ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jul700

# Vitamin D in Cancer Prevention, Therapy, and Survival Pharmacological Perspectives, Clinical Evidence and the Cancer Incidence–Mortality Paradox

Dr. Pasham Uma[1]*; Ch. Kheroda Devi[1]; Dr. R. L. Manisha[2]; Muvvala Sudhakar[3]

[1.] Assistant Professor, Department of Pharmacology, Malla Reddy College of Pharmacy, Maisammaguda, Dhullapally, Secunderabad, Telangana, India, 500100.

[2.]Department of Pharmacology, Malla Reddy College of Pharmacy, Maisammaguda, Dhulapally, Secunderabad–500100, Telangana, India.

Corresponding Author: Dr. Pasham Uma*

Publication Date: 2026/07/24

**Abstract: Vitamin D, classically known for its role in calcium homeostasis and bone health, has attracted enormous interest as a potential anticancer agent following the discovery of the vitamin D receptor (VDR) in numerous tissues and the demonstration of antiproliferative, pro-differentiating, pro-apoptotic, anti-angiogenic, and immunomodulatory effects of its active metabolite, 1,25-dihydroxyvitamin D, in preclinical models. A large body of observational epidemiological evidence has consistently associated higher vitamin D status (serum 25-hydroxyvitamin D) and higher sunlight/vitamin D intake with lower cancer incidence and mortality, particularly for colorectal cancer, generating substantial enthusiasm for vitamin D supplementation as a cancer-prevention strategy. However, this review emphasizes a critical and frequently under-appreciated distinction: the large randomized controlled trials of vitamin D supplementation (notably VITAL, D-Health, and ViDA) have largely FAILED to demonstrate a reduction in cancer INCIDENCE, contradicting the observational associations and suggesting that low vitamin D may be a marker of poor health rather than a cause of cancer (confounding and reverse causation). In contrast, a more consistent — though still debated — signal has emerged for a reduction in cancer MORTALITY with vitamin D supplementation, supported by meta-analyses suggesting an approximately 12-13% reduction in cancer death, and for benefit in specific subgroups (normal-weight individuals, daily rather than bolus dosing, and possibly those with baseline deficiency). This review provides a comprehensive pharmacological analysis including vitamin D metabolism and the VDR, the preclinical antineoplastic mechanisms, the observational epidemiology, the critical appraisal of the major randomized trials and the incidence-versus-mortality distinction, vitamin D in cancer patients and survival, the distinctive Indian context of paradoxically high vitamin D deficiency despite abundant sunshine, and future directions including personalized supplementation and the targeting of baseline-deficient populations.**

***Keywords:*** *Vitamin D; 25-Hydroxyvitamin D; Vitamin D Receptor; Cancer Prevention; Cancer Mortality; Colorectal Cancer; VITAL Trial; D-Health Trial; Calcitriol; Supplementation; Reverse Causation; Vitamin D Deficiency.*

**How to Cite:** Dr. Pasham Uma; Ch. Kheroda Devi; Dr. R. L. Manisha; Muvvala Sudhakar (2026) Vitamin D in Cancer Prevention, Therapy, and Survival Pharmacological Perspectives, Clinical Evidence and the Cancer Incidence–Mortality Paradox. *International Journal of Innovative Science and Research Technology*, 11(7), 975-984. https://doi.org/10.38124/ijisrt/26jul700

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jul700

## I. INTRODUCTION

Vitamin D is a fat-soluble secosteroid classically recognized for its central role in calcium and phosphate homeostasis and bone mineralization, with deficiency causing rickets in children and osteomalacia in adults. Over the past several decades, however, the discovery of the vitamin D receptor (VDR) in a wide range of tissues beyond those involved in calcium homeostasis — including many cancer cell types — and the demonstration of diverse 'non-classical' effects of vitamin D have generated enormous interest in its potential roles in numerous conditions, prominently including cancer. The hypothesis that vitamin D might prevent or modify cancer has been among the most extensively investigated, and most contentious, in nutritional and preventive oncology. [1]

The interest in vitamin D as an anticancer agent rests on two pillars. First, preclinical studies have demonstrated that the active vitamin D metabolite, 1,25-dihydroxyvitamin D (calcitriol), exerts antiproliferative, pro-differentiating, pro-apoptotic, anti-angiogenic, and immunomodulatory effects on cancer cells in vitro and in animal models, providing biological plausibility for an anticancer role. Second, a large and consistent body of observational epidemiological evidence has associated higher vitamin D status (measured as serum 25-hydroxyvitamin D, the standard indicator of vitamin D status) and higher sunlight exposure or vitamin D intake with lower incidence and mortality of several cancers, most consistently colorectal cancer. These observations generated substantial enthusiasm and widespread vitamin D supplementation for purported cancer prevention. [2]

However, this review emphasizes a critical and frequently under-appreciated distinction that has emerged from rigorous research: the discrepancy between the observational associations and the results of large randomized controlled trials (RCTs). While observational studies consistently associate low vitamin D with higher cancer risk, the major RCTs of vitamin D supplementation — designed to test causation — have largely failed to demonstrate a reduction in cancer incidence. This discrepancy strongly suggests that the observational associations may reflect confounding (low vitamin D being a marker of poor general health, obesity, or low physical activity, which independently increase cancer risk) and reverse causation (subclinical illness lowering vitamin D), rather than vitamin D deficiency causing cancer. This is a crucial lesson in the interpretation of nutritional epidemiology. [3]

