










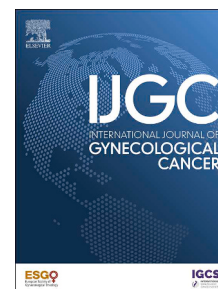


## ORIGINAL RESEARCH

# Efficacy of topical treatments for high-risk human papillomavirus in preventing CIN II+ lesions: a systematic review

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## ABSTRACT

**Objective:** This study aimed to systematically review the literature regarding topical therapies for reducing the risk of cervical intra-epithelial neoplasia (CIN) grade 2 or higher (CIN II+) lesions among women with high-risk human papillomavirus (HPV) infection and histologically confirmed CIN I or either no cervical lesions.

**Methods:** We conducted a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered the protocol in PROSPERO (CRD42024629608). We searched Ovid MEDLINE, Ovid EMBASE, Cochrane Central, and [ClinicalTrials.gov](https://www.clinicaltrials.gov) from inception through December 16, 2024 for randomized controlled trials evaluating any cervical topical treatment in women with high-risk HPV and, at most, CIN I. The primary outcome was progression to histologically confirmed CIN II+. Secondary outcomes were treatment-related adverse events.

**Results:** Of 305 records, 19 full-text articles were reviewed. Finally, 16 trials were assessed. None met all our eligibility criteria, with some trials being excluded for multiple reasons. Twelve were excluded due to an inadequate study population (included women with CIN II+, lacked histologic confirmation of lesion grade, or lacked confirmatory high-risk HPV testing), 4 used inappropriate interventions, and 2 did not include a placebo or watchful waiting comparator. Although many studies reported HPV clearance or cytologic regression, none were powered or designed to assess progression to CIN II+.

**Conclusions:** The current evidence from randomized trials is insufficient to determine whether topical cervical therapies reduce the risk of progression to CIN II+ in women with high-risk HPV infection. Future trials should prioritize histologic outcomes and adhere to current management protocols to establish the clinical utility of such therapies.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Most women with high-risk human papillomavirus (HPV) infection experience spontaneous clearance without treatment. Nonetheless, various topical agents have been investigated for enhancing HPV clearance to prevent lesion development and progression. Currently, none of these treatments are recommended by international guidelines, and observation remains the standard of care.

## WHAT THIS STUDY ADDS

This study systematically reviewed the literature to evaluate whether any topical treatment has demonstrated reduced progression to cervical intraepithelial neoplasia grade 2 or higher in women with high-risk HPV infection. Despite screening of over 300 studies, no randomized controlled trial met our inclusion criteria (appropriate population, intervention type, comparator design, and primary histologic outcome). This work highlights a significant gap in the literature and challenges the increasing promotion of topical agents that have not demonstrated efficacy in preventing high-grade cervical lesions.

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**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY**

*This study highlights the lack of high-quality evidence supporting the use of topical treatments for high-risk HPV infection. These findings support continued adherence to the current guideline recommendations of observation in patients with low-grade disease; caution against the routine use or promotion of topical therapies with unproven benefit in this population; and reinforce the need for future clinical trials with robust design, adequate power, and appropriate outcomes and comparators.*

**Keywords:**

Cervical Intraepithelial Neoplasia; Cervical Neoplasia Progression; High-Risk Human Papillomavirus; Systematic Review; Topical Treatment

**INTRODUCTION**

Cervical cancer is the fourth most common malignancy among women worldwide, with an estimated 604,127 new cases and 341,831 deaths in 2022 according to GLOBOCAN.<sup>1</sup> Persistent infection with high-risk genotypes of human papillomavirus (HPV) is an established cause of cervical cancer<sup>2,3</sup> and other HPV-related neoplasias such as vulvar, vaginal, oropharyngeal, and anal cancers.<sup>4</sup> HPV infection is the most common sexually transmitted infection worldwide, and the prevalence of high-risk genotypes vary widely.<sup>5</sup> In many high-resource countries, up to 40% to 80% of young adult women are infected, and the lifetime risk of acquiring HPV is estimated to be as high as 80% to 90%.<sup>6</sup> Most HPV infections resolve spontaneously without clinical signs or symptoms. However, approximately 4% to 10% of women remain persistent carriers of HPV into middle age, representing the true high-risk population for cervical cancer and other HPV-related malignancies.<sup>7</sup>

To reduce the risk of HPV-related cervical cancer, various topical therapies have been investigated to enhance HPV clearance in women without high-grade cervical lesions, with the goal of preventing disease progression.<sup>8</sup> Despite these efforts, current cervical dysplasia management guidelines continue to recommend observation only as the standard of care for women with HPV infection alone or with low-grade abnormalities. In contrast, active management is reserved for patients with histologically confirmed cervical intra-epithelial neoplasia (CIN) grade 2 or higher (CIN II+) lesions.<sup>9,10</sup> However, whether the investigated topical therapies provide any clinical benefit remains unclear.

