SERUM 25-HYDROXYVITAMIN D AND RISK OF HIGH-GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN2+): A STRUCTURED NARRATIVE REVIEW

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ABSTRACT & REFERENCES

Introduction

Cervical cancer remains the fourth most common malignancy affecting women worldwide, with approximately 660,000 new cases and 350,000 deaths annually. **Persistent infection with high-risk human papillomavirus (hrHPV)[1] drives cervical carcinogenesis, yet host metabolic and immunologic factors influencing hrHPV persistence and progression to cervical intraepithelial neoplasia (CIN) remain incompletely characterized[2].** Vitamin D regulates immune and epithelial pathways relevant to HPV clearance[3]. High-grade squamous intraepithelial lesion (HSIL) is a cytologic correlate of CIN2/3, both precursors to invasive squamous cell carcinoma (SCC). **This review evaluates the association between serum 25(OH)D, hrHPV persistence, and progression to CIN2+.**

Hypothesis

We hypothesize that serum 25-hydroxyvitamin D [25(OH)D] insufficiency impairs host immune surveillance of high-risk human papillomavirus (hrHPV), facilitating viral persistence and increasing the risk of progression to CIN2+. *Through coordinated vitamin D receptor (VDR)-mediated mechanisms—including epithelial barrier integrity, antimicrobial peptide expression, Th1/Th17 polarization, MDSC suppression, and Treg modulation—vitamin D deficiency may promote an immunologic environment conductive to HPV persistence and neoplastic progression. If supported, serum 25(OH)D status may represent a modifiable immunologic risk factor with direct implications for cervical cancer screening and prevention strategies.*

Methods

A structured narrative review was conducted using PubMed/MEDLINE (inception–March 2026). **Eligible studies measured serum 25(OH)D in women aged 18–65 with confirmed hrHPV infection or undergoing cervical screening, reporting outcomes of hrHPV persistence, CIN grade, CIN regression, or progression to CIN2+.** Vitamin D status was classified as deficient (<20 ng/mL), insufficient (20–29 ng/mL), or sufficient (⩾30 ng/mL). Study quality was assessed using the Newcastle–Ottawa Scale for observational studies and RoB2 for the sole RCT. Findings were synthesized narratively due to heterogeneity in assay methods and threshold definitions. **Final inclusion: 11 studies across 8 countries (2014–2025).**

Proposed Mechanistic Pathway

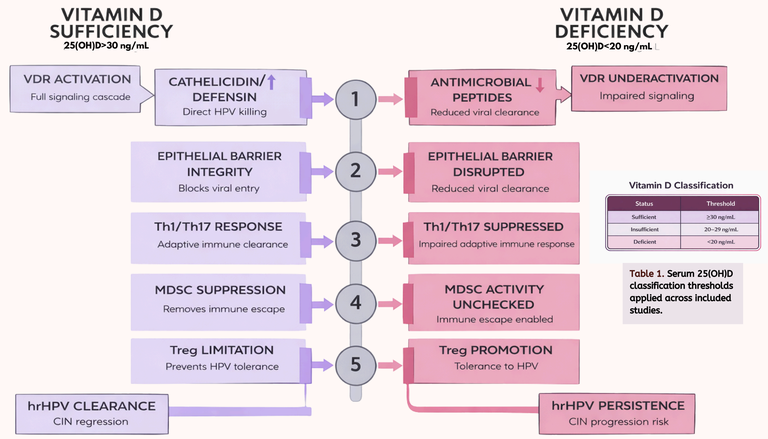


Figure 1. ***Proposed VDR-Mediated Mechanism Linking Serum 25(OH)D Status to hrHPV Persistence and CIN Progression.*** Vitamin D sufficiency activates five coordinated immune mechanisms promoting hrHPV clearance; deficiency impairs all five, facilitating viral persistence and CIN progression risk. *Adapted from He et al[14] and Khalili et al[11].*

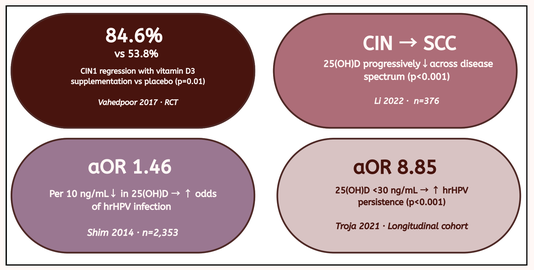
Vitamin D Classification

Status	Threshold
Sufficient	≥30 ng/mL
Insufficient	20–29 ng/mL
Deficient	<20 ng/mL

Table 1. Serum 25(OH)D classification thresholds applied across included studies.

