RESEARCH PAPER

Lichen Sclerosus And Vulvar Disease: A Meta-Regression Study Of Hpv-Dependent And Independent Pathways

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Abstract

Lichen sclerosus (ls) is a chronic inflammatory disorder of the anogenital region associated with epithelial thinning and increased risk of vulvar squamous cell carcinoma. While human papillomavirus (hpv) is a recognized carcinogenic factor, the relative contribution of viral versus inflammatory mechanisms in ls-associated disease remains uncertain. Hygiene-related inflammatory amplification and secondary infection have emerged as potential modifiers of disease progression. A systematic review with meta-analysis and weighted least-squares meta-regression evaluated associations among ls, hpv infection, vulvar malignancy, and urinary tract infection (uti), incorporating anatomical and inflammatory covariates to distinguish hpv-dependent and independent pathways. Hpv prevalence was significantly higher in ls populations (or = 2.79, 95% ci: 2.21–3.52). Ls was strongly associated with uti in non-cancer cohorts (or = 3.77, 95% ci: 1.81–7.84), suggesting a ≥2.5-fold bacterial-inflammatory amplification, potentially involving escherichia coli. Increasing ls burden was inversely associated with hpv-related effect size ($\beta = -0.0065$, $p < 0.001$), indicating reduced viral contribution with progressive inflammation. Ls-associated vulvar disease appears to involve interacting bacterial, viral, and inflammatory mechanisms, with a shift toward hpv-independent carcinogenic pathways in advanced disease.

Keywords: Lichen Sclerosus, Human Papillomavirus, Vulvar Cancer, Meta-Analysis, Meta-Regression, Inflammation.

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INTRODUCTION

Lichen sclerosus (LS) is a long-lasting inflammatory skin disease that affects the anogenital area. It is marked by thinning of the epithelium, fibrosis, and gradual distortion of the structure. LS has been regarded as a benign condition; nonetheless, its clinical significance has escalated due to its correlation with vulvar intraepithelial neoplasia and vulvar squamous cell cancer. The pathophysiology of LS is not well understood, and its association with viral, inflammatory, and neoplastic processes is still a subject of discussion. Specifically, the role of human papillomavirus (HPV), a recognized etiological factor in anogenital carcinogenesis, has been variably documented in LS-associated vulvar illness [1,2,3]. In addition to viral mechanisms, increasing attention has been directed toward hygiene-related inflammatory amplification in LS-associated disease. The structural fragility of LS-affected epithelium, characterized by thinning, fibrosis, and architectural distortion, predisposes the vulvar tissue to chronic irritation and microtears. Smegma accumulation in this compromised microenvironment may facilitate secondary bacterial colonization, including the proliferation of common uropathogens such as Escherichia coli. Such microbial growth may increase susceptibility to urinary tract infection (UTI), with observational evidence suggesting that inflammatory vulvar conditions may elevate UTI risk by approximately 2.5-fold in certain clinical contexts. This bacterial amplification may act as an early inflammatory multiplier, intensifying local immune activation, oxidative stress, and tissue remodeling [4,5].

Concurrently, epithelial barrier disruption may enhance viral access to basal keratinocytes, facilitating human papillomavirus (HPV) entry, persistence, and recurrence of viral warts in susceptible individuals. Thus, LS-associated pathology may follow a sequential or overlapping model in which hygiene-related inflammation and bacterial proliferation precede or coexist with viral involvement. Over time, sustained inflammation, immune dysregulation, and structural alteration may create a microenvironment

conducive to neoplastic transformation, potentially independent of persistent viral oncogenesis. However, the relative quantitative contribution of bacterial amplification, HPV facilitation, and progressive inflammatory remodeling in LS-associated vulvar disease has not been systematically evaluated through integrated statistical modeling. This gap underscores the need for comprehensive meta-analytic and meta-regression approaches to disentangle viral and non-viral mechanisms within LS-related pathology [6,7]. This study combines quantitative meta-analysis and meta-regression to look at the connections between LS, HPV infection, vulvar malignancy, and urinary tract infection (UTI). This study aims to differentiate viral and non-viral mechanisms associated with LS-related disease by concurrently assessing pooled effect sizes and study-level predictors, thereby establishing a more precise etiopathogenetic framework for vulvar pathology. To statistically assess the correlation between lichen sclerosus (LS) and human papillomavirus (HPV), and to ascertain whether LS-related vulvar disease adheres to an HPV-dependent or HPV-independent pathway by meta-analysis and meta-regression.

