: p. f7361–f7361.
- [7] Huh WK, Joura EA, Giuliano AR, et al. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16–26 years: a randomised, double-blind trial. *Lancet (London, England)* 2017;390(10108):2143–59.
- [8] Schiller JT, Lowy DR. Understanding and learning from the success of prophylactic human papillomavirus vaccines. *Nat Rev Microbiol* 2012;10(10):681–92.
- [9] Brotherton JM, Winch KL, Bicknell L, et al. HPV vaccine coverage is increasing in Australia. *Med J Aust* 2017;206(6):262.
- [10] Lacy, J., E. Tessier, J. White, et al. Human papillomavirus (HPV) vaccination coverage in adolescent females in England: 2018/19. 2019 21.06.2020; Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/851797/HPV_annual_coverage_report_2018_to_2019.pdf.
- [11] Robert Koch Institut, 2018 Epidemiologisches Bulletin Nr. 1/2018. Aktuelles aus der KV-Impfsurveillance – Impfquoten ausgewählter Schutzimpfungen in Deutschland. Berlin.
- [12] Group, F.I.I.S., J. Dillner, S.K. Kjaer, et al., Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial, *BMJ (Clinical research ed.)*, 2010. 341, p. c3493–c3493.
- [13] Barra F, Della Corte L, Noberasco G, et al. Advances in therapeutic vaccines for treating human papillomavirus-related cervical intraepithelial neoplasia. *J Obst Gynaecol Res* 2020. n/a(n/a).
- [14] Saftlas AF, Spracklen CN, Ryckman KK, et al. Influence of a loop electrosurgical excision procedure (LEEP) on levels of cytokines in cervical secretions. *J Reprod Immunol* 2015;109:74–83.
- [15] Scott ME, Shvetsov YB, Thompson PJ, et al. Cervical cytokines and clearance of incident human papillomavirus infection: Hawaii HPV cohort study. *Int J Cancer* 2013;133(5):1187–96.
- [16] Pieralli A, Bianchi C, Auzzi N, et al. Indication of prophylactic vaccines as a tool for secondary prevention in HPV-linked disease. *Arch Gynecol Obstet* 2018;298(6):1205–10.
- [17] Ghelardi A, Parazzini F, Martella F, et al. SPERANZA project: HPV vaccination after treatment for CIN2+. *Gynecol Oncol* 2018;151(2):229–34.
- [18] del Pino M, Martí C, Torras I, et al. HPV Vaccination as Adjuvant to Conization in Women with Cervical Intraepithelial Neoplasia: A Study under Real-Life Conditions. *Vaccines* 2020;8(2):245.
- [19] Kang WD, Choi HS, Kim SM. Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2–3)? *Gynecol Oncol* 2013;130(2):264–8.
- [20] Petrillo M, Dessole M, Tinacci E, et al. Efficacy of HPV Vaccination in Women Receiving LEEP for Cervical Dysplasia: A Single Institution's Experience. *Vaccines* 2020;8(1):45.
- [21] Ortega-Quinero P, Remezal-Solano M, Carazo-Díaz MC, et al. Impact of the human papillomavirus vaccination on patients who underwent conization for high-grade cervical intraepithelial neoplasia. *Eur J Gynaecol Oncol* 2019;40(3):402–7.
- [22] Hildesheim A, Gonzalez P, Kreimer AR, et al. Impact of human papillomavirus (HPV) 16 and 18 vaccination on prevalent infections and rates of cervical lesions after excisional treatment. *Am J Obstet Gynecol* 2016;215(2):212.e1–212.e15.
- [23] Garland SM, Paavonen J, Jaisamrarn U, et al. Prior human papillomavirus-16/18 AS04-adjuvanted vaccination prevents recurrent high grade cervical intraepithelial neoplasia after definitive surgical therapy: Post-hoc analysis from a randomized controlled trial. *Int J Cancer* 2016;139(12):2812–26.
- [24] Joura EA, Garland SM, Paavonen J, et al. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. *BMJ* 2012;344:e1401.
- [25] Sand FL, Kjaer SK, Frederiksen K, et al. Risk of cervical intraepithelial neoplasia grade 2 or worse after conization in relation to HPV vaccination status. *Int J Cancer* 2019.
- [26] Grześ B, Heimrath J, Cizek M. Minimally invasive surgery with the complementing immunotherapy in the treatment of intraepithelial neoplasia of cervix in women of child-bearing age. *Onkologia Polska* 2011;14.
- [27] Jentschke M, Lehmann R, Drews N, et al. Psychological distress in cervical cancer screening: results from a German online survey. *Arch Gynecol Obstet* 2020.
- [28] Lichter K, Krause D, Xu J, et al. Adjuvant Human Papillomavirus Vaccine to Reduce Recurrent Cervical Dysplasia in Unvaccinated Women: A Systematic Review and Meta-analysis. *Obstet Gynecol* 2020;135(5):1070–83.
- [29] Bartels HC, Postle J, Rogers AC, et al. Prophylactic human papillomavirus vaccination to prevent recurrence of cervical intraepithelial neoplasia: a meta-analysis. *Int J Gynecol Cancer* 2020;30(6):777.