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Recurrence Factors in Cervical Precancerous Lesions: A Narrative Exploration

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Abstract

Background: *Recurrent cervical pre-cancerous lesions remain a major clinical challenge in preventing progression to invasive cancer and achieving long-term remission. Persistent infection with high-risk human papillomavirus (HPV), particularly subtype 16, is strongly associated with recurrence, especially in women under 40 years of age.*

Method: *This narrative review analyzed recent literature focusing on the main determinants of recurrence after treatment of cervical pre-cancerous lesions, including viral, surgical, and immunological factors.*

Result: *The findings showed that incomplete surgical excision significantly increased the risk of recurrence. The type of surgical procedure also influenced outcomes, with cold knife and laser conization associated with lower recurrence rates than LLETZ. Post-treatment HPV vaccination was found to reduce recurrence by enhancing immunity against re-infection.*

Implication: *These findings highlight the importance of individualized treatment selection, complete lesion excision, and the use of HPV vaccination as part of a comprehensive strategy to minimize recurrence and improve long-term outcomes.*

Novelty: *This review provides an integrated overview of viral, surgical, and immunological factors influencing cervical lesion recurrence, emphasizing the importance of combining optimal surgical technique with preventive immunization.*

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INTRODUCTION

Cervical precancerous lesions, including cervical intraepithelial neoplasia (CIN), signify a crucial phase in the development of cervical cancer, a condition that continues to be a major contributor to cancer-related deaths among women globally. Even with progress in screening and treatment methods, the recurrence of these lesions after intervention remains a significant obstacle. Comprehending the elements that affect recurrence is essential for enhancing clinical results and minimizing the likelihood of advancement to invasive cervical cancer.(Gertig et al., 2013; Setiawan, Kotsopoulos, Wilschut, Postma, & Connolly, 2016)

Ongoing infection with high-risk human papillomavirus (HR-HPV), especially HPV type 16, is a thoroughly established factor contributing to the recurrence of cervical precancerous lesions. Research shows that the persistence rates of HR-HPV are considerable, with around 31% of women continuing to experience infection 12 months after treatment.(Hoffman et al., 2017) The risk is notably increased in women under 40, who show a greater tendency for recurrence when compared to their older counterparts. The results underscore the critical need to focus on HPV persistence within the framework of post-treatment management approaches.(Hariri et al., 2015)

The adequacy of surgical excision is another important factor influencing recurrence. Procedures such as the Large Loop Excision of the Transformation Zone (LLETZ) are frequently employed; nonetheless, they exhibit elevated rates of incomplete excision in comparison to techniques like cold knife conization, laser conization, or total hysterectomy. Incomplete excision results in residual disease, which may progress or recur, requiring further interventions.(Han & Zhang, 2023; Jiang, Chen, & Li, 2016) Furthermore, measures taken after treatment, such as HPV vaccination, have demonstrated potential in lowering recurrence rates by boosting immune defenses against reinfection.(Di Donato et al., 2022)

This narrative exploration seeks to integrate the existing evidence regarding the factors influencing recurrence in cervical precancerous lesions. This review aims to assess clinical and procedural factors, including HPV persistence, surgical methods, and additional therapies, to guide personalized treatment and follow-up approaches that enhance patient outcomes and reduce the likelihood of recurrence. It is crucial to tackle these factors in the worldwide initiative to reduce the impact of cervical cancer and enhance women's health.

METHOD

A literature search was performed utilizing databases including PubMed, Scopus, and ScienceDirect. The study examined keywords and search terms that encompassed combinations of “Cervical precancerous lesions”, “recurrence factors”, “cervical intraepithelial neoplasia”, and “HPV vaccination”. Only articles published in English within the last 15 years were included to maintain the relevance and accuracy of findings. Further references were obtained from the cited works within the selected articles.