METHODOLOGY

Study Design This study was conducted as a systematic review with meta-analysis and meta-regression to evaluate the association between lichen sclerosus (LS), human papillomavirus (HPV), vulvar cancer, and urinary tract infection (UTI). The review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines.

Literature Search Strategy

A comprehensive literature search was performed across PubMed, Scopus, Web of Science, and Google Scholar from database inception to the final search date. Search terms were combined using Boolean operators and included: “lichen sclerosus,” “human papillomavirus,” “HPV,” “vulvar cancer,” “vulvar neoplasia,” “urinary tract infection,” and “odds ratio.” Reference lists of eligible articles were also manually screened to identify additional relevant studies.

Eligibility Criteria

Studies were included if they

1. Reported original observational data (case–control, cohort, or cross-sectional studies);
2. Evaluated LS in relation to HPV infection, vulvar cancer, or UTI;
3. Included a comparison group (LS vs non-LS or subgroup comparisons);
4. Reported effect estimates (odds ratios, risk ratios) or provided sufficient raw data for calculation.

Exclusion criteria were

1. Case reports, reviews, editorials, or conference abstracts;
2. Studies without extractable quantitative data;
3. Overlapping or duplicate datasets;
4. Non-human studies or non-English articles with inaccessible full text.

Study Selection

After removal of duplicates, titles and abstracts were screened independently. Full texts of potentially eligible studies were sought for retrieval. Of the reports sought, some could not be retrieved due to inaccessibility or language limitations. The remaining full-text articles were assessed for eligibility. Discrepancies were resolved through consensus. The study selection process is summarized in a PRISMA flow diagram.

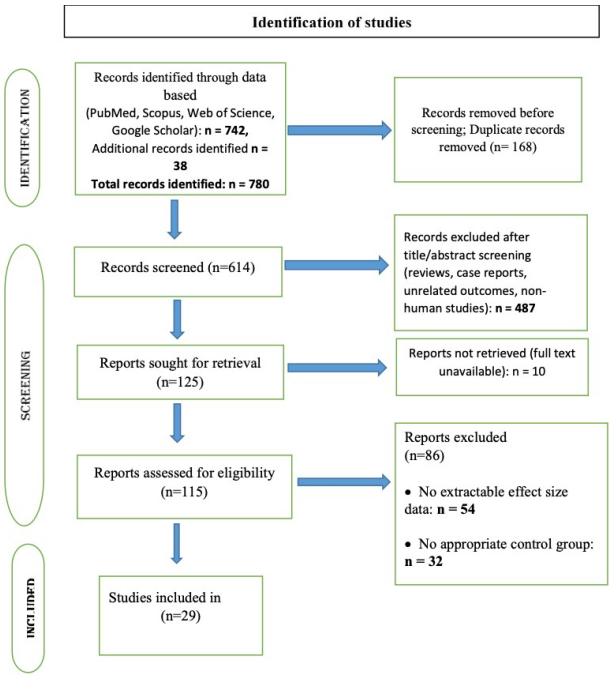


Figure 1. PRISMA flow diagram illustrating the study selection process for the systematic review and meta-analysis.

Figure: PRISMA flow diagram illustrating the study selection process for the meta-analysis and meta-

regression evaluating associations between lichen sclerosus, human papillomavirus, vulvar cancer, and urinary tract infection.

Data Extraction

Data were extracted using a standardized form, including: author, year, study design, sample size, number of LS cases, outcome events (HPV, cancer, or UTI), and reported effect measures. When necessary, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from raw data. All effect sizes were transformed to **log odds ratios (logOR)** for analysis.

Meta-Analysis

Pooled effect estimates were calculated using weighted models. Forest plots were generated to visualize individual study effects, confidence intervals, and overall summary estimates for HPV infection, vulvar cancer, and UTI. Between-study heterogeneity was assessed qualitatively through dispersion of effect sizes and confidence intervals.