The aim of this systematic literature review was to assess the efficacy of topical HPV treatments in preventing CIN II+ lesions among patients with high-risk HPV infections.

**METHODS****Information Sources and Search Strategy**

We used the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, and the protocol was registered in PROSPERO (CRD42024629608). We searched the Ovid MEDLINE, Ovid EMBASE, Cochrane Central, and [ClinicalTrials.gov](https://www.clinicaltrials.gov) databases from inception through December 16, 2024. Search structures, subject headings, and keywords were tailored to each database by a medical research librarian (KJK) specializing in

systematic reviews in consultation with the co-authors. As part of the search strategy, any topical agent was eligible for inclusion. In addition, the following agents were explicitly included as free-text keywords: bletilla, biological dressing, cidofovir, imiquimod, *Lactobacillus*, polyphenol, *Trametes versicolor*, turmeric, interferon, REBACIN, vaginal gel, DeflaGyn, deflated, Fuanning, paiteling, Papilocare, probiotic, and Sanhuang. Searches were restricted to human studies, English-language articles, and randomized controlled trials (RCTs); RCTs were identified using a hedge based on the Cochrane Highly Sensitive Search Strategy for Identifying RCTs. De-duplication was performed manually in EndNote. The full search strings for all databases and other resources can be found in [Table S](#).

We included only RCTs evaluating the efficacy of topical cervical treatments (in isolation from other HPV treatments) in women with high-risk HPV infection and either no cervical lesions, confirmed by normal colposcopy or histologic examination, or histologically confirmed CIN I. Eligible interventions included any topically administered agent, regardless of formulation, dosage, or treatment duration. Acceptable comparators were limited to placebo or watchful waiting comparators. Abstracts, case reports, case series, editorials, and observational studies were excluded.

The primary outcome was progression to histologically confirmed CIN II+ during follow-up. Secondary outcomes were adverse events, when reported.

**Selection Process**

After the initial search, citation screening was conducted using the Covidence systematic review software (Veritas Health Innovation). Two authors (RP, DV-C) independently screened the titles and abstracts of the articles to identify potentially relevant studies. Any disagreements were resolved by consensus or by consulting a third author (SV) when necessary. Articles deemed potentially eligible were retrieved for full-text review. Subsequently, 2 investigators (ES, NM-S) independently assessed the full-text articles for inclusion. Disagreements were resolved by consensus or by consulting a third reviewer (FH).

In accordance with the journal's guidelines, we will provide our data for independent analysis by a team selected by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

## RESULTS

## Study Selection

The search identified 305 unique records. After title and abstract screening, 19 full-text articles were reviewed. Of these 19 articles, 3 reports were from the same RCT<sup>11-13</sup> and two were analyses drawn from the same study,<sup>14,15</sup> reducing the total number of eligible trials to 16 independent RCTs. However, none of those 16 trials met the pre-specified inclusion criteria, so ultimately no studies were included in this systematic review. Figure shows the selection process. As no studies fulfilled the inclusion criteria, we did not proceed with a risk-of-bias assessment, and it was not possible to conduct a meta-analysis from the data collected.

## Reasons for Exclusion

Reasons for excluding the 16 potentially relevant trials fell into 4 main categories: study population, intervention type, comparator design, and outcome measures, with some trials excluded for multiple reasons. Complete details about the reasons for exclusion and study characteristics are provided in Table and Table S, respectively.

