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Recurrence of Precancerous Cervical Lesions After Loop Electrosurgical Excision Procedure (Leep): A Systematic Review

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Abstract

To qualitatively synthesize available evidence on recurrence rates of CIN 2/3 following LEEP and risk factors associated with recurrence precancerous cervical lesions. Reputable scientific databases were used to conduct a comprehensive literature search, with a focus on peer-reviewed journals found in PubMed and Scopus. We included cohort studies that reported histologically confirmed CIN2/3 recurrence rates and utilized statistical analysis to identify associated risk factors following LEEP. Key quantitative data on recurrence rates, follow-up duration, and results were critically extracted and synthesized. The study selection process yielded four studies that met the inclusion criteria. All included studies were retrospective in design. The reported incidence of CIN 2/3 recurrence post-LEEP varied widely across studies, ranging from 3,2 % to 9,8%. Most recurrences were detected within the first 12 to 18 months of follow-up. The most potent factor is the persistence of high-risk Human Papillomavirus (HR-HPV) infection post-treatment, showing an exceptionally strong association. Qualitative synthesis identified risk factors of recurrence: (1) persistent post-procedure infection with high-risk Human Papillomavirus (HR-HPV), (2) positive surgical margins, and (3) older patient age. Persistent HR-HPV infection is the most critical determinant governing the recurrence of precancerous cervical lesions after LEEP. These findings strongly advocate for post-treatment surveillance protocols that integrate HR-HPV testing with cytology to accurately stratify risk and ensure prompt, targeted re-intervention for high-risk patients.

INTRODUCTION

Cancers of the breast and cervix uteri were the major contributors to the cancer burden among young adults globally. HPV infection carries a heavy physiological and economic burden for patients. Its pathologenesis mediated by viral oncoproteins with infection occurring in the cervical mucosal epithelium allow the virus to access basal cells. Without adequate immune clearance, persistent infection may induce the development of cervical lesions (Ye et al., 2023; Fiddler et al., 2017; Siegel et al., 2023). Cervical cancer prevention in resource-limited settings can be done by adopting the combined vaccination and screening strategy (Sung et al., 2021). Persistent infection high-risk Human Papillomavirus (HR-HPV) types is the etiological agent for nearly all cases of cervical cancer and its precursor lesions (Bruno et al., 2019). These precancerous lesions, pathologically defined as Cervical Intraepithelial Neoplasia (CIN) represent a spectrum of disease. High-grade lesions, specifically CIN 2 and CIN 3 (collectively CIN 2/3 or High-Grade Squamous Intraepithelial Lesion, HSIL), are critical precursors that, if left untreated, possess a significant risk of progression to invasive cervical carcinoma (Bogani et al., 2020). Effective cervical cancer screening programs in developed nations reduce invasive cancer incidence and mortality, primarily by detecting and

treating the disease in this precancerous state (Fernandez et al., 2018). The Loop Electrosurgical Excision Procedure (LEEP) has become the preferred excisional method to remove any remaining dysplastic tissue while preserving as much healthy cervical tissue as possible and reducing the risk of recurrence (Fernandez et al., 2018; Papalia et al., 2020). Several therapeutic options for ovarian cancer include Large Loop Excision of the Transformation Zone (LLETZ) and Cold Knife Conization (CKC), although a recent meta-analysis showed there was no significant difference regarding residual and recurrence rates in LEEP/LLETZ compared with CKC for treating CIN (Jiang et al., 2016). Complications regarding procedure include bleeding and local infection, with LEEP presenting less complications and lower cost than CKC (Khunnarong et al., 2021). The recurrence rate of CIN without residual HPV and with negative margins after LEEP was reported quite low at 0.5%, although when HPV was residual, the recurrence rate of CIN significantly increased to 18% (Lin et al., 2024). LEEP is a highly effective procedure, persistent disease (diagnosed <6 months post-LEEP) or recurrent disease (diagnosed >6 months post-LEEP). Given the well-documented low risk of cervical cancer after LEEP and its minimally invasive nature, LEEP remains the preferred treatment option for CIN3 (Ozdemir et al., 2025). Current studies reported nearly 6.1% of women developed recurrent CIN2+ with high risk HPV, positive margins, baseline diagnosis, immunosuppression, and smoking were risk factors for its recurrence. Therefore, HPV-based testing at 6 months after treatment is recommended, regardless of margins (Ding et al., 2022; Ricci et al., 2025). Higher risk of recurrent CIN2/3+ lesions reported in patients older than 60 years old with any abnormal follow-up Pap smear results, including ASCUS and LSIL, in the first year after treatment (Shen et al., 2025).

