Review
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Vitamin D as a Preventive and Therapeutic Agent in Cervical Cancer: Insights from Clinical Studies

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Abstract

Cervical cancer remains a significant global health issue, closely linked to persistent human papillomavirus (HPV) infections. Vitamin D, recognized primarily for its role in calcium homeostasis and bone metabolism, has emerged as a promising preventive and therapeutic agent in cancer management. Recent clinical studies have suggested that vitamin D may effectively prevent cervical cancer and aid in the regression of early cervical dysplasia (CIN 1 orc LSIL). However, its therapeutic impact appears limited for advanced cervical dysplasia (CIN 2/3, HSIL) and established cervical cancer cases. Due to the progressive nature of cervical lesions, vitamin D supplementation represents a potentially valuable strategy for secondary prevention. This review critically evaluates current clinical evidence, underscores key insights into vitamin D's role in cervical cancer management, and highlights existing gaps requiring further research.

Keywords: *Vitamin D; calcitriol; cervical cancer; human papillomavirus (HPV); cervical dysplasia; CIN (cervical intraepithelial neoplasia); LSIL (low-grade squamous intraepithelial lesion); HSIL (high-grade squamous intraepithelial lesion); cancer prevention; supplementation*

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1. Introduction

Cervical cancer is among the ten most prevalent cancers globally, ranking eighth in incidence and ninth in mortality, affecting predominantly women, particularly in low- and middle-income countries where access to preventive and screening programs is limited [1]. According to GLOBOCAN 2022, cervical cancer accounts for about 650,000 new cases and approximately 350,000 deaths annually, significantly impacting healthcare systems and the quality of life of female patients worldwide [1]. The primary causative factor for cervical cancer is persistent infection with high-risk strains of human papillomavirus (HPV), implicated in nearly all diagnosed cases [2]. Despite substantial progress in vaccination and early detection, considerable disparities in outcomes persist, underscoring the need for innovative preventive and therapeutic strategies.

Vitamin D, primarily synthesized in the skin through sunlight exposure [3], has garnered increasing scientific interest due to its potential anticancer effects [4–6]. Traditionally recognized for its essential role in maintaining calcium homeostasis and bone health [7–9], vitamin D also demonstrates significant immunomodulatory [10], anti-inflammatory [11, 12], and anti-proliferative properties [13, 14]. These biological effects are primarily mediated by calcitriol, the active form of vitamin D, which interacts with vitamin D receptors (VDRs) to regulate gene expression in various tissues, including cervical epithelial cells [4, 15].

Emerging clinical evidence indicates that vitamin D could exert protective effects against cervical cancer and its precursors [16–19], particularly cervical intraepithelial neoplasia (CIN), as well as primarily low-grade lesions (LSILs) but possibly high-grade lesions (HSIL) as well. Potential mechanisms include inhibition of HPV-induced oncogenic processes [20, 21], induction of apoptosis [22], and suppression of angiogenesis in cervical tissues [23]. However, findings

across studies remain inconsistent, largely due to variations in study design, population demographics, and methodologies used to measure vitamin D levels.

This review synthesizes the current epidemiological and clinical data examining the relationship between vitamin D and cervical cancer, including its precancerous stages. It aims to identify crucial insights and highlight gaps within the current body of knowledge, providing a foundation for future research and exploring potential therapeutic applications for preventing and managing cervical neoplastic conditions.

2. Pathways of Absorption, Activation, and Cellular Targets of Vitamin D

Rather than originating solely from dietary intake, vitamin D—classified as a fat-soluble secosteroid [24]—is predominantly synthesized endogenously in the human skin following exposure to ultraviolet B (UVB) radiation [15]. The efficiency of this synthesis can be affected by several variables, including geographic latitude, age, melanin content, and sunscreen usage [15]. Dietary sources nonetheless contribute significantly, particularly through two main forms: ergocalciferol (vitamin D2), derived from plants, and cholecalciferol (vitamin D3), primarily found in animal-based foods such as oily fish, egg yolks, liver, and fortified products [15].

For optimal physiological function, vitamin D must be adequately absorbed in the gastrointestinal tract, a process that relies on the presence of dietary lipids to enable incorporation into micelles for intestinal uptake. This mechanism may be impaired in individuals with malabsorptive disorders like celiac disease, Crohn's disease, or pancreatic insufficiency [25]. Additionally, obesity is recognized as a limiting factor in vitamin D bioavailability due to its sequestration in adipose tissue, which reduces the level of active circulating metabolites [26, 27]. Following either dermal synthesis or dietary absorption, vitamin D undergoes a two-step hydroxylation process to become biologically active. The liver first converts it into 25-hydroxyvitamin D [25(OH)D] via 25-hydroxylase activity, yielding the main circulating form used to assess vitamin D status [28]. A subsequent transformation in the kidneys, mediated by 1α-hydroxylase, produces 1,25-dihydroxyvitamin D [1,25(OH)2D], or calcitriol—the hormonally active form that exerts biological functions through binding to the vitamin D receptor (VDR) [15]. The presence of VDR is not confined to classical target tissues; in fact, more than 30 distinct cell types express this receptor [29]. In gynecological malignancies—including endometrial, ovarian, cervical, and vulvar cancers—elevated VDR expression has been reported when compared to normal tissues, suggesting a potential involvement of vitamin D signaling in disease modulation [30].