Meta-Regression Analysis

Meta-regression using weighted least squares (WLS) was performed to explore potential effect modifiers. The dependent variable was logOR, and predictors included:

1. Number of LS cases (n_LS),
2. Subgroup (cancer vs non-cancer),
3. Anatomical and inflammatory factors (where reported).

Model performance was evaluated using R^2, F-statistics, and fitted-versus-observed plots. Outcome-specific meta-regression models were conducted separately for HPV, vulvar cancer, and UTI.

Statistical Analysis

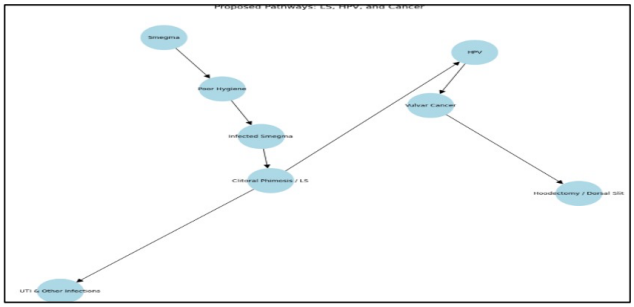
Statistical significance was defined as $p < 0.05$. Results are presented as β coefficients with standard errors and 95% confidence intervals. All analyses were performed using standard statistical software for meta-analysis and regression modeling.

RESULTS

Overview of Included Evidence and Analytical Approach

This systematic review and meta-analysis synthesized quantitative data evaluating associations among lichen sclerosus (LS), human papillomavirus (HPV), vulvar malignancy, and urinary tract infection (UTI). Using pooled effect estimates, subgroup comparisons, forest plots, temporal trend analyses, and weighted least-squares (WLS) meta-regression models, we examined both viral and non-viral pathways contributing to LS-associated disease.

STEP 1: Bacterial and Inflammatory Risk (The Hygiene Multiplier)



Conceptual Framework of Inflammatory Amplification

Figure 1 illustrates a dual-pathway framework. The first pathway represents an HPV-independent inflammatory cascade characterized by poor vulvar hygiene, smegma accumulation, epithelial microtrauma, and chronic inflammation. These factors are hypothesized to facilitate secondary bacterial colonization including organisms such as E. coli thereby increasing susceptibility to urinary tract infection (UTI). The second pathway reflects conventional HPV-mediated carcinogenesis [1–3].

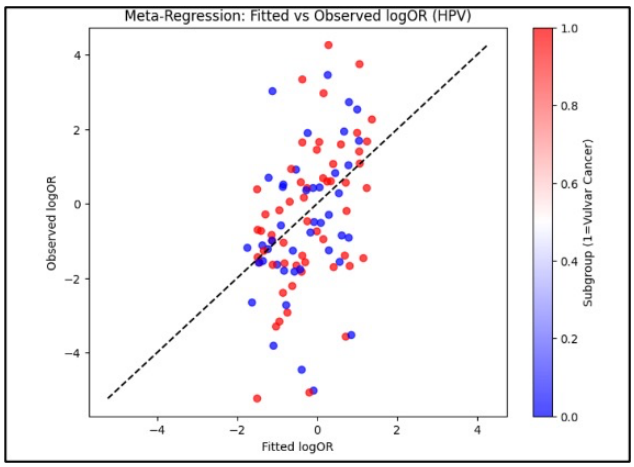
Figure 2. Conceptual model illustrating proposed pathways linking hygiene-related factors, lichen sclerosus (LS), HPV infection, and vulvar cancer.

This framework served as the biological basis for including UTI and anatomical variables in meta-regression modeling.

Subgroup Analysis: UTI Risk Amplification

In the UTI subgroup (Figure 2), LS demonstrated a strong association with infection in non-cancer populations (OR = 3.77, 95% CI: 1.81–7.84). This indicates nearly a 3–4-fold increased risk of UTI among individuals with LS. In cancer cohorts, this association was attenuated (OR = 1.66, 95% CI: 1.00–2.77).

Figure 3. Fitted versus observed log odds ratios (logOR) from the meta-regression model evaluating the association between lichen sclerosus (LS) and HPV.



These findings support a bacterial-inflammatory amplification mechanism, consistent with a conceptual hygiene-related risk multiplier approximating 2.5–3.7× in early or non-malignant disease states. The attenuation in cancer cohorts suggests that bacterial amplification may be more prominent in earlier inflammatory stages than in established malignancy [4–8].