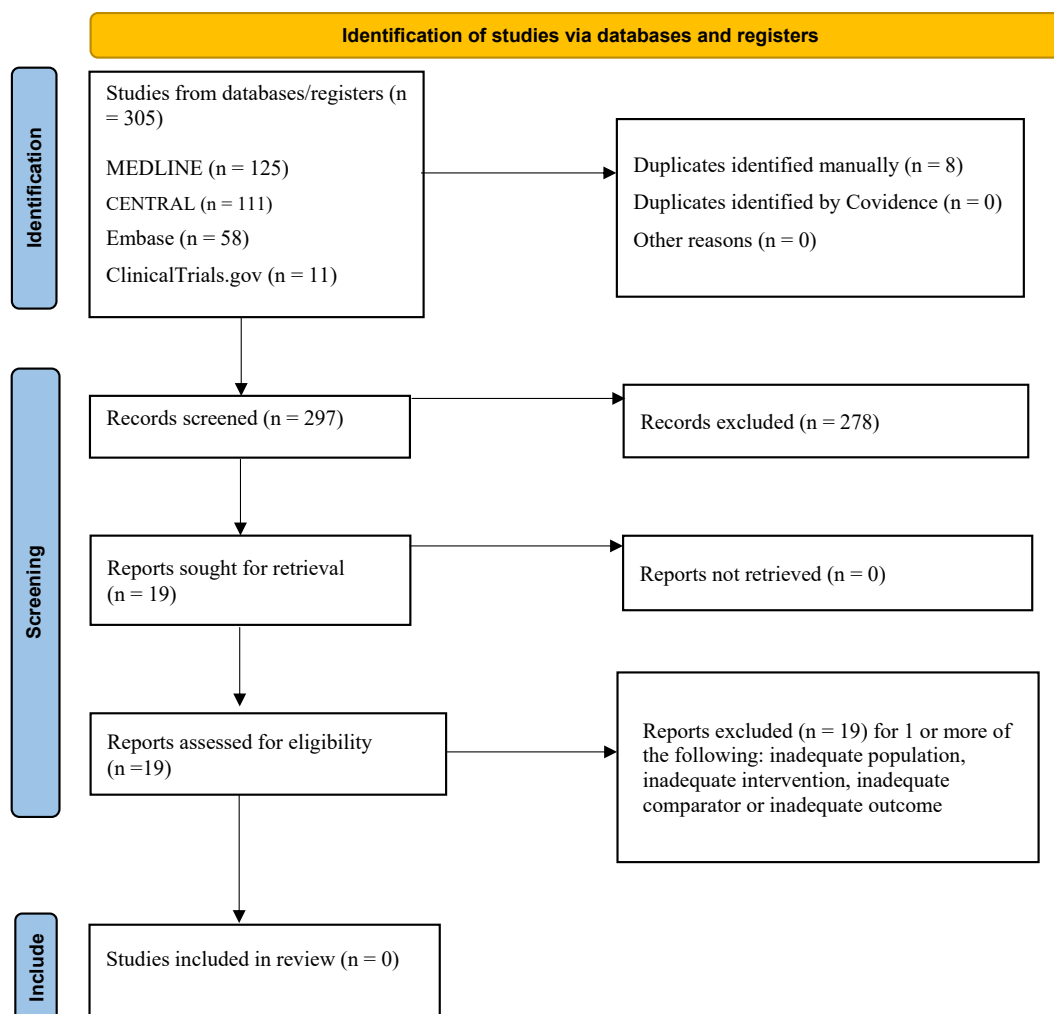
Twelve studies were excluded because of the study population. Of these, 6 studies<sup>11-13,16-20</sup> enrolled women with CIN II+ rather than women with HPV with no lesions or only CIN I; 9 studies<sup>14,15,19-25</sup> lacked systematic histologic confirmation, relying

solely on cytologic or visual inspection to assess lesion grade; and 6 studies<sup>11-13,15,16,18,20,26</sup> either did not confirm HPV diagnosis or used tests that failed to differentiate high-risk types.

Four trials were excluded because they tested interventions outside our pre-defined criteria for topically applied cervical therapies evaluated in isolation. Iljazović and colleagues<sup>19</sup> administered a combination of intra-vaginal interferon with aloe-propolis suppositories, systemic B-complex vitamins, and treatment of any genital infections in both partners. Ou and colleagues<sup>27</sup> evaluated a probiotic administered orally, not topically. Xu and colleagues<sup>24</sup> tested oral modified Ermiao granules alongside a topical interferon gel, but the study design did not allow the isolated evaluation of a single topical agent. Similarly, Riemma and colleagues<sup>28</sup> studied a dual regimen combining oral nutraceuticals with a hyaluronic acid vaginal gel.

Two trials were excluded because they lacked an appropriate placebo or watchful waiting comparator. Iljazović and colleagues<sup>19</sup> compared their intervention treatment against active ablative therapies (laser, cryotherapy, podophyllin), and Riemma and colleagues<sup>28</sup> tested a combination of oral supplements and a hyaluronic acid vaginal gel against 2 other active regimens (gel alone or supplement alone) without any placebo or observation-only group.