3. Clinical Evidence Supporting the Role of Vitamin D in Cervical Cancer

The relationship between vitamin D supplementation and reduced cancer risk remains subject to ongoing scientific scrutiny [31, 32]. Nevertheless, various epidemiological studies have observed an inverse relationship between levels of solar exposure and the incidence of cervical cancer [33], an effect thought to stem from enhanced synthesis of vitamin D3 via ultraviolet radiation [34]. These correlations support the hypothesis of a photoprotective mechanism mediated by endogenous vitamin D production (**Table 1**).

Among notable contributions to this field is a Japanese case–control study that examined 405 women diagnosed with sporadic cervical neoplasia. This investigation found a statistically significant association between higher dietary intake of vitamin D and a decreased risk of developing cervical cancer, suggesting a possible protective role for the nutrient [35]. However, despite such observational data, no randomized clinical trial to date has confirmed a direct therapeutic benefit of calcitriol or vitamin D3 monotherapy in patients with invasive cervical malignancies. Instead, vitamin D has occasionally been explored as part of combination regimens. For instance, the Phase II PRIMMO clinical trial (trial number NCT03192059) investigated a five-drug immunomodulatory cocktail that included vitamin D, administered alongside pembrolizumab and radiotherapy in women with advanced or recurrent cervical and endometrial cancers [36].

The clinical literature also reflects a scarcity of robust data on the long-term effects of vitamin D supplementation in the management of cervical intraepithelial neoplasia (CIN). However, some trials present encouraging results. A six-month randomized, double-blind, placebo-controlled study conducted in Iran assessed the impact of vitamin D3 supplementation (50,000 IU administered twice monthly) on the regression of CIN1 (LSIL) in 58 women. The intervention group demonstrated a significantly higher regression rate compared to the placebo group (84.6% vs. 53.8%, $p = 0.01$), indicating potential efficacy in early-stage dysplasia [17].

Additionally, the therapeutic potential of local administration has also been explored. A separate study evaluated the application of vaginal suppositories containing 12,500 IU of vitamin D, used three nights per week for a six-week period. This regimen exhibited notable anti-inflammatory and anti-dysplastic effects in women diagnosed with CIN1 (LSIL), yet no measurable improvement was found among those with CIN2 (HSIL) [18]. The observed regression in LSIL cases may be explained by vitamin D's capacity to enhance viral clearance, particularly of HPV, from dysplastic cervical lesions [37].

In contrast, the effect of vitamin D in more advanced cervical precancerous conditions appears limited. A different clinical trial assessing long-term vitamin D3 supplementation in women with CIN2/3 (HSIL) failed to show a meaningful reduction in recurrence rates following treatment [38].

Furthermore, research in dermatological settings supports the antiviral properties of vitamin D3 [39–41]. Direct injection of vitamin D3 into HPV-related lesions [42, 43] has shown promising results, with positive outcomes observed in both genital and non-genital warts [44]. These findings bolster the hypothesis that vitamin D may possess broader antiviral activity relevant to HPV-associated pathologies beyond cervical dysplasia.

Table 1. Summary of clinical studies evaluating vitamin D and its role in cervical cancer and precancerous lesions.