The review examined studies that assessed recurrence rates and related risk factors in cervical precancerous lesions, with particular emphasis on persistent high-risk HPV infection, surgical methods, and post-treatment vaccination. Inclusion criteria were restricted to studies providing comprehensive data on outcomes after the treatment of cervical intraepithelial neoplasia (CIN). Exclusion criteria included studies lacking full-text availability, non-English publications, and those not pertinent to CIN recurrence.

Data were systematically extracted, encompassing study design, population characteristics, treatment types, recurrence rates, and factors influencing recurrence. The study specifically examined persistent HPV infection rates, surgical margins, and outcomes associated with various surgical interventions, including LLETZ. Data on post-treatment vaccination, when accessible, were incorporated to assess its impact on recurrence reduction.

This study focused on identifying patterns and correlations in recurrence factors instead of establishing causality. The review synthesizes current evidence to offer actionable insights for the management and prevention of recurrent cervical precancerous lesions, facilitating the development of more individualized treatment strategies.

RESULT

The recurrence of cervical precancerous lesions is determined by a confluence of factors, including persistent high-risk human papillomavirus (HR-HPV) infections, the surgical techniques employed, and post-treatment interventions such as HPV vaccination. Each of these factors contributes uniquely to recurrence risk of cervical precancerous conditions, as described in Table 1.

Kreimer et al, demonstrated that persistent HR-HPV infections, particularly subtype 16, represent a dominant factor in lesion recurrence. Studies consistently link HPV 16's oncogenic activity, mediated by the E6 and E7 proteins, to immune evasion and promotion of cellular transformations. Kreimer et al., demonstrated recurrence rates of 37.5% and 50% for HPV16 and HPV18 infections, respectively.(Kreimer et al., 2012) This persistence correlates with the failure to clear the virus, especially in relatively younger age groups, whose odds ratio (OR) for recurrence with HPV16 according to Byun et al., reaches as high as 19.4. Younger women under 40 are particularly vulnerable to persistent HR-HPV infections, due to factors including reduced immune competence and hormonal influences, which subsequently impair viral clearance ability.(Byun, 2018)

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Table 1. Main results from several studies regarding recurrence factors in cervical precancerous lesions

Authors and Year	Study Design	Location	Study Population	Factors Associated with Recurrence	Significance
Arbyn M, et al., 2017	Systematic review and meta-analysis	Multinational studies	44,446 women treated for histologically confirmed CIN2+ lesions	Positive resection margins	RR = 4.8 (95% CI: 3.2–7.2)
				Large loop excision of the transformation zone (LLETZ)	Higher incomplete excision rate: 25.9% vs. cold-knife 20.2% vs. laser conization 17.8%
Violante Di Donato et al., 2021	Systematic review and meta-analysis	Multinational studies	21,310 women who had undergone surgical treatment for CIN2+	HPV vaccination	OR = 0.35 (95% CI: 0.21–0.56)
				HPV type (including HPV16/18)	Consistent risk reduction across types
Aimée R. Kreimer et al., 2012	Prospective study	Costa Rica	347 women treated for CIN2+	Persistent HPV infection (HPV16/18)	Recurrence rates: HPV16 (37.5%), HPV18 (50%)
				HPV16-mediated immune evasion and oncogenic activity (E6/E7)	CIN recurrence 3.5%
Byun, J.M., et al., 2018	Retrospective study	South Korea	72 women treated for CIN2+	Persistent HPV16 infection	OR = 19.4 (95% CI: 1.89–198.79)
				Age <40 years and persistent high-risk HPV infections	Strongly associated with CIN recurrence

abbreviation:

- CIN2+: Cervical Intraepithelial Neoplasia grade 2 or higher
- RR: Relative Risk
- OR: Odds Ratio
- CI: Confidence Interval
- LLETZ: Large Loop Excision of the Transformation Zone
- HPV: Human Papillomavirus

Surgical intervention remains the cornerstone for treating cervical precancerous lesions, but the efficacy of different techniques varies widely. The adequacy of intervention conducted critically influences recurrence outcomes.[10,11] Procedures like the Large Loop