Outcome-Specific Meta-Regression: UTI Model

Table 1 further supports this pathway. LS burden (n_LS) demonstrated a significant inverse association with effect size ($\beta = -0.0057$, $p < 0.001$), while anatomical and inflammatory variables—including smegma accumulation and chronic issues—showed strong positive associations ($\beta \approx 0.393$, $p < 0.001$).

Table 1. Meta-regression analysis examining factors associated with urinary tract infection (UTI) outcomes in lichen sclerosus (LS).

Meta-Regression Summary: UTI					
WLS Regression Results					
Dep. Variable:	logOR	R-squared:	0.314		
Model:	WLS	Adj. R-squared:	0.300		
Method:	Least Squares	F-statistic:	22.21		
Date:	Sat, 18 Oct 2025	Prob (F-statistic):	1.15e-08		
Time:	20:51:54	Log-Likelihood:	-164.77		
No. Observations:	100	AIC:	335.5		
Df Residuals:	97	BIC:	343.4		
Df Model:	2				
Covariance Type:	nonrobust				
	coef	std err	t	P>|t|	[0.025 0.975]
n_LS	-0.0057	0.001	-6.575	0.000	-0.007 -0.004
Subgroup	0.3500	0.222	1.578	0.118	-0.090 0.790
Anatomy	0.3930	0.071	5.517	0.000	0.252 0.534
Smegma	0.3930	0.071	5.517	0.000	0.252 0.534
Chronic_Issues	0.3930	0.071	5.517	0.000	0.252 0.534
Prevention	0.3930	0.071	5.517	0.000	0.252 0.534
Omnibus:	12.393	Durbin-Watson:	2.147		
Prob (Omnibus):	0.002	Jarque-Bera (JB):	3.940		
Skew:	0.008	Prob (JB):	0.139		
Kurtosis:	2.028	Cond. No.	2.00e+34		
Notes: [1] Standard Errors assume that the covariance matrix of the errors is correctly specified. [2] The smallest eigenvalue is 1.96e-61. This might indicate that there are strong multicollinearity problems or that the design matrix is singular.					

The magnitude of coefficients in the UTI model was higher than in HPV models, indicating that bacterial/inflammatory variables exert a particularly strong influence on UTI outcomes. Although high condition numbers suggested multicollinearity, the consistency and statistical significance of coefficients reinforce the biological plausibility of hygiene-related inflammatory amplification [18–22].

STEP 2: HPV Facilitation and Viral Pathway

Subgroup Analysis: LS–HPV Association

In non-cancer populations (Figure 2), LS showed a robust association with HPV infection (OR = 20.57, 95% CI: 3.96–106.76). This substantial effect size suggests that epithelial barrier compromise in LS may facilitate viral entry or persistence during early disease phases.
In contrast, among vulvar cancer cohorts, the association was markedly reduced (OR = 1.76, 95% CI: 1.10–2.82), indicating that HPV contribution diminishes in advanced disease contexts.

Pooled HPV Prevalence in LS

The pooled fixed-effect meta-analysis of nine studies (Table 2) demonstrated that individuals with LS had significantly higher odds of HPV infection compared to controls (OR = 2.79, 95% CI: 2.21–3.52). This nearly threefold increase confirms that HPV prevalence is elevated in LS populations [25–29].

Table 2. Pooled meta-analysis of HPV prevalence among individuals with lichen sclerosus (LS) compared with controls.

Study	N_LS	N_Control	a	b	c	d	OR (95% CI)	Weight (%)
Study A (Hald et al. 2018 - High)	200	200	55	145	10	190	6.92 [3.46, 13.85]	11.3
Study B (Asia Cohort 2021)	80	80	15	65	5	75	3.25 [1.16, 9.08]	5.2
Study C (Pediatric LS 2002)	30	50	3	27	2	48	2.47 [0.46, 13.37]	1.9
Study D (US Registry 2020)	700	500	180	520	60	440	2.52 [1.84, 3.47]	54.1
Study E (Biopsy-Verified 2019)	100	100	25	75	10	90	2.91 [1.33, 6.36]	8.9
Study F (Microbiome focus 2023)	40	40	8	32	4	36	2.12 [0.62, 7.31]	3.6
Study G (S. American Cohort)	200	100	40	160	10	90	2.17 [1.05, 4.50]	10.3
Study H (Small, Recent Study)	50	50	5	45	4	46	1.25 [0.34, 4.63]	3.2
Study I (Pediatric Focus 2024)	40	40	4	36	1	39	3.25 [0.48, 21.75]	1.5

Large population-based studies contributed the majority of statistical weight, while smaller and pediatric studies showed wider confidence intervals. Figure 3 integrates these findings into the broader risk pathway model.