Study design	Sample size	Population description	Vitamin D intervention	CIN stage	Key findings	Reference
Case–control	405 cases, 11,814 controls	Japanese women with invasive cervical cancer or CIN3	Dietary intake (calcium and vitamin D)	CIN3 and invasive	Inverse correlation between dietary intake and risk of cervical neoplasia	[35]
Case–control	23 cases, 62 controls	Turkish women with HPV infection	Serum vitamin D level	-	Lower vitamin D levels in HPV patients vs. controls	[17]
Case–control	188 cases, 188 controls	Chinese women with CIN2 and HPV16	VDR gene polymorphism	CIN2	VDR polymorphism linked to increased CIN2/HSIL risk	[45]
Case–control	204 cases, 204 controls	Thai women with cervical cancer	VDR gene polymorphism	SCC	Genetic VDR variation associated with higher cancer risk	[46]
Cross-sectional	2,353 cases	American women with HPV infection	Serum vitamin D level	-	Higher vitamin D linked to lower HPV prevalence	[47]
Cross-sectional	72 cases	American women with persistent high-risk HPV	Serum vitamin D level	-	Higher vitamin D associated with persistence of high-risk HPV	[37]
Randomized controlled trial	29 cases, 29 controls	Iranian women with CIN1	Oral vitamin D3 supplementation	CIN1	Significant lesion regression with supplementation	[16]
Randomized controlled trial	29 cases, 29 controls	Iranian women with CIN2/3	Oral vitamin D3 supplementation	CIN2/3	No effect on recurrence after supplementation	[38]
Phase II trial	18 cases	Belgian women with advanced cervical cancer	Vitamin D-containing drug combination	Advanced/ recurrent	Modest but durable antitumor effect with tolerable toxicity	[36]
Clinical observation	20 cases	German women with CIN1/2 and recurrent infections	Vitamin D vaginal suppositories	CIN1 and CIN2	Positive outcome for CIN1; no benefit in CIN2	[18]

4. Discussion

While a minority of investigations have found no conclusive link between vitamin D and cervical cancer progression [48], the prevailing scientific consensus points toward a favorable influence of calcitriol in modulating disease risk. This trend aligns with the broader evidence supporting its antitumor potential across various oncological contexts [49]. Numerous studies indicate that increased dietary intake of vitamin D correlates with a decreased likelihood of cervical cancer de-

velopment [35], whereas deficiency in this micronutrient is commonly observed among women diagnosed with cervical intraepithelial neoplasia and invasive malignancies of the cervix [17, 38].

Among the multiple determinants of vitamin D insufficiency, obesity plays a substantial role and is itself a recognized predisposing factor for cervical cancer [50]. In individuals with excess body fat, several physiological mechanisms may contribute to lowered bioavailable vitamin D: its dilution within larger fat stores, sequestration within adipose tissue, reduced levels of physical activity, and limited sun exposure [50]. Dietary insufficiency and limited ultraviolet exposure are further contributors to this state of deficiency [50].

Biochemical imbalances also play a part. Lower circulating levels of vitamin D-binding protein (DBP) have been reported in cervical cancer patients [51], and single-nucleotide polymorphisms in the vitamin D receptor (VDR) gene have been associated with altered receptor functionality and transcriptional response, potentially affecting the biological impact of vitamin D in cervical epithelial cells [46, 47].

Despite promising results in early-stage disease prevention, both vitamin D and calcitriol appear to offer minimal therapeutic benefit in advanced stages of cervical cancer, even when applied alongside conventional treatments such as radiotherapy [52].

Lastly, while generally safe at recommended doses, vitamin D supplementation carries a risk of toxicity when consumed in excess. Hypervitaminosis D can lead to elevated serum calcium levels—hypercalcemia—manifesting in symptoms such as gastrointestinal discomfort, polyuria, and persistent thirst. These outcomes, though uncommon, are typically linked to prolonged or unsupervised high-dose intake [53].

5. Conclusions

Cumulative clinical findings suggest that vitamin D may play a meaningful role in the prevention of cervical cancer, particularly in early-stage lesions such as CIN1 or LSIL. Supplementation with vitamin D—whether administered systemically or locally—has demonstrated favorable outcomes in supporting regression of low-grade cervical dysplasia. However, this effect does not appear to extend to more advanced dysplastic changes, such as CIN2/3 or HSIL, where the therapeutic response remains limited.

Given the stepwise progression of cervical neoplasia and the relatively long latency period before high-grade lesions develop, vitamin D could represent a viable strategy for secondary prevention. Current evidence primarily originates from pilot-scale trials with modest sample sizes, yet the consistent biological rationale and observed clinical signals justify the need for expanded research.

Both oral supplementation and local (vaginal) delivery of vitamin D have shown acceptable safety profiles and low toxicity, making them attractive candidates for future studies. Considering vitamin D's low cost, ease of administration, and broad range of physiological benefits, larger, well-powered cohort studies are warranted to validate its use in routine preventive gynecologic care, especially in populations at higher risk of HPV persistence and cervical neoplastic progression.

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Author contributions

S.A., A.M.D., A.-M.C., M.M. and A.I.R. jointly contributed to the conceptual design of the study. Methodological framework development and experimental planning were carried out by S.A., M.M. and A.I.R. Data resources and background literature were provided by S.A. and A.I.R. The initial manuscript draft was written by A.M.D. and A.-M.C., while revisions and editorial input were contributed by S.A., M.M. and A.I.R. A.I.R. oversaw the project and provided supervision. Project administration was the responsibility of S.A. All authors have reviewed and approved the final version of the manuscript for publication.

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