The urgency of this research is underscored by the global burden of cervical cancer and the need for evidence-based post-treatment surveillance strategies. With the increasing adoption of LEEP as the primary treatment for CIN 2/3, understanding factors that predict recurrence is essential for optimizing patient outcomes and resource allocation (Boisen et al. 2023; Bruno et al. 2025; Chung et al. 2021; Maiorano et al. 2026; Zhai et al. 2024). This systematic review provides a timely synthesis of evidence that can inform clinical guidelines and improve patient management. The findings are particularly relevant for healthcare providers in both developed and developing countries where cervical cancer screening and treatment programs are being implemented or expanded.

The novelty of this systematic review lies in its comprehensive and qualitative synthesis of evidence from multiple retrospective studies on recurrence of CIN 2/3 after LEEP. Unlike individual studies that may have limited generalizability, this review consolidates findings across different populations, settings, and time periods. The review identifies consistent risk factors across studies, providing a robust evidence base for clinical decision-making (Farrell et al. 2017; Frieden 2017; Larson et al. 2015; Lin et al. 2018). Additionally, this review highlights the critical role of post-LEEP HPV testing as a "Test of Cure" and emphasizes the importance of early follow-up within the first 12-24 months, which represents the period of highest recurrence risk.

The objective of this systematic review is to identify, assess, and qualitatively synthesize the existing literature from retrospective cohort study the incidence rates of CIN 2/3 recurrence after treatment with LEEP.

METHOD

Following PRISMA 2020 guidelines, literature search was conducted in the Pubmed and Scopus databases. The searches were restricted to English language and included only human studies. A structured search strategy were used to identify studies: "Cervical Intraepithelial Neoplasia" or "precancerous cervical lesion","high-grade squamous intraepithelial lesion", "Loop Electrosurgical Excision Procedure" or "LEEP", "LLETZ" or "large loop excision of the transformation zone", "Recurrence" or "relapse" or "disease recurrence" or "residual disease". Studies were included based on the following eligibility criteria (PICOS):

- Population (P): Patients with a histological diagnosis of CIN 2/3 who had undergone a LEEP procedure.
- Intervention (I): Loop Electrosurgical Excision Procedure (LEEP), also referred to as LLETZ.
- Comparator (C): A comparator group was not required. Single-arm observational cohorts were eligible.
- Outcomes (O): Reported incidence of recurrent CIN 2/3 after LEEP. Studies that also reported risk factors for recurrence were included.
- Study Design (S): Randomized Controlled Trials (RCTs) or observational studies (e.g., cohort, case-control, cross-sectional)

Exclusion criteria were as follows: (1) studies with inadequate data on the incidence of CIN 2 or CIN 3 recurrence; (2) studies conducted exclusively in individuals with Human Immunodeficiency Virus (HIV); (3) studies conducted exclusively in menopausal age groups; and (4) duplicate publications from the same data without additional analysis. Thus, four retrospective cohort studies were analyzed. The methodological quality and risk of bias of the included studies were assessed by two independent reviewers using the Newcastle-Ottawa Scale (NOS).

RESULTS AND DISCUSSION

This selection process resulted in a final cohort of four studies that met all eligibility criteria and were included in the qualitative systematic review. A PRISMA flow diagram detailing this process is presented in Figure 1.

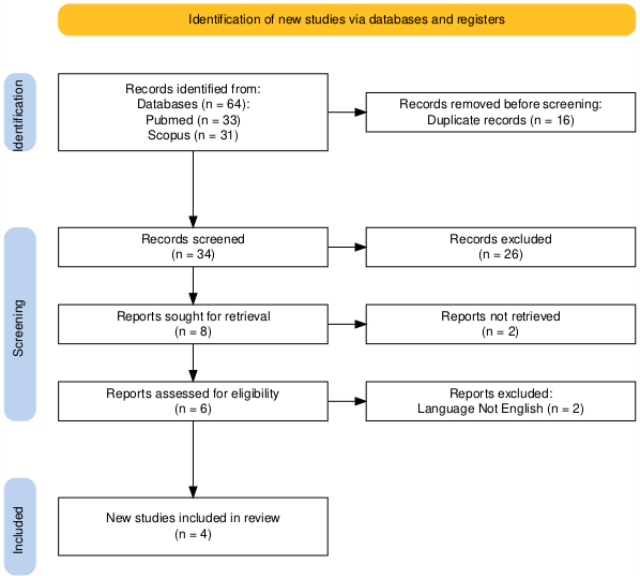

Figure 1. PRISMA 2020 Flow Diagram for Study Selection

The four included studies were published between 2018 and 2020. All four studies were retrospective study. The detailed characteristics of all four included studies are presented in Table 1.