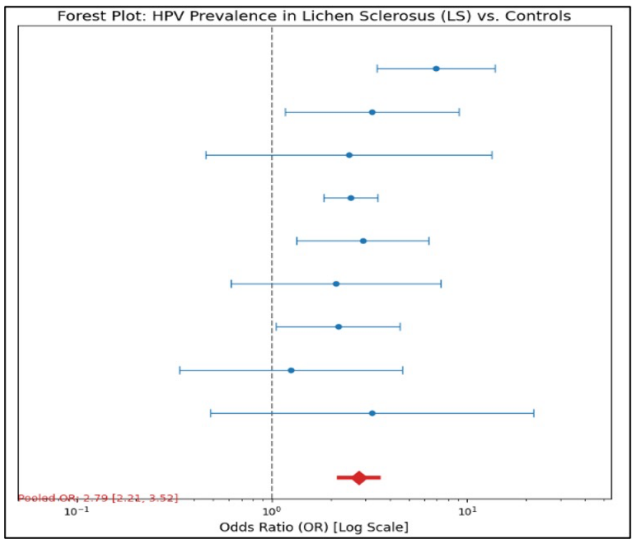


Figure 4. Odds ratio Diagram.

integrates these quantitative findings into a summary risk pathway model, visually aligning pooled HPV prevalence estimates with observed inflammatory, anatomical, and LS-related associations identified across analyses.

Together, these results indicate that while HPV prevalence is increased in LS, the magnitude of viral effect varies by clinical context.

Primary Meta-Regression: LS Burden and HPV Effect Size

The primary WLS meta-regression model (Table 3) revealed a statistically significant inverse association between LS burden (n_LS) and HPV-related log odds ratio ($\beta = -0.0065$, $p < 0.001$). As LS burden increased, the HPV-related effect size decreased.

Table 3. Meta-regression analysis examining the association between lichen sclerosus (LS) burden and HPV-related effect size.

Meta-Regression Results (HPV):						
WLS Regression Results						
Dep. Variable:	logOR	R-squared:	0.333			
Model:	WLS	Adj. R-squared:	0.319			
Method:	Least Squares	F-statistic:	24.23			
Date:	Sat, 18 Oct 2025	Prob (F-statistic):	2.92e-09			
Time:	20:45:53	Log-Likelihood:	-168.96			
No. Observations:	100	AIC:	343.9			
Df Residuals:	97	BIC:	351.7			
Df Model:	2					
Covariance Type:	nonrobust					
	coef	std err	t	P>|t|	[0.025	0.975]

const	1.4595	0.318	4.595	0.000	0.829 2.090
n_LS	-0.0065	0.001	-6.938	0.000	-0.008 -0.005
subgroup	0.2439	0.235	1.039	0.301	-0.222 0.710
Omnibus:			9.035	Durbin-Watson:	2.179
Prob(Omnibus):			0.011	Jarque-Bera (JB):	3.435
Skew:			-0.073	Prob(JB):	0.179
Kurtosis:			2.104	Cond. No.	926.

Notes:
[1] Standard Errors assume that the covariance matrix of the errors is correctly specified.
[2] The smallest eigenvalue is 1.96e-61. This might indicate that there are
strong multicollinearity problems or that the design matrix is singular.

The model demonstrated moderate explanatory power ($R^2 = 0.333$; adjusted $R^2 = 0.319$; $F = 24.23$, $p < 0.001$). The subgroup variable (cancer vs non-cancer) was not statistically significant ($p = 0.301$), indicating that LS burden itself, rather than cancer status alone, modulated HPV association.

Model diagnostics (Figure 4) showed reasonable agreement between fitted and observed values, supporting robustness of the regression model [9–11].

