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The incidence of human papillomavirus infection following treatment for cervical neoplasia: A systematic review

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Abstract

Objective—To systematically review the published literature in order to estimate the incidence and describe the variability of human papillomavirus (HPV) infection in women following treatment for cervical neoplasia.

Methods—Several scientific literature databases (e.g. PubMed, ISI Web of Science) were searched through January 31, 2012. Eligible articles provided data on (i) baseline HPV infection status within 6 months prior to or at time of treatment (pre-treatment); and (ii) HPV test results for women's first visit after treatment occurring within 36 months (post-treatment). We abstracted and summarized the post-treatment incidence of newly detected HPV genotypes that were not present at pre-treatment, overall and stratified by study and other population characteristics.

Results—A total of 25 studies were included, reporting post-treatment HPV incidence in nearly 2000 women. Mean patient age ranged from 31 to 43 years (median 36). Most studies used cervical exfoliated cell specimens to test for HPV DNA (n = 20; 80%), using polymerase chain reaction (n = 21; 84%). Cervical neoplasia treatment included loop electrical excision procedure (n = 11; 44%); laser conization (n = 2; 8%); laser ablation, surgical conization, cryotherapy, alpha-interferon (n = 1; 4% each); or multiple treatment regimens (n = 8; 32%). Follow-up times post-treatment ranged from 1.5 to 36 months (median 6). More than half of studies (n = 17; 68%)

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estimated the incidence of any HPV type following treatment, while 7 (28%) focused specifically on high-risk (HR) HPV. HPV incidence after treatment varied widely, ranging from 0 to 47% (interquartile range: 0%-15%) in up to 3 years of follow-up after treatment. Lower HPV incidence was observed among studies that included relatively younger women, used laser conization, focused on HR-HPV rather than overall HPV infection, and had a lower proportion of recurrent cervical disease.

Conclusions—These modest summary incidence estimates from the published literature can guide clinicians, epidemiologists and health economists in developing best practices for post-treatment cervical cancer prevention.

Keywords

Human papillomavirus; Incidence; Post-treatment; Cervical neoplasia; LEEP; Cryotherapy

Introduction

Cervical cancer remains a leading cause of morbidity and mortality in women worldwide [1,2]. It is caused by the acquisition and persistence of high-risk (oncogenic) types of human papillomavirus (HR-HPV) infection and the subsequent malignant transformation of cervical epithelial cells [3]. To prevent progression of these cervical precancerous lesions to invasive cancer, women with cervical intraepithelial neoplasia (CIN) grade 2/3 are commonly treated using ablative and excisional treatment modalities such as laser ablation, loop electrical excision procedure (LEEP), cryotherapy, and cold-knife conization [4]. Women previously treated for CIN 2/3 and those with HR-HPV infections post-treatment have an increased risk of subsequent high-grade neoplasia and invasive cervical cancer as compared with women in the general population [5–8].

Recurrent CIN may result from the inadequate treatment of precancerous cervical lesions or treatment failure, re-infection with an HR-HPV type, incomplete removal of latent HPV infections or long-term persistence of HR-HPV infections not associated with the previously treated cervical lesion [9–11]. Therefore, continued monitoring of women following cervical treatment is currently recommended. American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines recommend follow-up HPV testing at 6 to 12 months for women treated for CIN 2/3 [4], since women at highest risk for recurrent cervical disease are those with positive post-treatment HPV test results [12]. Post-treatment screening with cytology alone, or in combination with colposcopy, at 6-month intervals are alternative recommended approaches [4].

Despite the growing use of HPV testing for post-treatment follow-up, there are currently no summary data on the burden of newly detected HPV infections following treatment for CIN. Therefore, we conducted a systematic literature review to describe study- and population-specific factors that may contribute to the magnitude and variability of estimates of HPV incidence following cervical treatment. The focus of this review is on newly detected HPV genotypes that were not detected prior to or at cervical treatment, which most likely represent newly acquired or newly reactivated latent infections, as opposed to type-specific reinfection or infections associated with incomplete excision of precancerous lesions.

Methods

Literature search strategy

We searched PubMed, EMBASE, ISI Web of Science, Cochrane Library, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) through January 31, 2012 without date or language restrictions to identify peer-reviewed articles reporting incident HPV data from women treated for HPV-associated cervical neoplasia. Our keyword search was designed in consultation with a reference librarian at the University of North Carolina Health Sciences Library. The search contained a combination of terms including HPV (i.e., HPV, papillomaviridae, human papillomavirus, papillomavirus infection), cervical neoplasia (i.e., cervical neoplasms, cervical cancer, cervical neoplasia, cervical intraepithelial neoplasia), occurrence (i.e., incidence, newly detected, persistence, clearance, duration, epidemiology, cohort study), and treatment- or screening-related terms (i.e., post-treatment, follow-up, over time, long-term, therapeutics, cryotherapy, LEEP, laser, and colposcopy).

Citations were imported into a reference managing software program (EndNote X5, Thomson Reuters) and duplicate citations were removed. Backward citation tracking was used to ensure appropriate keywords were selected for the literature search and resulted in modification of these terms followed by an updated search of databases. Titles and abstracts of search results were selected for full-text evaluation with respect to two inclusion criteria: (i) women receiving treatment for cervical neoplasia; and (ii) post-treatment HPV acquisition data.

Eligibility criteria

Eligible articles provided data on HPV infection within 6 months prior to or at time of treatment (i.e., pre-treatment time point) and incident HPV detection occurring during follow-up, with the first follow-up visit with HPV test results occurring within the first 36 months post-treatment. Thus, it must have been clear in the article that an HPV infection was newly detected in the post- compared to pre-treatment period. The majority of results were type-specific, based on HPV genotyping assays, although four studies used non-type-specific Hybrid Capture II among pre-treatment HPV-negative women, where a positive result would indicate a new HPV type.

Studies of women with human immunodeficiency virus (HIV) infection were only included if HPV data were available on the HIV-negative subpopulation. Articles that did not state HIV serostatus were assumed to be HIV-negative and thus included. Studies that included women treated for invasive cervical carcinoma (ICC) in their study population were included only if HPV data were also available on the subset of women treated for earlier stages of CIN. Studies that tested for cervical HPV infections using polymerase chain reaction (PCR) and hybrid capture DNA were included. HPV serology-only studies and studies that included only anal, vulvar or labial specimens were excluded. Studies that reported exclusively on men, oral HPV infection or oral cancer, animal studies, or simulation studies were ineligible.

Data abstraction

From articles meeting our inclusion criteria, we abstracted data on study characteristics, participants, cervical treatment type, and pre- and post-treatment HPV infection and testing. Study characteristics included journal of publication, publication date, study dates, study design, geographic region, and sample size. Participant characteristics included age and population description (e.g., clinical patients, population-based screening participants). Treatment characteristics included methods used to grade cervical lesions (cytology vs. histology), grade of cervical lesions at time of treatment (e.g., CIN 1, CIN 2, and CIN 3), and treatment type. HPV infection and testing characteristics included HPV specimen type (cervical cells vs. biopsy), HPV testing method (PCR vs. hybrid capture 2), specific HPV types tested, HPV testing time relative to treatment, pre-treatment HPV prevalence in the study population, and if applicable, pre-treatment HPV types in HPV-positive women. Post-treatment characteristics included unit of analysis for incidence results (i.e., women, infections), follow-up HPV testing intervals, number of incident HPV infections reported, post-treatment incident HPV types, and stage of post-treatment cervical disease. All data were independently double-abstracted to ensure data accuracy.