Table 1: Characteristics of Included Studies (N=4)

Author, Year	Study design	Sample size	Age of participants	Range Duration follow up after LEEP
Bruno et al. (2019)	Retrospective study	182	Mean age: 39.3 years	6-30 months
Bogani et al. (2020)	Retrospective multi-institutional study	2966	Median age: 40 years	60 months
Fernández-Montolía et al. (2018)	Retrospective cohort study	242	Median age: 35 years	30 months
Papalia et al. (2020)	Retrospective cohort study	221	Median age: 32 years	12 months

The risk of bias assessment using the Newcastle-Ottawa Scale (NOS) is summarized in Table 2. The methodological quality of the four included studies was rated as moderate to high.

Table 2: Risk of Bias Assessment using Newcastle-Ottawa Scale (NOS)

Studies	Selection (Stars)	Comparability (Stars)	Exposure/Outcome (Stars)	Overall Rating (Stars)
Fernández-Montolía et al., 2018	3/4	1/2	3/3	7/9
Bruno MT et al., 2019	3/4	1/2	3/3	7/9
Papalia N et al., 2020	3/4	1/2	3/3	7/9
Bogani et al., 2020	4/4	2/2	3/3	9/9

The incidence rate of recurrent CIN 2/3 post-LEEP ranging from 3,2% to 9,8%. The timing of recurrence was consistently concentrated in the early post-treatment period. Most recurrences were detected within the first 12 to 18 months of follow-up, though one study (Fernández-Montolía et al, 2018) reported detection at 24 months. Reported Recurrence Rate of CIN 2 or CIN 3 summarized in Table 3.

Table 3: Reported Recurrence Rates of CIN 2or CIN 3 Across Included Studies

Study	Recurrence rate CIN 2vor CIN 3	Detected precancerous lession after LEEP	Risk Factor of recurrence	Test for follow up precancerous lession after LEEP
Bruno et al. (2019)	9,8%	18 months	1. Persistent HPV 16 infection 2. Positive margins	1. Pap test 2. HPV test 3. Colposcopy Confirmed histologically

Study	Recurrence rate CIN 2vor CIN 3	Detected precancerous lession after LEEP	Risk Factor of recurrence	Test for follow up precancerous lession after LEEP
Bogani et al. (2020)	6%	18 months	1. HPV persistence 2. Positive margins	1. HPV test 2. Pap smear 3. Colposcopy 4. Colposcopic guided biopsy
Fernández-Montolía et al. (2018)	5.3%	24 months	1. Age > 35 years 2. Positive HR-HPV post LEEP 3. Involvement endocervical margin	1. Pap smear 2. Colposcopy 3. HPV test
Papalia et al. (2020)	3.2%	18 months	Not specifically analyzed	1. Colposcopy 2. Cytology

The qualitative synthesis revealed three consistent themes: (1) surgical margin status, (2) HPV infection status, and (3) patient age. Post-procedure HPV status emerged as exceptionally strong, and perhaps. the most important predictor of recurrence. Fernández-Montolía et al. (2018) reported a high risk associated with a positive post-LEEP HR-HPV test. Bruno et al. (2019) specifically implicated persistent HPV 16 infection, especially in combination with positive margins. Positive surgical margins were identified as a risk factor in two studies (Bruno et al., Bogani et al.,). Fernández-Montolía et al. (2019) specifically noted the involvement of the endocervical margin. Older patient age was identified as a risk factor of recurrence CIN 2 or CIN 3. Fernández-Montolía et al. (2018) found that an age greater than 35 years was a significant predictor of recurrency.

Recurrence or persistence of lesions after LEEP represents a primary focus of this systematic review. The research data were derived from several retrospective studies with relatively large sample sizes, ranging from 182 to 2,966 patients. This broad population provides remarkable data of the effectiveness of LEEP in clinical practice, as well as the risk factors associated with lesion recurrence. From the included studies, it can be identified that the majority of participants were within reproductive age, with median ages ranging from 32 to 40 years and the highest mean age reported in the study by Bruno (39.3 years). This age range is consistent with the population at risk for cervical precancerous lesions and those undergoing LEEP. The predominance of reproductive-age individuals aligns with the epidemiology of cervical precancerous disease.