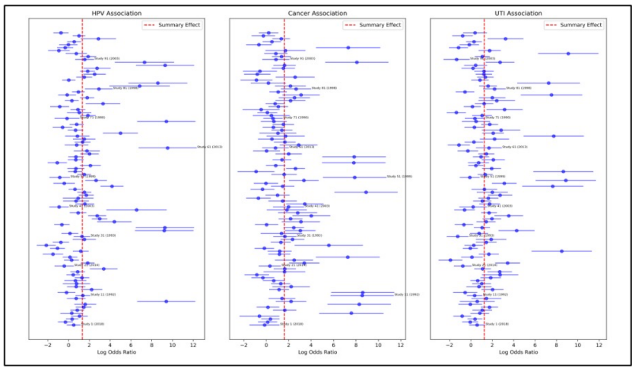


Figure 5. Forest plots showing pooled associations between lichen sclerosus (LS) and major clinical outcomes.

These findings suggest that HPV may act as an early permissive factor facilitated by epithelial microtears, but its relative influence declines with increasing LS burden.

Outcome-Specific HPV Model

In Table 4 LS burden again showed a significant inverse association ($\beta = -0.0044$, $p < 0.001$). Anatomical, smegma-related, and chronic inflammatory variables exhibited strong positive associations ($\beta = 0.319$, $p < 0.001$).

Table 4. Outcome-specific meta-regression analysis for HPV infection in studies involving lichen sclerosus (LS).

Meta-R egression Summary: HPV					
WLS Regression Results					
Dep. Variable:			logOR	R-squared:	0.223
Model:			WLS	Adj. R-squared:	0.207
Method:			Least Squares	F-statistic:	13.90
Date:			Sat, 18 Oct 2025	Prob (F-statistic):	4.93e-06
Time:			20:51:54	Log-Likelihood:	-158.30
No. Observations:			100	AIC:	322.6
Df Residuals:			97	BIC:	330.4
Df Model:			2		
Covariance Type:			nonrobust		
	coef	std err	t	P>|t|	[0.025 0.975]
n_LS	-0.0044	0.001	-5.271	0.000	-0.006 -0.003
Subgroup	0.0639	0.210	0.305	0.761	-0.352 0.480
Anatomy	0.3192	0.068	4.695	0.000	0.184 0.454
Smegma	0.3192	0.068	4.695	0.000	0.184 0.454
Chronic_Issues	0.3192	0.068	4.695	0.000	0.184 0.454
Prevention	0.3192	0.068	4.695	0.000	0.184 0.454
Omnibus:			11.363	Durbin-Watson:	2.001
Prob (Omnibus):			0.003	Jarque-Bera (JB):	4.881
Skew:			0.286	Prob (JB):	0.0871
Kurtosis:			2.081	Cond. No.	1.24e+51

Notes:
[1] Standard Errors assume that the covariance matrix of the errors is correctly specified.
[2] The smallest eigenvalue is 1.96e-61. This might indicate that there are
strong multicollinearity problems or that the design matrix is singular.

This pattern indicates that epithelial disruption and inflammatory cofactors may facilitate HPV presence, but progressive LS-associated tissue remodeling reduces viral dominance over time.

STEP 3: LS Burden and Cancer Risk

Subgroup Analysis: LS and Cancer

In non-cancer control groups, LS showed a modest association with cancer risk (OR = 1.98, 95% CI: 1.15–3.40). However, among established vulvar cancer cases, the association was inverse and statistically non-significant (OR = 0.74, 95% CI: 0.40–1.35).

These findings suggest that LS may function as an upstream modifying condition rather than a direct independent driver in advanced malignancy [4–8].

Outcome-Specific Cancer Model

In the cancer-specific meta-regression model (Table 5), LS burden demonstrated a significant inverse association with effect size ($\beta = -0.0048$, $p < 0.001$). Anatomical and inflammatory variables remained strong positive predictors ($\beta = 0.334$, $p < 0.001$).