Excision of the Transformation Zone (LLETZ) are associated with incomplete excision rates of 25.9%, compared to 20.2% for cold knife colonization and 17.8% for laser conization, as stated by Arbyn et al. Further, positive surgical margins increase the relative risk of recurrence nearly fivefold. LLETZ are often considered as a minimally invasive and more accessible procedure, however it often fails to achieve the precision necessary for high-grade lesions, leading to higher recurrence rates.(Arbyn et al., 2017) On the other hand, Di Donato et al, noted that cold knife conization outperforms LLETZ in reducing recurrence rates, particularly in high-grade case. Vaccination against HPV following surgical treatment offers substantial protection against recurrence. Di Donato et al, demonstrated a 65% reduction in recurrence rates among vaccinated patients (OR: 0.35). Vaccines targeting the L1 protein of HR-HPV elicit strong immune responses, preventing reinfections, especially for oncogenic subtypes like HPV16 and HPV18 (Di Donato et al., 2022) .

As we analyze these factors, persistent HR-HPV infection emerges as the primary cause of recurrence, necessitating interventions that target viral clearance. Surgical adequacy, particularly margin status, directly determines the risk of residual disease. Among surgical techniques, cold knife and laser conization demonstrate superior efficacy in recurrence prevention compared to LLET. Meanwhile, vaccination serves as an important adjunct to surgical treatment, significantly reducing reinfection risks but requiring integration into broader treatment protocols. Summary of recurrence factors in cervical precancerous lesions can be seen in Figure 1.

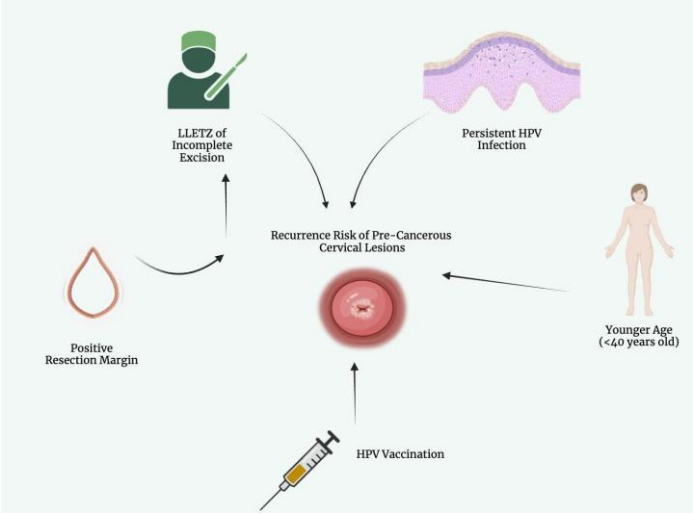

Figure 1. Factor related to cervical precancerous lesion recurrence
(Image created by the author)

DISCUSSION

Persistent High-Risk HPV Infections

Persistent infection with high-risk human papillomavirus (HR-HPV), especially subtype 16, significantly impacts the recurrence of cervical precancerous lesions. Multiple studies highlight the significant association between HR-HPV persistence and lesion recurrence, underscoring its critical role in disease progression following treatment. The oncogenic

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activity of HPV16, facilitated by the viral E6 and E7 proteins, plays a crucial role in its persistence by evading immune responses and inducing cellular transformations that result in recurrent cervical intraepithelial neoplasia (CIN).(Williams, Filippova, Soto, & Duerksen-Hughes, 2011; L. Zhang et al., 2022; Zhou, Tuong, & Frazer, 2019) Studies have demonstrated a robust association between HR-HPV persistence and the recurrence of CIN lesions, indicating that unresolved infections are critical in the progression of cervical disease following treatment. (Koshiol et al., 2008; Lacey, 2023; Vargas, Valente, Almeida, Neves, & Calhaz-Jorge, 2019) Specifically, HPV16 is responsible for approximately 57% of cervical cancers globally, with persistent infections correlating with higher risks of developing CIN3 and invasive cervical cancer.[9,19] (Byun, 2018; Wang et al 2017')