Definition of HPV incidence measures

Incident HPV infections were defined as detection of a new genotype after treatment for cervical neoplasia that was not present before or at the time of treatment. For example, a woman who was HPV 18 positive at pre-treatment, received treatment, and tested positive for HPV 16 following treatment would be classified as having a post-treatment incident HPV 16 (type-specific) infection. Among populations of women with a completely HPV-negative result before or at the time of treatment, incidence was defined as any positive HPV test result at a post-treatment visit.

HPV incidence estimation

To estimate the incidence of HPV infection in women following treatment for cervical neoplasia, the number of women with newly detected (type-specific) HPV infections and the number of women in each subgroup were used to calculate the HPV incidence with corresponding Mid-P exact 95% confidence limits for each study [13]. Most studies report HPV incidence measured at a specific time point (incidence proportion); however if only HPV incidence up to and including a specific time point (cumulative incidence) estimates were reported, these were abstracted. Incidence estimates were categorized by pre-treatment HPV status in the study population: (i) a population or subgroup of women who all tested negative for all HPV prior to or at the time of treatment (pre-treatment HPV negative); (ii) a population or subgroup where some women tested HPV-positive and some tested HPV-negative prior to or at the time of treatment (mixed HPV pre-treatment status); and (iii) a population or subgroup of women who all tested positive for HPV prior to or at the time of treatment (pre-treatment HPV positive).

HPV incidence estimates were graphically displayed according to study and population-specific characteristics and corresponding study follow-up time. HPV incidence estimates calculated using less than 5 women were not graphically displayed, although they are presented in the tables.

Results

Eligible studies

Of the 2549 abstracts identified, 166 full-text articles were screened, and a total of 26 studies met the inclusion criteria (Fig. 1). One study [14] included cohorts previously described in two other eligible studies [7,15]. One eligible study was excluded, as it reported HPV incidence rate ratios in treated compared to untreated women, but did not report HPV incidence data for treated women alone [16].

The 25 included studies provided estimates on post-treatment HPV incidence in nearly 2000 women. Most studies were conducted in Europe (n = 14; 56%) and Asia (n = 5; 20%), with 8% (n = 2) from South America and 4% (n = 1) each from North America, Africa, the Middle East, and multiple regions (Table 1). Eighty-eight percent (n = 22) of eligible studies were cohort studies, though two randomized controlled trials [15,17] and one case–control study [18] were also included. Study participants were recruited primarily through clinical settings (n = 19; 76%) although 16% (n = 4) included women referred from population-based screening programs. Mean patient age ranged from 31 to 43 years (median 36), and mean age was not reported for two studies [19,20]. Most studies (n = 20; 80%) used cervical cell specimens as opposed to biopsy specimens to test for HPV DNA, and 84% (n = 21) of studies used PCR to detect HPV infection. Sixty percent (n = 15) provided HPV incidence in populations entirely HPV positive at the time of treatment, 48% (n = 12) of studies provided an estimate of HPV incidence in a population that was completely HPV negative at the time of cervical treatment, and 60% (n = 15) reported estimates in a population with pre-treatment mixed HPV status.

The majority of studies (n = 24; 96%) used histology to diagnose cervical neoplasia (Table 1). While 48% (n = 12) provided estimates of HPV incidence in populations treated for CIN 2/3 and 32% (n = 8) had populations treated for CIN 1/2/3, other studies provided estimates in women with specifically CIN 1 (n = 2, 8%), CIN 2 (n = 3, 12%), or CIN 3 (n = 6, 24%). One study treated women who had acetowhite lesions detected using visual inspection with acetic acid (VIA) [17]. There was heterogeneity in treatment type among the studies: 44% (n = 11) used LEEP; 8% (n = 2) used laser conization; 4% (n = 1) each used laser ablation, surgical conization, cryotherapy and alpha-interferon; and 32% (n = 8) used multiple treatment regimens.

Post-treatment HPV incidence

Follow-up time for measuring HPV incidence ranged from 1.5 to 36 months (median 6) following cervical treatment (Table 2). Sixty-eight percent (n = 17) of studies estimated any-HPV type incidence following treatment for cervical neoplasia, while 28% (n = 7) of studies focused specifically on HR-HPV infection. In most cases, studies reported the HPV incidence proportion at the specific time point, however, three studies reported the cumulative incidence of HPV over a period of time [17,21,22]. Some studies solely provided an HPV incidence estimate for their entire study population, while other studies provided sufficient data to calculate separate HPV incidences for different subgroups, such as pre-

treatment HPV negative patients, pre-treatment HPV positive patients, those with particular stages of pre-treatment cervical disease, and those with residual or recurrent disease.

Estimates of HPV incidence for whole study populations and reported subpopulations are presented in Table 2. In 14 studies, HPV incidence was 0% over follow-up periods ranging from 2 to 31.8 months post-treatment among subpopulations of women who were pre-treatment HPV negative [6,23–28], of mixed HPV status [7,19,28–30], or HPV positive [20,28,30–32]. Only two small subpopulations of women, both of which were pre-treatment HPV negative, reported HPV incidences of 100% at 3 months [20] and at 4 months [22] post-treatment. Of the 25 total studies, 16 (64%) specifically reported the incidence of HPV types 16 and 18 (see Supplemental Table 1), finding only 3 incident cases of HPV 16/18 among 32 women negative for HPV 16/18 at the pre-treatment visit. HPV 16/18 incidence ranged from 0% [6,7,19,23,28,30] to 29% [20] among populations of women with mixed pre-treatment HPV statuses and from 0% [7,20,23,28,30–32] to 20% [20,32] among pre-treatment HPV-positive women over 2–19 months of post-treatment follow-up.

Age-stratified post-treatment HPV incidence

Among studies with a mean patient age at treatment of 30–34 years, HPV incidence estimates were fairly low up to 19 months post-treatment, with estimates ranging from 0% to 5% (Fig. 2). There was more variation at 24 months post-treatment: one study among women with pre-treatment mixed HPV status found an HPV incidence of 5% [14], while another found HPV incidence of 30% among pre-treatment HPV negative women and 47% among pre-treatment HPV positive women [21].

In studies with a mean patient age of 35–39 years, HPV incidence ranged from 0% to 18% at 2 to 6 months post-treatment and from 0% to 24% >6 to 35 months post-treatment. Of the three studies where the mean age was 40–44 years and HPV incidence estimates included at least 5 women, one study reported no incident HPV infections [28], one reported HPV incidence of 24% at 6 months [18], and another found an increasing cumulative HPV incidence over time from 6% at 6 months to 13% at 36 months post-treatment [17].