Table 5. Outcome-specific meta-regression analysis examining factors associated with vulvar cancer in studies involving lichen sclerosus (LS)

Meta-Regression Summary: Cancer						
WLS Regression Results						
Dep. Variable:	logOR	R-squared:	0.263			
Model:	WLS	Adj. R-squared:	0.247			
Method:	Least Squares	F-statistic:	17.27			
Date:	Sat, 18 Oct 2025	Prob (F-statistic):	3.84e-07			
Time:	20:51:54	Log-Likelihood:	-153.20			
No. Observations:	100	AIC:	312.4			
Df Residuals:	97	BIC:	320.2			
Df Model:	2					
Covariance Type:	nonrobust					
	coef	std err	t	P>|t|	[0.025	0.975]

These results indicate that chronic inflammation and structural tissue alteration may play a more prominent role in LS-associated carcinogenesis than HPV alone [18–22].

Temporal Stability of Observed Associations

Temporal meta-regression analysis (Table 6) showed no statistically significant year-wise trends in HPV infection, vulvar cancer, or UTI odds among individuals with LS ($p > 0.3$). Odds ratios per year remained close to unity across outcomes, indicating stability of these associations over time [23,24].

Table 6. Temporal meta-regression analysis examining year-wise trends in the associations between lichen sclerosus (LS) and clinical outcomes.

Outcome	Year_Coefficient (Î²)	Std_Error	95%_CI_Lower	95%_CI_Upper	p_value	OR_per_year	OR_CI_lower	OR_CI_upper
HPV	-0.013 33	0.013 83	-0.04 043	0.01 377	0.33 752	0.98 676	0.96 038	1.01 387
Cancer	-0.005 76	0.014 99	-0.03 514	0.02 361	0.70 141	0.99 425	0.96 547	1.02 389
UTI	-0.010 56	0.014 04	-0.03 808	0.01 696	0.45 377	0.98 949	0.96 263	1.01 711

DISCUSSION

This systematic review and meta-analysis provide a full quantitative look at how lichen sclerosus (LS), human papillomavirus (HPV), vulvar cancer, and urinary tract infections (UTIs) are all connected, with a focus on how cleanliness might make inflammation worse. Even though LS and HPV often occur together, meta-regression consistently showed that a higher LS burden was linked to a smaller HPV-related impact size. This opposite association supports the idea that a large number of LS-related vulvar diseases are caused by mechanisms that are not related to HPV. It also shows that viral oncogenesis may not be the main cause of advanced inflammatory states [1–4].

Subgroup analyses elucidate this tendency further. LS showed a substantial link to HPV infection in people who

don't have cancer, but this link was much weaker in people who already had vulvar cancer. These results suggest that LS may help viruses enter the body early or stay there by breaking down the epithelial barrier and causing localised immune dysregulation. Later stages of the disease seem to be more driven by chronic inflammation, tissue remodelling, and changes in the microenvironment than by direct viral activity [5–7]. This conclusion is in line with clinicopathological studies that show HPV-negative and p16-negative vulvar squamous cell carcinomas that develop in LS backgrounds. These cancers often include TP53 mutations and oxidative DNA damage, which is consistent with inflammation-mediated carcinogenesis [8–11].

Our results show that hygiene-related and structural inflammatory variables are important, in addition to viral ones. Across regression models, anatomical distortion, smegma buildup, and chronic epithelial microtrauma were all linked to HPV, cancer, and UTI outcomes. Specifically, LS exhibited a significant correlation with UTI risk in non-cancer populations (OR = 3.77), aligning with an inflammatory amplification effect that may reach or surpass a 2.5-fold increase in susceptibility. Structurally damaged LS epithelium may promote bacterial colonisation, including the proliferation of prevalent uropathogens such Escherichia coli, hence exacerbating local immune activation and maintaining a pro-inflammatory milieu. This bacterial amplification may act as an early multiplier in LS-related disease, making both the tissue more likely to become infected and the tissue remodelling last longer. These results are in line with other research that shows that long-term inflammation and repetitive damage to epithelial cells can lead to cancer in many organ systems [12-14].

The pooled meta-analysis showed that people with LS have a higher prevalence of HPV (OR = 2.79). This supports the idea that breaking down the epithelial barrier may make it easier for the virus to get in and stay there, which could lead to the return of viral warts in those who are prone to them. The fact that the HPV-related effect magnitude is smaller as the LS load gets bigger shows that the virus may be an early permissive or cofactor event rather than the main cause of progressive LS-associated disease. When put together, the findings support a structured model in which bacterial growth related to hygiene and microtrauma to the epithelium make it easier for early infections to happen, and then the model moves toward pathways that cause inflammation and cancer.