Finally, none of these 16 trials met the primary outcome criterion: no study was designed or powered to evaluate



**Figure** PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**Table** Summary of Excluded Randomized Clinical Trials (*N* = 16)

Study/year	Reason for exclusion				Observations
	Study population	Intervention type	Comparator design	Outcome measures	
Byrne and colleagues, <sup>16</sup> 1986	X			X	Enrolled women with CIN II/III. Small sample size; not powered to evaluate progression to CIN II+.
Yliskoski and colleagues, <sup>17</sup> 1990	X			X	Mixed cervical lesions, not limited to ≤CIN I. HPV16 genotyping only. Measured remission, persistence, or regression and HPV disappearance. Small sample size.
Holmes and colleagues, <sup>26</sup> 1999	X			X	HPV diagnosed by cytology/biopsy examination only (no molecular high-risk-HPV confirmation). Primary endpoint was cytologic regression, secondary endpoints included cytologic progression. Small sample size.
Ahn and colleagues, <sup>18</sup> 2003	X			X	Included a heterogeneous mix of lesion grades (chronic cervicitis through CIN III). Measured disease regression and HPV DNA clearance.
Ilijazović and colleagues, <sup>19</sup> 2006	X	X	X	X	Mixed lesion grades (chronic cervicitis through CIN III). Combined topical (interferon, aloe-propolis) and systemic (B-complex vitamins) treatment; also included partner therapy. Comparator was active ablative therapies (laser, cryotherapy, podophyllin). Primary endpoint was HPV clearance.
Shukla and colleagues, <sup>22</sup> 2009	X			X	Enrolled only women infected with HPV16 with CIN I or without lesion by cytologic examination. Primary endpoint was HPV clearance by PCR.
Guo and colleagues, <sup>23</sup> 2016	X			X	Enrolled only women infected with HPV without histologically confirmed low-risk lesions CIN status. Outcomes measured HPV clearance and viral load.
Baleka Mutombo and colleagues, <sup>20</sup> 2019	X			X	Enrolled patients with positive acetowhite lesion without histologic confirmation. No HPV high-/low-risk typing. Endpoints were partial/complete regression or persistence/progression at 2 months by cytologic examination.
Ou and colleagues, <sup>27</sup> 2019		X		X	Oral probiotic intervention. Endpoints were lesion

Table (continued)

Study/year	Reason for exclusion				Observations	
	Study population	Intervention type	Comparator design	Outcome measures		
Yang and colleagues, <sup>25</sup> 2019				X	regression and HPV clearance. Primary endpoints were high-risk HPV clearance and CIN I regression.	
Major and colleagues, <sup>11,12</sup> 2021 and Major and colleagues, <sup>13</sup> 2023 <sup>a</sup>	X				Enrolled women with CIN II lesions. Did not require HPV infection for inclusion. Primary endpoints were histologic regression and p16/Ki-67 biomarker clearance.	
Gil-Antuñano and colleagues, <sup>14</sup> 2022 and Serrano and colleagues, <sup>15</sup> 2021 <sup>b</sup>	X				<b>No</b> histologic confirmation at baseline or during follow-up. Included both low- and high-risk HPV cases. Endpoints were lesion repair (determined via cytology/colposcopy) and HPV clearance.	
Xu and colleagues, <sup>24</sup> 2021	X	X			Two recruitment pathways: Only the biomedical cohort pathway had biopsy-confirmed CIN I; the TCM cohort used symptom/tongue/pulse criteria without histology. Intervention included oral TCM. Endpoints were HPV clearance and CIN I reversal.	
Riemma and colleagues, <sup>28</sup> 2022		X	X		X	Intervention combined oral supplement with topical agent (not purely cervical topical). Comparators were active treatments (hyaluronic acid alone or oral supplement alone), not placebo/watchful-waiting comparators. Sample size calculation for primary endpoint was CIN I regression.
Zhou and colleagues, <sup>29</sup> 2022					X	Primary endpoint was clearance of high-risk HPV E6/E7 mRNA. Follow-up relied solely on mRNA assay with <b>no</b> colposcopic or histologic lesion assessment.
Laurie and colleagues, <sup>21</sup> 2023	X				X	Enrolled regardless of CIN status (no lesion requirement) and HPV positivity. Endpoints measured HPV incidence and clearance.

Abbreviations: CIN, cervical intra-epithelial neoplasia; HPV, human papillomavirus; mRNA, messenger RNA; PCR, polymerase chain reaction; TCM, traditional Chinese medicine.

<sup>a</sup> Includes 3 studies with distinct objectives based on the same randomized controlled trial cohort.

<sup>b</sup> Includes 2 sub-analyses from the same randomized controlled trial cohort. Sub-group analysis was limited to women >40 years within the original 30- to 65-year-old study population.

progression to CIN II+. Instead, all trials reported surrogate outcomes, such as HPV clearance, cytologic result improvement, or biomarker shifts.