The four retrospective studies were assessed using the Newcastle–Ottawa Scale (NOS). The NOS evaluates three main domains: Selection, Comparability, and Exposure/ Outcome, with a maximum total score of 9 stars. Most studies received 3 out of 4 stars in the selection domain, indicating generally eligible participant selection methods. Bogani et al. (2020) was the only study to achieve the maximum score (4/4), indicating the strongest sampling approach with minimal bias and the highest level of representativeness. In the Comparability domain, three studies (Fernández-Montolía, Bruno, and Papalia) received only 1 out of 2 stars, suggesting limited control of potential confounders such as margin status, age, HPV status, or contraceptive use. Bogani et al. achieved the full 2/2 stars, indicating a stronger design with more adequate adjustment for variables that could influence post-LEEP outcomes. All studies received the maximum 3/3 stars for the Exposure/ Outcome domain, demonstrating that outcome assessment was performed using valid methods and that follow-up was sufficient to

identify persistent or recurrent lesions with minimal risk of bias. Overall scores ranged from 7 to 9 out of 9 stars, indicating moderate to high methodological quality. The most prominent limitation across studies was inadequate control of confounding factors, which may influence the precision of risk estimates for post-LEEP lesion recurrence

Analysis of the four retrospective studies indicates that the recurrence rate of CIN 2 or CIN 3 after Loop Electrosurgical Excision Procedure (LEEP) is relatively low and heterogeneous, reported between 3,2% and 9,8%. This variability is likely driven by differences in patient populations and follow-up duration. The low recurrence rate remains clinically significant, particularly in patients with specific risk factors. The period for detecting post-LEEP precancerous lesions ranged from 18 to 24 months, consistent with the period of highest recurrence risk. These findings suggest that the first and second years following LEEP represent a critical period requiring close surveillance.

Four retrospective studies identified risk factors following: 1) persistent HPV infection (particularly HPV-16), (2) positive excision margins, (3) patient age ≥35 years, and (4) endocervical involvement. Persistent HPV infection emerged as the strongest and most consistent risk factor. Positive surgical margins indicate that dysplastic tissue was not completely excised. Patient age (≥35 years) was identified as a risk factor potentially related to immunological changes and the ability to clear a persistent HPV infection. Endocervical involvement reflects deeper dysplastic invasion. Further investigation into the association between these risk factors and cervical cancer recurrence is needed to clarify the underlying pathophysiology and to support preventive strategies in patients following LEEP.

The Limitations of the Review Process**,** such as (1) the search was limited to two databases (Pubmed, Scopus), which may have resulted in missed studies from other major databases, (2) the exclusion criteria, while intended to improve homogeneity, limit the generalizability of the findings. Specifically, the exclusion of studies on HIV-positive and menopausal women means these results cannot be extrapolated to these known high-risk populations (3) the review was restricted to a qualitative synthesis as per the protocol.

The findings from this review strongly support post-LEEP surveillance centered on virological status. A positive HR-HPV “Test of Cure” at 6–12 months post-procedure should be considered the primary indicator of high recurrence risk. These findings provide a strong evidence-based rationale for modern clinical guidelines. Follow-up examinations to detect recurrence may include a combination of Pap smear cytology, HPV testing, colposcopy, and targeted biopsy. HPV testing was used in almost all studies due to its high sensitivity for detecting residual or recurrent disease

The limitations of the current retrospective evidence highlight the need for large-scale, prospective cohort studies. Future research should be designed to simultaneously track margin status (including endo- vs. ectocervical involvement), pre- and post-LEEP HPV genotyping, and patient age to build comprehensive predictive models that can accurately quantify the complex interplay and relative contributions of these factors of recurrency.

CONCLUSION

Recurrence of high-grade precancerous cervical lesions after LEEP is a significant clinical problem, with incidence rates varying based on follow-up and population characteristics. This systematic review of four studies confirms that recurrence of precancerous cervical lesion is a multifactorial outcome. The risk factor of predictors was identified: positive surgical margins, older patient age, and persistent post-procedure HR-HPV infection. This

study emphasizes the importance of complete excision with clear margins and HPV eradication in preventing recurrence. Optimal follow-up is conducted within the first 12–24 months, as this is the period when residual or recurrent lesions are most frequently detected.

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