Treatment-stratified post-treatment HPV incidence

The majority of HPV incidence estimates were among women treated for cervical neoplasia using LEEP (Fig. 3), where HPV incidence ranged from 0% to 18% at 2 to 6 months post-treatment and 0% to 24% at >6 to 35 months post-treatment. Among women treated with laser conization, HPV incidence appeared relatively lower: one study found no incident HPV infections at 3, 6, or 12 months post-treatment [26], and another found HPV incidences of 1% in pre-treatment HPV positive women and 7% in pre-treatment HPV negative women after a longer follow-up duration of 35 months [33]. Only one study used laser ablation, and found an incidence of 15% in all women and 0% in pre-treatment HPV positive women at 3 months [20]. One study that used surgical conization found cumulative HPV incidences ranging from 6% at 6 months to 13% at 36 months [17], while another that used alpha-interferon found no incident HPV infections at 2 months [19]. Studies that utilized multiple treatment modalities reported a wider range of HPV incidences, ranging from 0% to 24% at 2 to 6 months and 0% to 47% at 6 to 24 months. The three highest HPV incidence estimates

(24% at 6 months, 30% at 24 months, 47% at 24 months) were all found by studies using multiple treatment regimens. Stratification by cervical disease status (CIN 1/2/3 vs. CIN 2/3) did not produce any clear patterns over follow-up time (Supplemental Fig. 1). However, women with recurrent cervical disease tended to have higher HPV incidence, as opposed to total study populations, ranging from 0% to 29% at 2 to 6 months and 3% to 47% at 14 to 24 months (Supplemental Fig. 2).

Post-treatment HPV incidence stratified by HPV type

Most studies measured any incident HPV type that was included in the diagnostic assay used (Fig. 4). However, incidence estimates from a subset of studies specific to HR-HPV (n = 7), which varied in number and genotypes included in the HR-HPV subset, tended to be somewhat lower than those including all HPV types as would be expected, ranging from 0% to 24% at 3 to 11 months; and 2% to 21% at 12 to 36 months. One study examined only HPV types 6 and 16 and found noincident infections over two months of follow-up [19].

Discussion

Post-treatment HPV testing as confirmation of successful cervical treatment may allow women to return to routine, extended cervical cancer screening intervals. However, it is important to distinguish between and understand differences in the incidence and natural history of newly detected HPV genotypes compared to recurrent detection of lesion-associated HPV genotypes. Little is known about the frequency of newly detected HPV genotypes following treatment for cervical precancer and cancer, yet these estimates are important for determining the optimal use and interpretation of post-treatment HPV screening results, and may also aid in determining whether vaccination may have any benefit in these women. In this systematic literature review summarizing 25 studies with post-treatment HPV data on over 2000 women, most studies reported low, although non-negligible estimates of HPV incidence even over relatively short periods of follow-up. Estimates of post-treatment HPV incidence varied by patient and treatment-related variables. Specifically, HPV incidence estimates appeared lower among populations of women treated with laser conization compared to those treated with LEEP, relatively younger aged women, and among women without recurrent cervical disease. Women with pre-treatment HPV infections had higher incidence of post-treatment HPV infections compared to women who were HPV negative at or before treatment.

Women who have previously developed cervical disease may be more likely to develop subsequent cervical precancer and cancer than women without previous disease and treatment [34]. Although a substantial proportion of post-treatment precancer and cancers likely result from incomplete excision of the lesion or persistence of the lesion-associated HPV type, women are also at risk of developing a second cervical precancer due to the acquisition and persistence of newly acquired HPV types. Unfortunately, data on type-specific HPV infection associated with development of cervical disease after treatment are limited [35–38] and most studies have focused on, or did not distinguish between, recurrent or residual cervical disease outcomes rather than newly acquired HPV associated-lesions. In addition, the natural history of newly detected HPV infections likely differ from persistent

post-treatment infections and may require a longer follow-up period to assess true risk of disease. Thus, in this review, we take the first step to summarize the burden of newly acquired HPV genotypes after cervical treatment. Our review indicates that in studies with up to 36 months of follow-up after treatment, HPV incidence ranges widely from 0% to 47%, with most published estimates ranging from 0% to 15%. These incidence estimates suggest a need to better understand the risk and timing of new high-grade cervical precancer following treatment for cervical disease.

Our summary of newly detected HPV 16 and 18 after treatment (Supplemental Table 1) are valuable as the research continues regarding the utility of HPV vaccination at the time of treatment. Although this literature review clarifies that the frequency of incident HPV-16/18 infections is non-negligible among women post-treatment, they are observational data which give no indication of the efficacy of HPV vaccination post-treatment. However, recent evidence from a retrospective analysis of a subset of young women aged 15–26 years from two randomized control trials of prophylactic HPV vaccination [39], and from men treated for high-grade anal disease [40], highlight the potential for HPV vaccination to prevent subsequent disease after treatment. In a prospective study of vaccination after LEEP, the risk of recurrent disease was significantly higher in the unvaccinated women (adjusted hazard ratio: 2.84 and 95% confidence interval: 1.34–6.04) [41]. Previous studies suggest that vaccination provides no therapeutic benefit for those already infected with HPV vaccine types so it is likely that any observed benefit from post-treatment vaccination would be due to prevention of incident HPV infections after treatment. These incident infections may reflect newly reactivated latent HPV rather than truly new HPV infections, particularly in older women [42].

The mean ages of the study populations in this review ranged from 31 to 43 years, with a median of 36 years. Patterns of newly detected HPV genotypes after cervical treatment seem to indicate a slight trend of lower incidence in younger aged populations, in contrast to the higher HPV incidence observed in younger compared to older women in the general population [43,44]. Explanations for these observed differences are not clearly understood, but could possibly be attributable to immunological differences between younger and older women. Although this review includes data on women aged 18 to 82 years of age, data were extremely limited from populations of women with a mean age of 40 years and older, with only 3 available studies. Thus, additional literature is needed regarding post-treatment HPV incidence in populations of perimenopausal and older women.

A recent meta-analysis found that the sensitivity of HR-HPV testing was higher than cytology at detecting high-grade post-treatment disease, but with a slightly lower corresponding specificity [45]. Data from cost-effectiveness analysis suggests that HPV testing combined with cytology under a select protocol, as opposed to cytology only, would reduce the cost and number of colposcopies post-treatment [46]. Together, these studies support inclusion of HR-HPV testing in screening algorithms after cervical treatment. However, previous cost-effectiveness analyses or studies of sensitivity, to our knowledge, have not examined the role of HPV genotyping to distinguish between HR-HPV infections that were present pre-treatment versus those that were newly detected HPV types, as we have done in this review. If the risk of developing cervical precancer or cancer after

treatment associated with persistent pre-treatment HPV genotypes differs from newly detected genotypes [35], then more data are needed to determine if type-specific HPV testing could potentially improve the sensitivity and specificity of HPV detection in screening for post-treatment cervical disease.