### Adverse Effects

Of the 16 excluded trials, 12 mentioned adverse events or tolerability. Overall, the safety profile of topical cervical agents

appeared acceptable across diverse formulations. Most studies either reported no serious adverse effects or described the interventions as well tolerated. Minor adverse events, such as vulvar irritation or non-specific local discomfort, were occasionally noted,<sup>12,18,20,21,29</sup> but no trial identified a safety signal. In studies in which systemic or combined treatments were tested, common adverse effects (nausea, dizziness, leukopenia) were linked to the systemic agents rather than the topical treatment. The most comprehensive adverse effect reporting came from Laurie and colleagues<sup>21</sup> who found similar adverse effect rates between the carrageenan and placebo groups (approximately 35% vs 40%), with most complaints related to vaginal irritation or difficulty using the gel. Overall, the available evidence suggests that these topical interventions are well tolerated because no study reported a higher withdrawal rate due to adverse effects in the intervention arm compared with the control arm(s).

## DISCUSSION

### Summary of the Main Results

No RCT met our eligibility criteria for evaluating topical treatments to prevent the progression of high-risk HPV infection or high-risk HPV-related CIN I to histologically confirmed CIN II+, although 16 independent RCTs explored topical or related interventions in this setting. Most of these trials did not include the appropriate population or reported only surrogate end points such as HPV clearance or cytologic regression changes. None of the studies were powered to detect progression to CIN II+, which was our pre-defined clinically relevant primary outcome. These findings underscore the current lack of high-quality evidence for topical HPV treatment efficacy in preventing pre-cancerous cervical lesions.

Our eligibility criteria were purposefully strict, given the real clinical need for high-quality evidence that could meaningfully modify clinical practice. We limited inclusion to studies in patients with high-risk HPV infection because persistent infection with oncogenic HPV genotypes accounts for more than 95% of all cervical cancers.<sup>30</sup> Without the confirmed presence of a high-risk HPV type, it is not possible to determine whether a patient is truly at risk of progression or whether any observed effect of treatment is clinically relevant. We also required histologic confirmation of the patients' cervical status at baseline in cases of cytologic abnormalities, restricting inclusion to women with CIN I or less, because cytology and colposcopy impressions alone can vary widely between observers and cannot be considered diagnostic tests.<sup>31</sup> This histologic criterion allows the objective and precise definition of the population and the outcome.

Interventions of interest could have included any topically applied agent, from imiquimod, an immune response modifier with antiviral effects, or an antiviral such as cidofovir to natural compounds such as probiotics, antioxidants, or plant extracts, regardless of formulation or dosing regimen. However, we considered only trials that used placebo or watchful waiting comparators. These controls reflect the current international standard of care for women with high-risk HPV and no more than CIN I, as endorsed by major guidelines such as those from the World Health Organization<sup>32</sup> and American Society of Colposcopy and Cervical Pathology.<sup>9</sup> Given the high likelihood of spontaneous

regression in these women, aggressive treatment without robust evidence risks unnecessary harm and may foster unrealistic expectations.

We defined our primary outcome as progression to histologically confirmed CIN II+ because it represents the clinically meaningful cutoff in the natural history of cervical disease for determining treatment. Unlike surrogate measures, such as HPV clearance or cytologic regression, progression to CIN II+ reflects actual pre-cancerous progression requiring intervention.<sup>9</sup> This end point aligns with data showing that although up to 70% to 90% of CIN I lesions regress spontaneously within 2 years, 11% of CIN I lesions progress to CIN II+, and only 0.03% of CIN I lesions progress to invasive cancer.<sup>33</sup> By focusing on CIN II+ progression, we ensured that our review targeted interventions with the potential to meaningfully alter the natural history of high-risk HPV infection and impact clinical outcomes.

### Results in the Context of Published Literature

The spontaneous clearance of HPV infection was found to occur in over 90% of cases within 7 years of diagnosis, regardless of genotype, as was consistently demonstrated through HPV molecular assays, which allow accurate longitudinal observation. In contrast, in 7 years, the rate of cumulative progression to histologically confirmed lesions was reported to be approximately 3%, and the rate of persistent infection was 5%.<sup>34</sup> Therefore, any proposed topical intervention should demonstrate a benefit that clearly exceeds the natural course of HPV clearance. Most importantly, the critical outcome for HPV interventions is not merely HPV clearance but rather the prevention of progression to CIN II+ that could ultimately lead to cervical cancer.

Among the excluded trials, several recurring methodologic weaknesses were apparent. Most studies were small, single-center RCTs that did not explain how sample size was determined, often enrolling fewer than 50 participants per arm. This potential lack of power made them unlikely to detect clinically meaningful differences, even if those differences existed. Moreover, none of the trials were designed to evaluate progression to CIN II+ as a primary end point. Instead, the outcomes varied widely and were often limited to surrogate markers, such as HPV clearance or cytologic changes, and the length of follow-up was insufficient to assess long-term effects of these treatments. Intervention protocols and outcome assessments also lacked standardization, and blinding was frequently absent or poorly described, further increasing the risk of bias. These design flaws severely limit the interpretability and generalizability of the findings.