Results

Figure 2. Key findings from included studies evaluating the association between serum 25(OH)D levels and hrHPV-related outcomes. Lower vitamin D status is associated with increased hrHPV prevalence, persistence, and disease severity, while supplementation is linked to improved CIN regression.[1–6,8,12]



Study	Country	Design	N	Outcome	Key Finding	Direction
El-Zein 2020	Canada	Prospective cohort	490	HPV clearance	VitD <30 ng/mL → borderline ↑ clearance (NS)	↔
Özgü 2016	Turkey	Case-control	85	HPV/CIN	↓ VitD in HPV(+) women (p=0.009)	Inverse (protective)
Shim 2014	USA	Cross-sectional	2,353	hrHPV	↓ VitD → ↑ hrHPV (aOR 1.46 per 10 ng/mL ↓)	Inverse (protective)
Troja 2021	USA	Longitudinal cohort	72	HPV persistence	VitD <30 → ↑ persistence (aOR 8.85)	Inverse (protective)
Chu 2021	Taiwan	Prospective cohort	52,220	HPV prevalence	VitD deficiency → ↑ HPV prevalence (p<0.05)	Inverse (protective)
Li 2022	China	Case-control	376	CIN spectrum	↓ VitD across CIN → SCC (p<0.001)	Inverse (protective)
Punchoo 2025	S. Africa	Cross-sectional	109	HSIL	Mixed; HIV modifies association	Positive (paradoxical)
Vahedpoor 2017	**Iran**	**RCT**	**58**	**CIN regression**	**Vitamin D ↑ CIN1 regression (84.6% vs 53.8%)**	**Inverse (protective)**

Table 2. Characteristics and key findings of studies assessing the relationship between serum 25(OH)D status and hrHPV infection outcomes, including HPV prevalence, persistence, CIN severity, and regression.[1–6,8,12]

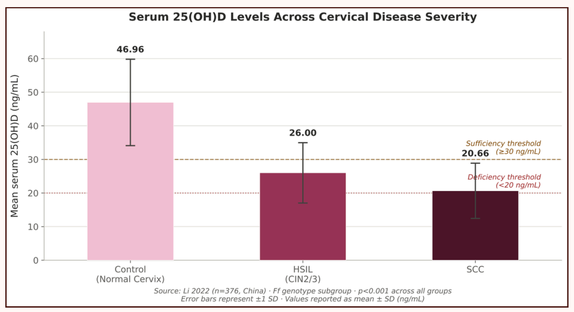


Figure 3. Mean serum 25(OH)D levels by cervical disease severity and FokI VDR genotype (Ff). Dashed lines show sufficiency (⩾30 ng/mL) and deficiency (<20 ng/mL). LSIL = CIN 1; HSIL = CIN 2–3; CIN = biopsy-based, SIL = cytology-based. Both HSIL and SCC fell below sufficiency. Source: Li et al4, Table 5; n=376, Shanxi, China. p<0.001; F=81.000.

Limitations

Predominantly cross-sectional study designs limit causal inference. **Heterogeneity in 25(OH)D assay methods and variable cutoff definitions limits comparability across studies.** The single randomized controlled trial (n = 58) limits generalizability, and several studies lacked adjustment for key confounders, including BMI, smoking, and sexual behavior. **Both null and paradoxical findings were observed, including no association with HPV clearance in a prospective cohort[6] and a paradoxical positive association in an HIV-stratified analysis[12], suggesting effect modification and outcome-specific variability rather than a consistent absence of association.** Methodological heterogeneity across study designs, exposure definitions, and outcome measures precluded meta-analysis.

Conclusion

Current evidence supports a predominant inverse association between serum 25-hydroxyvitamin D [25(OH)D] and hrHPV persistence[2,5], cervical dysplasia severity, and CIN2+ risk. Vitamin D insufficiency may impair immune surveillance, facilitating HPV persistence and progression to high-grade cervical neoplasia[4,12]. Preliminary interventional evidence demonstrates improved CIN1 regression with vitamin D supplementation, though larger prospective and randomized studies are needed to establish clinical utility. Given the disproportionate burden of cervical cancer in low- and middle-income countries where vitamin D insufficiency is common, optimizing 25(OH)D status may represent a scalable, low-cost adjunct to existing prevention strategies.

Future Directions

(1) *Standardized prospective cohorts with consistent 25(OH)D thresholds and validated LC-MS/MS assays;* ***(2)*** *larger RCTs targeting vitamin D optimization in CIN1/CIN2 populations prior to surgical intervention;* ***(3)*** *mechanistic studies examining FokI, BsmI, and TaqI VDR polymorphism interactions with hrHPV clearance;* ***(4)*** *longitudinal studies with ⩾12-month genotype-specific hrHPV persistence endpoints;* ***(5)*** *evaluation of vitamin D as a low-cost adjunct in cervical cancer prevention in LMICs.*