Strengths of our study include a systematic approach, with a large sample size of women with data on HPV incidence. Given a priori evidence regarding the potential heterogeneity of study and population characteristics on the natural history of HPV infection, we did not conduct a statistical meta-analysis of HPV incidence estimates post-treatment. Furthermore, twelve studies included a relatively small number of women (Table 2) with HPV-negative CIN pre-treatment (one study specifically focused on HPV-negative, VIA-positive women [17]). Since these cases likely differ, for example representing regressing lesions, from those with detectable HPV, we present stratified results. In addition, it is possible that HPV detection prior to or at the time of treatment missed an HPV genotype that was actually present or recently became undetectable, in which case, its detection post-treatment is not truly new. This potential source of misclassification may be most evident in the cases of HPV-negative CIN. In addition, we did not systematically assess HPV serological status of women, an important indicator of previous HPV infection.

The reported HPV incidence estimates are absolute measures of frequency and do not provide specific information regarding statistical or causal relationships among factors which may influence post-treatment HPV incidence. Because there were small numbers of women in many of the subgroups, HPV incidence estimates are relatively unstable for several studies included in this review, as indicated by relatively wide confidence limits. However, clinically relevant trends were consistently observed within large studies, including an increase in HPV incidence over follow-up time [17,22]. Patterns were also observed across studies, such as the low incidence of HPV in women treated by laser conization [26,33] relative to other treatment modalities.

By providing summaries of post-treatment HPV incidence by key factors, we aim here to inform clinicians, researchers, and health economists about the burden of newly detected HPV infections among women following treatment for cervical disease. The current ASCCP recommendation following treatment for CIN 2/3 in women 25 years and older is the use of HPV testing with cytology (cotesting) at 12 and 24 months[47]. As HPV genotyping assays become increasingly utilized in clinical practice, further research will be needed to determine whether type-specific HPV results can improve the identification of women most at risk of developing cervical disease after treatment since this systematic review highlights that new HPV infections are a potential source for future disease risk after treatment for cervical precancer and cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Women with post-treatment HPV have a higher risk of subsequent cervical precancer.
- This review of post-treatment HPV included nearly 2000 women from 25 studies.
- Post-treatment HPV incidence ranged from 0 to 47% in up to 3 years of follow-up.

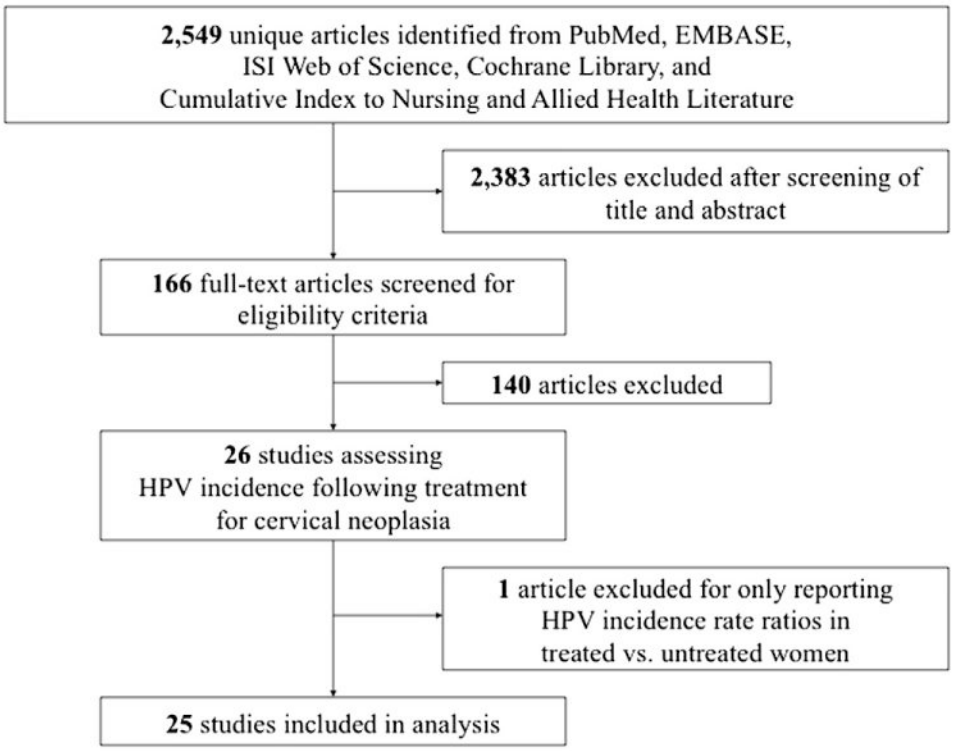

Fig. 1.
Identification and selection of eligible studies.

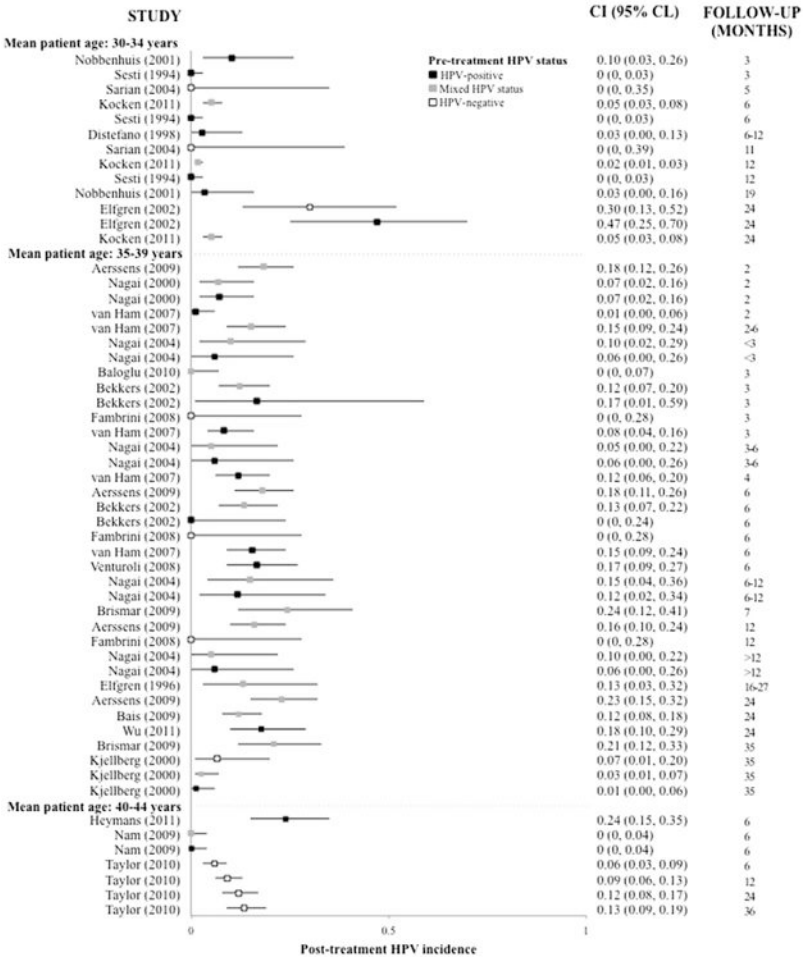

Fig. 2.

Post-treatment HPV incidence, stratified by mean patient age at treatment.