A previously published narrative review evaluated the use of topical treatments for HPV infection and CIN, emphasizing the potential of topical treatments to serve as alternatives to surgical management in patients with CIN II/III. The analysis included 41 studies, categorized into 5 groups according to the therapy's active ingredient: immune modulators, anti-proliferative agents, antivirals, hormonal therapies, and herbal options. The authors concluded that, to date, none of these topical treatments demonstrated sufficient evidence or efficacy to support their use as a primary treatment for HPV infection or CIN.<sup>35</sup> In addition, a recent systematic review and meta-analysis evaluated the effectiveness of various topical treatments for promoting the regression

of high-risk HPV infection, an end point that may not adequately reflect long-term clinical benefit or disease progression risk. The review included 9 studies involving 961 patients with high-risk HPV or cytologic abnormalities and suggested that anti-HPV biological dressing treatment could be effective in promoting high-risk HPV (HR-HPV) clearance. However, 2 of the included studies appeared to originate from the same patient cohorts, suggesting that data were duplicated in the analysis. This duplication undermines the accuracy of the reported sample size and compromises the validity of the pooled effect estimates; moreover, the included studies scored poorly on quality appraisal.<sup>36</sup>

### Strengths and Weaknesses

To the best of our knowledge, this is the first systematic synthesis of RCTs assessing topical agents for cervical high-risk HPV infection or high-risk HPV-related CIN I. The strengths of our review include its strict eligibility criteria, comprehensive search strategy, and independent data extraction by multiple reviewers. By asking a very focused PICO (Population, Intervention, Comparator, Outcome) question, we aimed to capture trials targeting a clinically relevant population, using standardized diagnosis methods, and examining a meaningful clinical outcome (CIN II+ progression). This approach minimized misclassification and ensured that any observed effect would be applicable to the real-world management of early HPV-related cervical disease. The limitations of our review include publication bias because trials with negative or inconclusive results may have been under-reported.

### Implications for Practice and Further Research

Current evidence does not support the clinical use of topical agents for the treatment of high-risk HPV or CIN I lesions. Although some interventions showed promise in achieving surrogate end points such as HPV clearance or cytologic improvement, none were designed to assess progression to CIN II+. The misalignment with clinically relevant outcomes underscores a significant gap in the existing literature.

Future trials should be designed with methodological rigor, including formal power calculations, the use of placebo or observation-only comparators, and CIN II+ progression as the primary end point. Given that transient HPV infection often resolves spontaneously, clearance alone cannot serve as a meaningful outcome; the end point must be oncologically relevant. Uniform eligibility criteria and standardized outcome measures will be essential to ensure comparability across studies. Importantly, baseline progression risk is known to vary according to HPV genotype and persistence; therefore, sample size calculations and the generalizability of trial results must carefully account for the specific case mix of enrolled women. Until such data emerge, the use of topical agents should remain investigational and should not be used or prescribed in general clinical practice for CIN II+ progression.

### CONCLUSIONS

Topical therapies for high-risk HPV cervical infection and CIN I have not yet demonstrated efficacy in preventing progression to CIN II+ disease. Although some interventions may impact

surrogate outcomes, the methodologic weaknesses of current evidence preclude us from making any clinical recommendations in favor of its use. Robust, well-powered trials are needed to clarify the role of topical treatments in managing early-stage cervical HPV-related disease.