Women under the age of 40 exhibit a notable demographic susceptibility to HR-HPV persistence. Studies show that younger patients exhibit elevated recurrence rates attributed to diminished HPV clearance efficiency relative to older patients.[20] This may be due to differences in immune competence and hormonal influences within this age group. Byun et al. reported an odds ratio (OR) of 19.4 for recurrence in younger women with persistent HPV16 infection, highlighting the significant impact of unresolved HR-HPV infections on clinical outcomes (Byun, 2018) This increased risk may be attributed to variations in immune competence and hormonal influences prevalent in this age group, which can affect the body's ability to clear HPV infections effectively. (Hewavisenti, Arena, Ahlenstiel, & Sasson, 2023)

Despite treatment efforts, clearance rates of HR-HPV remain inadequate. A systematic review indicated that as many as 31% of women experience persistent infections at 12 months following treatment, with the proportion rising over time in the absence of targeted intervention. Persistent HPV infections are particularly concerning as they are linked to increased recurrence rates of CIN2+ lesions.(Depuydt et al., 2016) Post-treatment vaccination has emerged as a promising strategy to mitigate the impact of HR-HPV persistence. The administration of prophylactic HPV vaccines demonstrates efficacy in decreasing the risk of reinfection and strengthening immune responses against high-risk subtypes, such as HPV16. Vaccination, while insufficient to eliminate existing infections, is crucial in post-treatment care to reduce recurrence risks and enhance long-term outcomes. (Movahed et al., 2024; Pinto, Dillner, Beddows, & Unger, 2018; Yokomine et al., 2017)

Targeted follow-up strategies, such as regular HPV DNA testing and cytology, are essential for the monitoring and management of patients at risk for persistent infection. The integration of these efforts with vaccination and tailored treatment plans constitutes a thorough strategy for tackling the issue of HR-HPV-related recurrence in cervical precancerous lesions.

Surgical Factors and Margins

Surgical intervention is fundamental in managing cervical precancerous lesions; however, the risk of recurrence is notably affected by the procedure's adequacy. Incomplete excision, especially in procedures such as the Large Loop Excision of the Transformation Zone (LLETZ), correlates significantly with increased rates of residual disease and lesion recurrence. Achieving clear surgical margins, which signify complete lesion excision, is crucial for minimizing the risk of recurrence. (Arbyn et al., 2017; Scherer-Quenzer et al., 2024)

Among various surgical techniques, LLETZ is widely utilized due to its accessibility and minimally invasive nature; however, it has shown higher rates of incomplete excision when compared to cold knife conization, laser conization, or total hysterectomy. Research indicates incomplete excision rates of 25.9% associated with LLETZ, compared to 20.2% and 17.8% for cold knife and laser conization, respectively. The discrepancy is attributable to the depth and precision of the excision attained by the latter methods. Cold knife and laser

conization facilitate a more precise excision of the transformation zone and deeper cervical tissue, thereby decreasing the likelihood of residual precancerous cells remaining. (Kliemann et al., 2012)The existence of positive resection margins following excision, indicated by histopathological analysis showing residual precancerous cells, serves as a strong predictor of recurrence. Data suggest that positive margins elevate the relative risk of recurrent or residual CIN2+ lesions by nearly five times. This highlights the importance of comprehensive preoperative planning and intraoperative evaluation to achieve complete lesion excision while reducing harm to adjacent healthy tissue. (Arbyn et al., 2017; Giannini et al., 2023; H. Zhang, Zhang, You, & Zhang, 2015)

In high-risk cases, especially those with persistent high-risk HPV infections or advanced lesion grades, more radical surgical interventions, including total hysterectomy, may be warranted.(Li, Barron, Hong, Karunamurthy, & Zhao, 2013)Total hysterectomy offers a definitive treatment by completely excising the cervix, thus removing the primary site for potential recurrence.(Zeng, Guo, Xia, & He, 2024)Its application is generally limited to situations where fertility preservation is not a primary concern or in cases that are recurrent or resistant to treatment. (Burmeister et al., 2022)