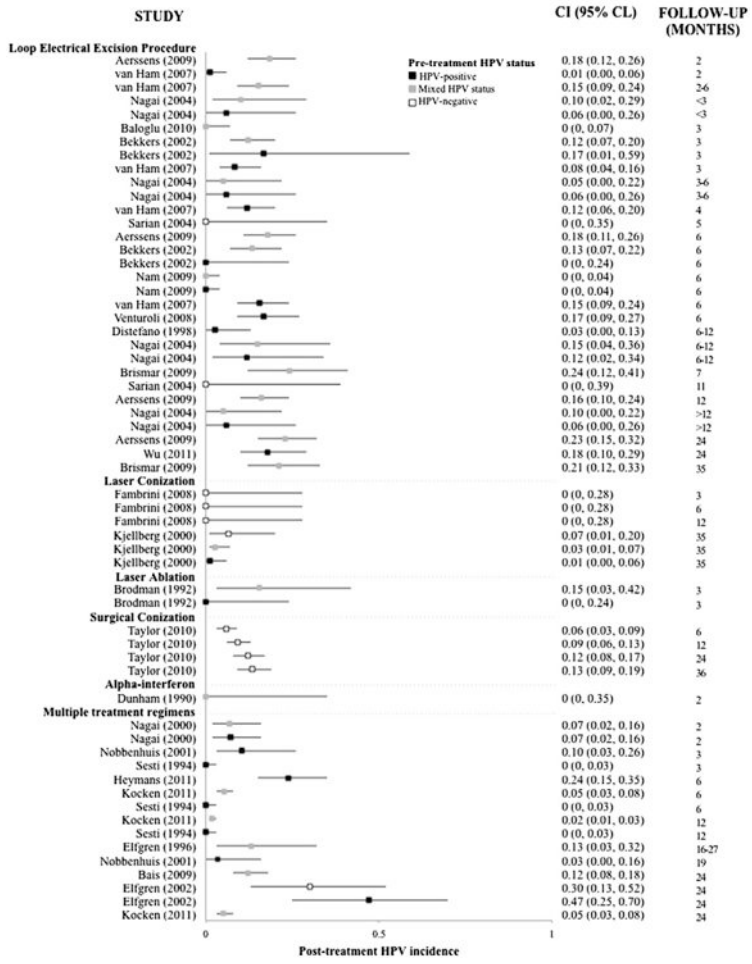

Fig. 3.

Post-treatment HPV incidence, stratified by cervical neoplasia treatment type.

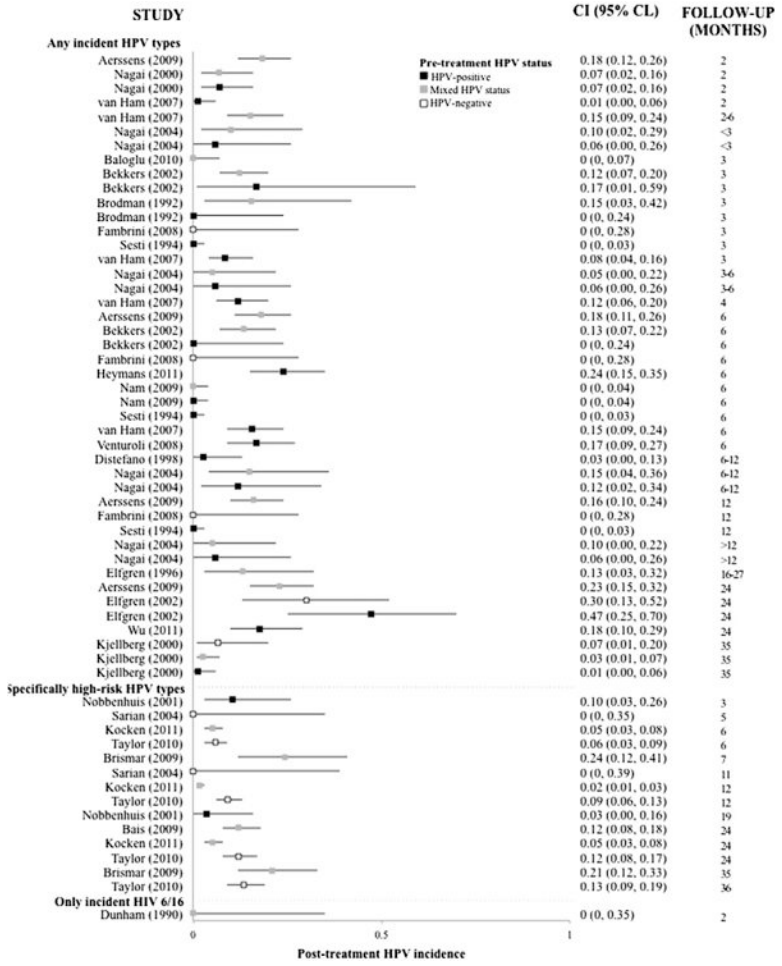

Fig. 4.

Post-treatment HPV incidence, stratified by incident HPV types reported.

Table 1

Descriptive characteristics of 25 studies with human papillomavirus incidence data following treatment for cervical neoplasia.

	No. of studies (%)	References
Study characteristics		
Study design		
Cohort	22 (88)	[6,7,14,19–33,48–51]
Randomized controlled trial	2 (8)	[15,17]
Case–control	1 (4)	[18]
Study region		
Europe	14 (56)	[7,14,15,18,19,21,22,26,29,31,33,48–50]
Asia	5 (20)	[6,23,25,28,51]
South America	2 (8)	[24,32]
North America	1 (4)	[20]
Africa	1 (4)	[17]
Middle East	1 (4)	[30]
Multi-region[a]	1 (4)	[27]
Population characteristics		
Study population		
Clinical patients	19 (76)	[6,7,14,19–21,23–28,30–32,48–51]
Screening program referrals	4 (16)	[18,22,29,33]
Randomized controlled trial participants	2 (8)	[15,17]
Mean age of study populations in years[b]		
30–34	6 (24)	[7,14,21,24,31,32]
35–39	13 (52)	[6,15,22,23,26,27,29,30,33,48–51]
40–44	4 (16)	[17,18,25,28]
Unspecified	2 (8)	[19,20]
HPV testing		
HPV specimen type		
Cervical cells	20 (80)	[6,7,14,15,17,18,21,23–28,30,31,33,48–51]
Biopsy	3 (12)	[19,20,32]
Cervical cells and/or biopsy	2 (8)	[22,29]
HPV detection method		
PCR	21 (84)	[6,7,14,15,18–23,26,27,29–33,48–51]
Hybrid capture 2	4 (16)	[17,24,25,28]
Pre-treatment HPV prevalence[c,d]		
Completely HPV negative	12 (48)	[6,17,20–28,33]
Mixed, incident type negative	15 (60)	[6,7,14,15,19,20,22,23,27–30,33,48,49]
Positive, incident type negative	15 (60)	[6,7,18,20–23,28–33,50,51]
Treatment characteristics		
Diagnostic method		
Histology	24 (96)	[6,7,14,15,18–33,48–51]