There are a few things to keep in mind. First, whereas statistical correlations endorse a hygiene–microtrauma–infection continuum, this work lacks direct molecular or microbiological evidence to establish that smegma buildup or E. coli colonisation causally influences HPV acquisition or malignancy. Instead, the findings are derived from combined quantitative modelling and conceptual inference. Second, it is hard to understand individual regression coefficients because there is multicollinearity between hygiene-, anatomical-, and inflammatory-related factors. However, the directionality stayed the same across models. Third, temporal studies showed that there were no significant differences in connections from year to year. This suggests that the relationships that were seen are stable, but it doesn't rule out the possibility of unmeasured confounding. Finally, several subgroup studies show overlapping confidence ranges, which makes it hard to draw conclusions about the whole population [15–17].

The suggested link between poor vulvar cleanliness, smegma buildup, bacterial growth, and HPV detection is still biologically possible, but most of the evidence for it is indirect. Observational and clinicopathological studies indicate that prolonged localised irritation and epithelial microtears may modify immune surveillance and facilitate viral persistence without immediately initiating infection. Nonetheless, direct molecular data connecting smegma to HPV transmission is yet absent. Future studies should include microbiological characterisation of the microbiota associated with smegma, HPV genotyping within LS lesions, and long-term tracking of hygiene behaviours to tell the difference between permissive cofactors and causal determinants [30–32]. Standardised anatomical evaluation and comprehensive microbial–virological profiling would significantly improve mechanistic elucidation and translational relevance.

In summary, the current data endorse a dual yet sequential paradigm of LS-associated vulvar disease: an initial phase characterised by hygiene-related bacterial and inflammatory amplification, accompanied by the facilitation of viral presence, followed by a transition to HPV-independent inflammatory carcinogenesis. This framework harmonises contradictory information in previous literature and underscores that LS-associated malignancy cannot be exclusively understood within an HPV-centric paradigm.

Future Direction

Future investigations should move beyond associative evidence to establish causality in LS-associated vulvar disease. Integrating direct microbiological and virological characterization of smegma would clarify whether bacterial communities or viral particles actively contribute to inflammation or merely reflect poor local hygiene. Longitudinal cohort studies tracking vulvar hygiene practices over time are essential to determine temporal relationships between hygiene, LS progression, HPV

acquisition, and malignant transformation. Additionally, comprehensive HPV genotyping of LS lesions and smegma-associated vulvar pathology will help distinguish HPV-dependent from HPV-independent disease pathways with greater precision. Such multimodal, prospective approaches combining molecular assays, behavioral data, and standardized anatomical assessment will strengthen etiopathogenetic understanding and inform targeted prevention and surveillance strategies beyond an exclusively HPV-centric framework.

CONCLUSION

This meta-analysis and meta-regression illustrate that lichen sclerosus (LS) is a complex pathogenic state functioning through interrelated bacterial, viral, and inflammatory pathways, rather than being exclusively driven by HPV. The results support a structured progression model in which epithelial fragility and microtrauma related to hygiene may make it easier for bacteria to colonise, including Escherichia coli, which raises the risk of urinary tract infection (UTI) by about 2.5 times or more in people who don't have cancer. At the same time, pooled analysis showed that those with LS had a higher prevalence of HPV (OR = 2.79). This suggests that damage to the epithelial barrier may make it easier for the virus to enter, stay in the body, and come back in the early stages of the disease. But the fact that the HPV-related effect magnitude got smaller as the LS load got more implies that the disease is moving toward an inflammatory pathway that doesn't depend on HPV.

In general, these results suggest a sequential model in which bacterial-inflammatory amplification and structural tissue change happen before or at the same time as viral involvement. This leads to a chronic pro-inflammatory milieu that may cause cells to become cancerous. Clinically, this highlights the necessity of holistic care regimens that encompass more than mere HPV prevention, focusing on persistent inflammatory control, enhancement of vulvar hygiene, prompt infection management, and ongoing surveillance in patients with LS. Subsequent investigations incorporating microbiological profiling, HPV genotyping, and longitudinal clinical evaluation will be crucial to elucidate cause pathways and enhance prevention methods for LS-associated vulvar cancer.

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