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## REFERENCES

- Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. <https://doi.org/10.3322/caac.21834>.
- Bosch FX, Lorincz A, Muñoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol*. 2002;55(4):244–265. <https://doi.org/10.1136/jcp.55.4.244>.
- zur Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. *Nat Rev Cancer*. 2002;2(5):342–350. <https://doi.org/10.1038/nrc798>.
- Alhamlan FS, Alfageeh MB, Al Mushait MA, Al-Badawi IA, Al-Ahdal MN. Human papillomavirus-associated cancers. *Adv Exp Med Biol*. 2021;1313:1–14. [https://doi.org/10.1007/978-3-030-67452-6\\_1](https://doi.org/10.1007/978-3-030-67452-6_1).
- Markowitz LE, Unger ER. Human papillomavirus vaccination. *N Engl J Med*. 2023;388(19):1790–1798. <https://doi.org/10.1056/NEJMc2108502>.
- Bosch FX, Broker TR, Forman D, et al. Comprehensive control of human papillomavirus infections and related diseases. *Vaccine*. 2013;31(suppl 6):G1–31. <https://doi.org/10.1016/j.vaccine.2013.10.002>.
- Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med*. 1998;338(7):423–428. <https://doi.org/10.1056/NEJM199802123380703>.
- Zhuang Y, Yang H. The significance of nonsurgical therapies for cervical infection of high-risk human papilloma virus: a systematic review and meta-analysis. *J Obstet Gynaecol Res*. 2023;49(9):2213–2231. <https://doi.org/10.1111/jog.15726>.
- Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis*. 2020;24(2):102–131. <https://doi.org/10.1097/LGT.0000000000000525>.
- Wang W, Arcá E, Sinha A, Hartl K, Houwing N, Kothari S. Cervical cancer screening guidelines and screening practices in 11 countries: a systematic literature review. *Prev Med Rep*. 2022;28:101813. <https://doi.org/10.1016/j.pmedr.2022.101813>.
- Major AL, Dvořák V, Schwarzová J, et al. Efficacy and safety of an adsorbent and anti-oxidative vaginal gel on CIN1 and 2, on high-risk HPV, and on p16/Ki-67: a randomized controlled trial. *Arch Gynecol Obstet*. 2021;303(2):501–511. <https://doi.org/10.1007/s00404-020-05816-8>.
- Major AL, Skřivánek A, Grandjean EM, et al. An adsorptive and antioxidant vaginal gel clears high-risk HPV- and p16/Ki-67-associated abnormal cytological cervical findings: a post-hoc subgroup analysis of a prospective randomized controlled trial on CIN2 and p16 positive CIN1. *Front Med (Lausanne)*. 2021;8:645559. <https://doi.org/10.3389/fmed.2021.645559>.
- Major AL, Mayboroda I, Riger A. Successful preventive treatment of oncogenic transforming HPV infections in low-grade cytology (ASC-US/LSIL) patients with an adsorptive and antioxidant vaginal gel. *J Clin Med*. 2023;12(12):4142. <https://doi.org/10.3390/jcm12124142>.
- Gil-Antuñano SP, Serrano Cogollor L, López Díaz AC, et al. Efficacy of a Coriolus versicolor-based vaginal gel in human papillomavirus-positive women older than 40 years: a sub-analysis of PALOMA study. *J Pers Med*. 2022;12(10):1559. <https://doi.org/10.3390/jpm12101559>.
- Serrano L, López AC, González SP, et al. Efficacy of a Coriolus versicolor-based vaginal gel in women with human papillomavirus-dependent cervical lesions: the PALOMA study. *J Low Genit Tract Dis*. 2021;25(2):130–136. <https://doi.org/10.1097/LGT.0000000000000596>.
- Byrne MA, Møller BR, Taylor-Robinson D, et al. The effect of interferon on human papillomaviruses associated with cervical intraepithelial neoplasia. *Br J Obstet Gynaecol*. 1986;93(11):1136–1144. <https://doi.org/10.1111/j.1471-0528.1986.tb08634.x>.
- Yliskoski M, Cantell K, Syrjänen K, Syrjänen S. Topical treatment with human leukocyte interferon of HPV 16 infections associated with cervical and vaginal intraepithelial neoplasias. *Gynecol Oncol*. 1990;36(3):353–357. [https://doi.org/10.1016/0090-8258\(90\)90141-7](https://doi.org/10.1016/0090-8258(90)90141-7).
- Ahn WS, Yoo J, Huh SW, et al. Protective effects of green tea extracts (Polyphenon E and EGCG) on human cervical lesions. *Eur J Cancer Prev*. 2003;12(5):383–390. <https://doi.org/10.1097/00008469-200310000-00007>.
- Iljazović E, Ljuca D, Sahimpasić A, Avdić S. Efficacy in treatment of cervical HRHPV infection by combination of beta interferon, and herbal therapy in woman with different cervical lesions. *Bosn J Basic Med Sci*. 2006;6(4):79–84. <https://doi.org/10.17305/bjbm.2006.3128>.
- Baleka Mutombo A, Tozin R, Kanyiki H, Van Geertruyden JP, Jacquemyn Y. Impact of antiviral AV2 in the topical treatment of HPV-associated lesions of the cervix: results of a phase III randomized placebo-controlled trial. *Contemp Clin Trials Commun*. 2019;15:100377. <https://doi.org/10.1016/j.conctc.2019.100377>.