	No. of studies (%)	References
Cytology	1 (4)	[17]
Stage at treatment[c,e]		
VIA positive	1 (4)	[17]
CIN 1	2 (8)	[20,32]
CIN 1/2	1 (4)	[20]
CIN 1/2/3	8 (32)	[19,21,30–33,48,50]
CIN 2	3 (12)	[20,29,32]
CIN 2/3	12 (48)	[14,15,18,22,24–29,49,51]
CIN 3	6 (24)	[6,7,22,23,29,32]
Treatment type		
LEEP[f]	11 (44)	[22–24,27–30,32,48,50,51]
Laser conization	2 (8)	[26,33]
Laser ablation	1 (4)	[20]
Surgical conization	1 (4)	[25]
Cryotherapy	1 (4)	[17]
Alpha-interferon	1 (4)	[19]
Multiple treatment regimens	8 (32)	[6,7,14,15,18,21,31,49]
HPV outcome ascertainment		
Unit of analysis for incidence results		
Women	25 (100)	[6,7,14,15,17–33,48–51]
HPV testing interval for first incident infection		
<6 months	14 (56)	[6,7,19–24,26,27,29–31,48]
6–12 months	8 (32)	[14,17,18,25,28,32,50,51]
>12 months	3 (12)	[15,33,49]
Reported incident HPV types		
Any HPV	17 (68)	[6,18,20–23,26–33,49–51]
Specifically HR-HPV	7 (28)	[7,14,15,17,24,25,48]
Only HPV 6/16	1 (4)	[19]

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HR-HPV, high-risk HPV; LEEP, loop electrical excision procedure; PCR, polymerase chain reaction; VIA, visual inspection with acetic acid.

[a] Multi-region = Belgium and Nicaragua.

[b] References [14,18] reported median age instead of mean age. For references [15,17], mean age was estimated from reported age distributions using the midpoint for each age category. Reference [29] did not report mean age, however this data was reported in a related publication [52].

[c] A study can be listed in more than one category if they reported estimates for various patient subgroups, therefore the number of studies may sum to >100%.

[d] Pre-treatment HPV prevalence refers to the prevalence of HPV infection within 6 months prior to or at the time of cervical treatment.

[e] 54% of women in Reference [20] had koilocytosis.

[f] The LEEP category also includes studies that described treatment as large loop excision of the transformation zone (LLETZ) or diathermic large loop excision (DLLE); Reference [48] included one woman treated with cryotherapy.

Table 2

Study-specific characteristics and post-treatment human papillomavirus incidence estimates from 25 studies.

Author, Year, Country	HPV types tested	Specimen type; detection method	Pre-treatment HPV status	Stage of cervical disease at time of treatment; testing method	Treatment	Stage of post-treatment cervical disease	Post-treatment time (months)	HPV incidence at post-treatment time point (cumulative HPV incidence over post-treatment time point)	95% CL
Pre-treatment HPV negative populations and subpopulations									
Brodman [20] United States	HR- and LR- HPV types: 6, 11, 16, 18, 31, 35, 51	Biopsy; PCR	100% HPV negative	Koilocytosis/CIN 1; Histology	Laser ablation	Koilocytosis, CIN 1	3	2/2 = 1	0.22, 1
Kjellberg [33] Sweden	HR- and LR-HPV types: 11, 16, 18, 33	Cervical cells; PCR	100% HPV negative	CIN 1/2/3; Histology	Laser conization	With and without squamous cell atypia	35.4	2/30 = 0.07	0.01, 0.20
Nagai [6] Japan	HR- and LR-HPV types: 16, 18, 31, 33, 35, 58	Cervical cells; PCR	100% HPV negative	CIN 3; Histology	Surgical or laser conization	Normal cytology	31.8	0/2 = 0	0, 0.78
Elfgren [21] Sweden	HR- (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) and LR- (6, 11, 40, 42, 43, 44) HPV types	Cervical cells; PCR	100% HPV negative	CIN 1/2/3; Histology	Conization or cryotherapy	Not specified	24	6/20 = (0.30)	0.13, 0.52
Nagai [23] Japan	HR- and LR-HPV types, including 6, 11, 16, 18, 30, 31, 33, 34, 35, 39, 42, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 66, 68, 70	Cervical cells; PCR	100% HPV negative	CIN 3; Histology	LEEP	CIN 1	<3	0/3 = 0	0, 0.63
							3–6	0/3 = 0	0, 0.63
							6–12	0/3 = 0	0, 0.63
							>12	0/3 = 0	0, 0.63
Sarian [24] Brazil	HR-HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	Cervical cells; HC II	100% HR-HPV negative	CIN 2/3; Histology	LEEP	Not specified	4.8	0/7 = 0	0, 0.35
							10.9	0/6 = 0	0, 0.39
Song [25] Korea	HR-HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	Cervical cells; HC II	100% HR-HPV negative	CIN 2/3; Histology	Surgical conization	Not specified	6	0/2 = 0	0, 0.78
van Ham [22] Netherlands	HR- and LR-HPV types, including 16, 18, 31, 33, 39, 45, 51, 52, 56, 58	Cervical cells and/or biopsy; PCR	100% HPV negative	CIN 3; Histology	LEEP	ASCUS	4	1/1 = (1)	0.05, 1
Fambrini [26] Italy	HR- (16, 18, 31, 33, 35, 45, 52, 58) and LR- (6, 11) HPV types	Cervical cells; PCR	100% HR-HPV negative	CIN 2/3; Histology	Laser conization	Without cytological abnormalities	3	0/9 = 0	0, 0.28
							6	0/9 = 0	0, 0.28
							12	0/9 = 0	0, 0.28
Aerssens [27] Belgium and Nicaragua	HR- and LR-HPV types, including 16, 31, 51, 52, 58	Cervical cells; PCR	100% HPV negative	CIN 2/3; Histology	LEEP	CIN 2/3	14	0/2 = 0	0, 0.80