Implementing rigorous intraoperative and postoperative protocols is essential for minimizing recurrence linked to surgical factors. Real-time colposcopy and loop electrosurgical excision margin assessments contribute to ensuring sufficient excision. Additionally, the implementation of follow-up strategies, such as HPV DNA testing and cytology, facilitates the early detection of residual or recurrent disease. (Hilal et al., 2018; Simms et al., 2023)

The selection of surgical technique must be informed by specific patient characteristics, such as age, lesion severity, HPV status, and fertility considerations.[35] Personalized surgical planning, along with careful follow-up is essential for minimizing recurrence risks and enhancing patient outcomes in the treatment of cervical precancerous lesions.

Post-Treatment HPV Vaccination

Post-treatment HPV vaccination is a promising approach for preventing recurrent cervical precancerous lesions. Excision procedures effectively remove precancerous tissue; however, the risk of reinfection or persistent infection with high-risk human papillomavirus (HR-HPV) types, especially HPV16, continues to be substantial. Post-surgical vaccination can improve immunity and act as an important adjunct in decreasing recurrence rates.(Han & Zhang, 2023)

Clinical studies indicate that vaccination with prophylactic HPV vaccines, including bivalent, quadrivalent, or nonavalent formulations, significantly reduces the risk of reinfection with high-risk HPV types. These vaccines elicit strong antibody responses that target the L1 protein of HPV, thereby neutralizing the virus and preventing the establishment of new infections. HPV16 is particularly significant due to its association with the highest recurrence rates, attributed to its capacity to evade immune detection and enhance oncogenic activity. (Ashique, Hussain, Fatima, & Altamimi, 2023; Wang et al., 2020)

Post-treatment vaccination demonstrates significant effects as shown in multiple clinical studies. A systematic review and meta-analysis by Violante Di Donato et al. indicated that the recurrence of CIN2+ was significantly reduced in vaccinated patients compared to unvaccinated controls (Odds Ratio [OR] = 0.35; 95% CI: 0.21–0.56). The protective effect was noted across various HPV types, including HPV16 and HPV18, highlighting the extensive applicability of vaccination as a preventive strategy. The recurrence of lower-grade lesions, such as CIN1, was reduced, indicating the vaccine's effectiveness in comprehensive cervical disease management. (Di Donato et al., 2022)

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Incorporating HPV vaccination into post-treatment care plans provides multiple advantages beyond the prevention of recurrence. Vaccination reduces the risk of reinfection and may contribute to herd immunity in populations with high vaccine uptake. Additionally, it functions as a secondary preventive strategy for patients at elevated risk, including those with positive surgical margins or ongoing HR-HPV infections after excision. (Pathak, Pajai, & Kesharwani, 2024; Stern & Roden, 2019)

Post-treatment vaccination, despite its advantages, remains underutilized in numerous clinical environments. Factors hindering widespread implementation include insufficient awareness among healthcare providers and patients, financial concerns, and logistical difficulties in vaccine administration. (Galagali, Kinikar, & Kumar, 2022; Jacobson, St. Sauver, Griffin, MacLaughlin, & Finney Rutten, 2020) Addressing these barriers necessitates coordinated actions, such as patient education, policy advocacy, and the incorporation of vaccination protocols into established guidelines for managing cervical precancerous lesions.

CONCLUSION

The recurrence of cervical precancerous lesions is influenced by persistent high-risk HPV infections, surgical adequacy, and post-treatment vaccination. Persistent HR-HPV, particularly subtypes 16 and 18, significantly increases recurrence risk, especially among younger women under 40 due to immune and hormonal factors. Surgical techniques such as cold knife and laser conization offer better outcomes compared to LLETZ, with positive surgical margins strongly associated with recurrence. Post-treatment HPV vaccination has shown substantial efficacy in reducing recurrence rates by enhancing immune defenses against reinfections.

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