- Laurie C, El-Zein M, Botting-Provost S, et al. Efficacy and safety of a self-applied carrageenan-based gel to prevent human papillomavirus infection in sexually active young women (CATCH study): an exploratory phase IIB randomised, placebo-controlled trial. *Eclinicalmedicine*. 2023;60:102038. <https://doi.org/10.1016/j.eclinm.2023.102038>.
- Shukla S, Bharti AC, Hussain S, et al. Elimination of high-risk human papillomavirus type HPV16 infection by 'praneem' polyherbal tablet in women with early cervical intraepithelial lesions. *J Cancer Res Clin Oncol*. 2009;135(12):1701–1709. <https://doi.org/10.1007/s00432-009-0617-1>.
- Guo X, Qiu L, Wang Y, et al. A randomized open-label clinical trial of an anti-HPV biological dressing (JB01-BD) administered intravaginally to treat high-risk HPV infection. *Microbes Infect*. 2016;18(2):148–152. <https://doi.org/10.1016/j.micinf.2015.10.004>.
- Xu WW, Tian J, Zhu YM, Ren QL. Clinical observation and mechanism of the elimination of HPV16/18/58 subtype infection and the reversal of grade I cervical intraepithelial neoplasia in Han Chinese women treated with modified Ermliao granules. *Eur J Gynaecol Oncol*. 2021;42(2):293–299.
- Yang Y, Meng YL, Duan SM, et al. REBACIN® as a noninvasive clinical intervention for high-risk human papillomavirus persistent infection. *Int J Cancer*. 2019;145(10):2712–2719. <https://doi.org/10.1002/ijc.32344>.
- Holmes MM, Weaver 2nd SH, Vermillion ST. A randomized, double-blind, placebo-controlled trial of 5-fluorouracil for the treatment of cervicovaginal human papillomavirus. *Infect Dis Obstet Gynecol*. 1999;7(4):186–189. [https://doi.org/10.1002/\(SICI\)1098-0997\(1999\)7:4<186::AID-IDOG4>3.0.CO;2-Z](https://doi.org/10.1002/(SICI)1098-0997(1999)7:4<186::AID-IDOG4>3.0.CO;2-Z).
- Ou YC, Fu HC, Tseng CW, Wu CH, Tsai CC, Lin H. The influence of probiotics on genital high-risk human papilloma virus clearance and quality of cervical smear: a randomized placebo-controlled trial. *BMC Womens Health*. 2019;19(1):103. <https://doi.org/10.1186/s12905-019-0798-y>.
- Riemma G, Schettino MT, Munno GM, et al. Echinacea angustifolia and Echinacea purpurea supplementation combined with vaginal hyaluronic acid to boost the remission of cervical low-grade squamous intraepithelial lesions (L-SILs): a randomized controlled trial. *Medicina (Kaunas)*. 2022;58(5):646. <https://doi.org/10.3390/medicina58050646>.
- Zhou SG, Wu DF, Yao H, et al. REBACIN® inhibits E6/E7 oncogenes in clearance of human papillomavirus infection. *Front Oncol*. 2022;12:1047222. <https://doi.org/10.3389/fonc.2022.1047222>.
- Bosch FX, de Sanjosé S. Human papillomavirus and cervical cancer—burden and assessment of causality. *J Natl Cancer Inst Monogr*. 2003;31:3–13. <https://doi.org/10.1093/oxfordjournals.jncimonographs.a003479>.
- Massad LS, Collins YC, Meyer PM. Biopsy correlates of abnormal cervical cytology classified using the Bethesda system. *Gynecol Oncol*. 2001;82(3):516–522. <https://doi.org/10.1006/gyno.2001.6323>.
- WHO guidelines approved by the guidelines review committee. *WHO Guideline for Screening and Treatment of Cervical Pre-cancer Lesions for Cervical Cancer Prevention*. World Health Organization © World Health Organization; 2021. <https://www.who.int/publications/i/item/9789240030824>.
- Loopik DL, Bentley HA, Eijgenraam MN, Inthout J, Bekkers RLM, Bentley JR. The natural history of cervical intraepithelial neoplasia grades 1, 2, and 3: a systematic review and meta-analysis. *J Low Genit Tract Dis*. 2021;25(3):221–231. <https://doi.org/10.1097/LGT.0000000000000604>.
- Demarco M, Hyun N, Carter-Pokras O, et al. A study of type-specific HPV natural history and implications for contemporary cervical cancer screening programs. *Eclinicalmedicine*. 2020;22:100293. <https://doi.org/10.1016/j.eclinm.2020.100293>.
- Desravines N, Miele K, Carlson R, Chibwesa C, Rahangdale L. Topical therapies for the treatment of cervical intraepithelial neoplasia (CIN) 2-3: a narrative review. *Gynecol Oncol Rep*. 2020;33:100608. <https://doi.org/10.1016/j.gore.2020.100608>.
- Wang DY, Cui YY, Zhang WW, Fan MS, Qiu KX, Yan L. Effect of different interventions on the treatment of high-risk human papillomavirus infection: a systematic review and network meta-analysis. *Front Med (Lausanne)*. 2024;11:1274568. <https://doi.org/10.3389/fmed.2024.1274568>.