Author, Year, Country	HPV types tested	Specimen type; detection method	Pre-treatment HPV status	Stage of cervical disease at time of treatment; testing method	Treatment	Stage of post-treatment cervical disease	Post-treatment time (months)	HPV incidence at post-treatment time point (cumulative HPV incidence over post-treatment time point)	95% CL
Nam [28] Korea	HR- (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68) and LR- group (6, 11, 34, 40, 42, 43, 44, 70) HPV types	Cervical cells; HC II	100% HR-HPV negative	CIN 2/3; Histology	LEEP	Not specified	6	0/4 = 0	0, 0.53
Taylor [17] South Africa	HR-HPV types	Cervical cells; HC II	100% HR-HPV negative	VIA positive; Cytology	Cryotherapy	Not specified	6	15/256[a] = (0.06)	0.03, 0.09
							12	21/229[a] = (0.09)	0.06, 0.13
							24	25/206[a] = (0.12)	0.08, 0.17
							36	28/209[a] = (0.13)	0.09, 0.19
Pre-treatment mixed HPV status populations and subpopulations									
Dunham [19] England	HPV types 6 and 16	Biopsy; PCR	43% HPV 16 positive; 57% HPV negative	CIN 1/2/3; Histology	α-interferon	With and without CIN1/2	2	0/7 = 0	0, 0.35
			40% HPV 16 positive; 60% HPV negative			CIN 1/2	2	0/5 = 0	0, 0.45
Brodman [20] United States	HR- and LR- HPV types: 6, 11, 16, 18, 31, 35, 51	Biopsy; PCR	85% HPV positive; 15% HPV negative	Koilocytosis/CIN 1/2; Histology	Laser ablation	With and without Koilocytosis, CIN 1	3	2/13 = 0.15	0.03, 0.42
			71% HPV positive; 29% HPV negative	Koilocytosis/CIN 1/2; Histology		Koilocytosis, CIN 1	3	2/7 = 0.29	0.05, 0.67
			80% HPV positive; 20% HPV negative	CIN 1; Histology		With and without Koilocytosis, CIN 1	3	1/5 = 0.20	0.01, 0.67
Elfgren [49] Sweden	HR- and LR-HPV types, including 6, 11, 16, 18, 31, 33	Cervical cells; PCR	78% HPV positive; 22% HPV negative	CIN 2/3; Histology	Surgical or laser conization, or	With and without CIN 1/CIS microneedle diathermy	16–27	3/23 = 0.13	0.03, 0.32
Kjellberg [33] Sweden	HR- and LR-HPV types: 11, 16, 18, 33	Cervical cells; PCR	73% HPV positive; 27% HPV negative	CIN 1/2/3; Histology	Laser conization	With and without squamous cell atypia	35.4	3/112 = 0.03	0.01, 0.07
Nagai [6] Japan	HR- and LR-HPV types: 16, 18, 31, 33, 35, 58	Cervical cells; PCR	97% HPV positive; 3% HPV negative	CIN 3; Histology	Surgical or laser conization	With and without CIN 1/2/3	2	4/58 = 0.07	0.02, 0.16
Nobbenhuis [7] Netherlands	HR-HPV types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	Cervical cells; PCR	100% HR-HPV negative	CIN 3; Histology	LEEP or cone biopsy	CIN 2/3	3	0/3 = 0	0, 0.63
Bekkers [29] Netherlands	HR- and LR-HPV types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 54, 56, 58, 59, 68	Cervical cells and/or biopsy; PCR	93% HR-HPV positive; 7% HR-HPV negative	CIN 2/3; Histology	LEEP	With and without CIN 1/2/3	3	11/90 = 0.12	0.07, 0.20
							6	12/90 = 0.13	0.07, 0.22

Author, Year, Country	HPV types tested	Specimen type; detection method	Pre-treatment HPV status	Stage of cervical disease at time of treatment; testing method	Treatment	Stage of post-treatment cervical disease	Post-treatment time (months)	HPV incidence at post-treatment time point (cumulative HPV incidence over post-treatment time point)	95% CL
			90% HR-HPV positive; 10% HR-HPV negative	CIN 2/3; Histology		CIN 1/2/3	3	2/10 = 0.20	0.03, 0.52
							6	1/10 = 0.10	0.01, 0.40
			75% HR-HPV positive; 25% HR-HPV negative	CIN 2; Histology		CIN 1/2	3	1/4 = 0.25	0.01, 0.76
							6	0/4 = 0	0, 0.53
Nagai [23] Japan	HR- and LR-HPV types, including 6, 11, 16, 18, 30, 31, 33, 34, 35, 39, 42, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 66, 68, 70	Cervical cells; PCR	85% HPV positive; 15% HPV negative	CIN 3; Histology	LEEP	With and without CIN 1/2/3	<3	2/20 = 0.10	0.02, 0.29
							3–6	1/20 = 0.05	0.00, 0.22
							6–12	3/20 = 0.15	0.04, 0.36
							>12	1/20 = 0.10	0.00, 0.22
van Ham [22] Netherlands	HR- and LR-HPV types, including 16, 18, 31, 33, 39, 45, 51, 52, 56, 58	Cervical cells and/or biopsy; PCR	94% HR-HPV positive; 5% LR-HPV positive; 1% HPV negative	CIN 2/3; Histology	LEEP	With and without ASCUS, LSIL, HSIL	2–6	13/85 = (0.15)	0.09, 0.24
Aerssens [27] Belgium and Nicaragua	HR- and LR-HPV types, including 16, 31, 51, 52, 58	Cervical cells; PCR	78% HR-HPV; 1% LR-HPV;	CIN 2/3; Histology	LEEP	With and without CIN 2/3	1.5	20/109 = 0.18	0.12, 0.26
			5% HPV type X positive;				6	18/100 = 0.18	0.11, 0.26
			11% HPV negative				12	15/94 = 0.16	0.10, 0.24
							24	21/92 = 0.23	0.15, 0.32
			85% HR-HPV positive; 15% HPV negative			CIN 2/3	14	2/13 = 0.15	0.03, 0.42
Bais [15] Netherlands	HR-HPV types: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 73, 82	Cervical cells; PCR	95% HR-HPV positive; 5% HPV negative	CIN 2/3; Histology	LEEP, surgical or laser conization	With and without CIN 2/3	24	21/174 = 0.12	0.08, 0.18
						CIN 2/3	24	5/16 = 0.31	0.12, 0.56
Brismar [48] Sweden	HR-HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Cervical cells; PCR	72% HR-HPV positive;	CIN 1/2/3; Histology	LEEP[b]	With and without HSIL/LSIL	6.5[c]	8/33 = 0.24	0.12, 0.41
			28% HR-HPV negative				35[d]	12/57 = 0.21	0.12, 0.33
Nam [28] Korea	HR- (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68) and LR- group (6, 11, 34, 40, 42, 43, 44, 70) HPV types	Cervical cells; HC II	95% HR-HPV positive 5% HR-HPV negative	CIN 2/3; Histology	LEEP	With and without CIN 2/3	6	0/77 = 0	0, 0.04
Baloglu [30] Turkey	HR- and LR-HPV types: 16, 18, 31, 45 and 51	Cervical cells; PCR	86% HR-HPV positive, 14% HR-HPV negative	CIN 1/2/3; Histology	LEEP	With and without HSIL	3	0/42 = 0	0, 0.07

Author, Year, Country	HPV types tested	Specimen type; detection method	Pre-treatment HPV status	Stage of cervical disease at time of treatment; testing method	Treatment	Stage of post-treatment cervical disease	Post-treatment time (months)	HPV incidence at post-treatment time point (cumulative HPV incidence over post-treatment time point)	95% CL
Kocken [14] Netherlands	HR-HPV types: 6, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	Cervical cells; PCR	93% HR-HPV positive; 7% HR-HPV negative	CIN 2/3; Histology	LEEP or surgical conization	With and without CIN 2/3 CIN 2/3	6	22/424 = 0.05	0.03, 0.08
							12	7/400 = 0.02	0.01, 0.03
							24	18/348 = 0.05	0.03, 0.08
			95% HR-HPV positive; 5% HR-HPV negative				6	7/76 = 0.09	0.04, 0.17
Pre-treatment HPV positive populations and subpopulations									
Brodman [20] United States	HR- and LR- HPV types: 6, 11, 16, 18, 31, 35, 51	Biopsy; PCR	100% HPV positive	Koilocytosis/CIN 1/2; Histology	Laser ablation	With and without Koilocytosis, CIN 1	3	0/11 = 0	0, 0.24
				CIN 1; Histology		With and without Koilocytosis, CIN 1	3	1/5 = 0.20	0.01, 0.67
				CIN 2; Histology		Koilocytosis	3	0/1 = 0	0, 0.95
				Koilocytosis/CIN 1/2; Histology		Koilocytosis, CIN 1	3	0/5 = 0	0, 0.45
Sesti [31] Italy	HR- and LR-HPV types: 6, 11, 16, 18, 33	Cervical cells; PCR	100% HPV positive	CIN 1/2/3; Histology	Laser conization and ablation	With and without HSIL or LSIL	3	0/113 = 0	0, 0.03
							6	0/113 = 0	0, 0.03
							12	0/113 = 0	0, 0.03
Distefano [32] Argentina	HR- and LR-HPV types: 6, 11, 16, 18, 31, 33	Biopsy; PCR	100% HPV positive	CIN 1/2/3; Histology	LEEP	With and without CIN 1/2/3	6–12	1/36 = 0.03	0.00, 0.13
				CIN 1; Histology			6–12	1/5 = 0.20	0.01, 0.67
				CIN 2; Histology			6–12	0/5 = 0	0, 0.45
				CIN 3; Histology			6–12	0/26 = 0	0, 0.11
	HR- and LR-HPV types: 11, 16, 18, 33	Cervical cells; PCR	100% HPV positive	CIN 1/2/3; Histology	Laser conization		35.4	1/82 = 0.01	0.00, 0.06
Kjellberg [33] Sweden						With and without squamous cell atypia			
Nagai [6] Japan	HR- and LR-HPV types: 16, 18, 31, 33, 35, 58	Cervical cells; PCR	100% HPV positive	CIN 3; Histology	Surgical or laser conization	With and without CIN 1/2/3		4/56 = 0.07	0.02, 0.16
						CIN 1/2/3		1/5 = 0.20	0.01, 0.67
Nobbenhuis [7] Netherlands	HR-HPV types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	Cervical cells; PCR	100% HR-HPV positive	CIN 3; Histology	LEEP or cone biopsy	CIN 2/3	3	3/29 = 0.10	0.03, 0.26
							19	1/29 = 0.03	0.00, 0.16
Bekkers [29] Netherlands	HR- and LR-HPV types, including 16, 18, 31, 33, 35,	Cervical cells and/or biopsy; PCR	100% HR-HPV positive	CIN 3; Histology	LEEP	CIN 1/2/3	3	1/6 = 0.17	0.01, 0.59

Author, Year, Country	HPV types tested	Specimen type; detection method	Pre-treatment HPV status	Stage of cervical disease at time of treatment; testing method	Treatment	Stage of post-treatment cervical disease	Post-treatment time (months)	HPV incidence at post-treatment time point (cumulative HPV incidence over post-treatment time point)	95% CL
	39, 45, 51, 52, 53, 54, 56, 58, 59, 68						6	1/6 = 0.17	0.01, 0.59
Elfgren, 2002[21] Sweden	HR- (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) and LR-(6, 11, 40, 42, 43, 44) HPV types	Cervical cells; PCR	100% HPV positive	CIN 1/2/3; Histology	Conization or cryotherapy	ASCUS, CIN 1/2	24	8/17 = (0.47)	0.25, 0.70
Nagai [23] Japan	HR- and LR-HPV types, including 6, 11, 16, 18, 30, 31, 33, 34, 35, 39, 42, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 66, 68, 70	Cervical cells; PCR	100% HPV positive	CIN 3; Histology	LEEP	With and without CIN 1/2/3	<3	1/17 = 0.06	0.00, 0.26
							3–6	1/17 = 0.06	0.00, 0.26
							6–12	2/17 = 0.12	0.02, 0.34
							>12	1/17 = 0.06	0.00, 0.26
van Ham [22] Netherlands	HR- and LR-HPV types, including 16, 18, 31, 33, 39, 45, 51, 52, 56, 58	Cervical cells and/or biopsy; PCR	95% HR-HPV positive; 5% LR-HPV positive;	CIN 2/3; Histology	LEEP	With and without ASCUS, LSIL, HSIL	2	1/84 = (0.01)	0.00, 0.06
							3	7/84 = (0.08)	0.04, 0.16
							4	10/84 = (0.12)	0.06, 0.20
							6	13/84 = (0.15)	0.09, 0.24
Venturoli [50] Italy	HR- and probable HR- (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82), LR- (6, 11, 40, 42, 54, 61, 70, 72, 81, CP6108), and undetermined-risk (55, 62, 64, 67, 69, 71, 83, 84, IS39) HPV types	Cervical cells; PCR	100% HR-HPV positive 26% LR-or undetermined-risk HPV positive	CIN 1/2/3; Histology	LEEP	With and without CIN1/2/3	6	12/72 = 0.17	0.09, 0.27
Nam [28] Korea	HR- (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68) and LR- group (6, 11, 34, 40, 42, 43, 44, 70) HPV types	Cervical cells; HC II	100% HR-HPV positive	CIN 2/3; Histology	LEEP	With and without CIN 2/3	6	0/73 = 0	0, 0.04
Baloglu [30] Turkey	HR- and LR-HPV types: 16, 18, 31, 45 and 51	Cervical cells; PCR	100% HR-HPV positive	CIN 1/2/3; Histology	LEEP	HSIL	3	0/4 = 0	0, 0.53
Heymans [18] Belgium	HR- (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59), probable HR- (53, 66, 68) and LR- (6, 11, 67) HPV types	Cervical cells; PCR	95% HR-HPV positive	CIN 2/3; Histology	Surgical conization or LEEP	With and without CIN 2/3	6	15/63 = 0.24	0.15, 0.35

Author, Year, Country	HPV types tested	Specimen type; detection method	Pre-treatment HPV status	Stage of cervical disease at time of treatment; testing method	Treatment	Stage of post-treatment cervical disease	Post-treatment time (months)	HPV incidence at post-treatment time point (cumulative HPV incidence over post-treatment time point)	95% CL
			5% probable HR-HPV positive				6	10/42 = 0.24	0.13, 0.38
			93% HR-HPV positive			Without CIN 2/3	6	5/21 = 0.24	0.09, 0.45
			7% probable HR-HPV positive						
			100% HR-HPV positive			CIN 2/3			
Wu [51] China	HR- (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68), LR- (6, 11, 41, 42, 44), and other (53, 66, CP8304) HPV types	Cervical cells; PCR	100% HR-HPV types	CIN 2/3; Histology	LEEP	CIN 2/3	6–24	11/62 = 0.18	0.10, 0.29

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ; CL, confidence limits; HPV, human papillomavirus; HC II, hybrid capture 2; HR-HPV, high-risk HPV; HSIL, high grade squamous intraepithelial lesion; LEEP, loop electrical excision procedure; LR-HPV, low-risk HPV; LSIL, low grade squamous intraepithelial lesion; PCR, polymerase chain reaction; VIA, visual inspection with acetic acid.

[a] Denominators were estimated based on an HIV-negative prevalence of 88% and the number of women testing at each time point during follow-up.

[b] One patient was treated with cryotherapy instead of LEEP.

[c] Mean follow-up time among patients with a follow-up visit <12 months following LEEP.

[d] Mean follow-up time among patients with a follow-up visit ≥12 months following LEEP.