Importantly, however, the picture is nuanced rather than simply negative. While the RCTs have not shown reduced cancer incidence, a more consistent — though still debated — signal has emerged for a reduction in cancer MORTALITY (death from cancer) with vitamin D supplementation, supported by meta-analyses suggesting an approximately 12-13% reduction in cancer death, and for benefit in specific subgroups (normal-weight individuals, those receiving daily rather than infrequent bolus dosing, and possibly those with baseline deficiency). The distinction between cancer incidence (whether vitamin D prevents cancer developing) and cancer mortality (whether it reduces death once cancer occurs), and the identification of subgroups who may benefit, are central to a balanced contemporary understanding. [4]

This review provides a comprehensive pharmacological analysis of vitamin D in cancer prevention, treatment, and survival. We examine vitamin D metabolism and the VDR; the preclinical antineoplastic mechanisms; the observational epidemiology; the critical appraisal of the major randomized trials (VITAL, D-Health, ViDA, and others) and the crucial incidence-versus-mortality distinction; vitamin D in cancer patients and survival; the distinctive Indian context of paradoxically high vitamin D deficiency despite abundant sunshine; and future directions including personalized supplementation and the targeting of baseline-deficient populations. Throughout, we emphasize a balanced, evidence-based appraisal that distinguishes the genuine signals from the over-interpreted associations.

## II. VITAMIN D METABOLISM AND THE VDR

### ➢ *Vitamin D Synthesis and Metabolism*

Vitamin D is obtained from cutaneous synthesis and dietary sources. In the skin, ultraviolet B (UVB) radiation converts 7-dehydrocholesterol to previtamin D3, which isomerizes to vitamin D3 (cholecalciferol); vitamin D2 (ergocalciferol) and D3 are also obtained from diet and supplements. Vitamin D is biologically inert and requires two hydroxylation steps for activation: first in the liver, by 25-hydroxylase (CYP2R1), to 25-hydroxyvitamin D [25(OH)D] — the major circulating form and the standard measure of vitamin D status; and second in the kidney (and other tissues), by 1-alpha-hydroxylase (CYP27B1), to the active hormone 1,25-dihydroxyvitamin D [1,25(OH)2D, calcitriol]. Renal 1-alpha-hydroxylase is tightly regulated for calcium homeostasis, but importantly, many extra-renal tissues (including many cancer cells) express 1-alpha-hydroxylase, enabling local production of active calcitriol for autocrine/paracrine effects — central to the non-classical anticancer hypothesis. [5]

### ➢ *The Vitamin D Receptor*

The active metabolite calcitriol exerts its effects predominantly through the vitamin D receptor (VDR), a nuclear receptor that, upon binding calcitriol, heterodimerizes with the retinoid X receptor (RXR) and binds vitamin D response elements (VDREs) in target gene promoters, regulating the transcription of hundreds of genes. The VDR is expressed not only in tissues involved in calcium homeostasis (intestine, bone, kidney, parathyroid) but in a wide range of tissues including immune cells, skin, and many epithelial tissues — and critically, in many cancer cell types. The widespread VDR expression, including in cancers, and the regulation of genes involved in proliferation, differentiation, apoptosis, and

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jul700

angiogenesis, underlie the biological rationale for vitamin D's hypothesized anticancer effects. [6]

## III. PRECLINICAL ANTINEOPLASTIC MECHANISMS

In preclinical studies, calcitriol and its analogs exert multiple antineoplastic effects on cancer cells. These include: antiproliferative effects (cell cycle arrest, predominantly at the G1/S checkpoint, through upregulation of cyclin-dependent kinase inhibitors such as p21 and p27 and downregulation of proliferative signaling); pro-differentiating effects (promoting cancer cells toward a more differentiated, less malignant phenotype); pro-apoptotic effects (promoting programmed cell death, including modulation of Bcl-2 family proteins); anti-angiogenic effects (inhibiting tumor blood vessel formation); anti-invasive and anti-metastatic effects; and immunomodulatory effects (modulating immune responses relevant to tumor surveillance). [7]

These pleiotropic antineoplastic effects, demonstrated across numerous cancer cell lines and animal models, provide substantial biological plausibility for an anticancer role of vitamin D. However, an important caveat is that the concentrations of calcitriol required to produce these effects in vitro are often substantially higher than those achievable systemically in humans without causing hypercalcemia (the dose-limiting toxicity of calcitriol). This gap between the preclinical concentrations and physiologically/therapeutically achievable levels is one explanation for the discrepancy between the promising preclinical data and the disappointing clinical trial results for cancer prevention, and motivated the development of vitamin D analogs with reduced calcemic effects (deltanoids) for potential therapeutic use, though these have not achieved clinical success in oncology. The preclinical promise must be interpreted with this translational gap in mind.

## IV. OBSERVATIONAL EPIDEMIOLOGY

A large body of observational epidemiological evidence has associated vitamin D with cancer. Early ecological studies (Garland and colleagues, from the 1980s) observed that cancer mortality, particularly colorectal cancer, was higher in regions with less sunlight (higher latitudes, less UVB), generating the 'sunlight/vitamin D hypothesis.' Subsequent observational studies — case-control and prospective cohort studies — generally found that higher serum 25(OH)D levels were associated with lower risk of several cancers, with the most consistent evidence for colorectal cancer. Associations have also been reported, less consistently, for breast, prostate, and other cancers, and higher 25(OH)D has been associated with lower cancer mortality. [8]

However, observational evidence, however consistent, cannot establish causation, and is subject to important limitations in the vitamin D-cancer context. Confounding is a major concern: low vitamin D status is associated with obesity (vitamin D is sequestered in adipose tissue, and obese individuals have lower 25(OH)D), physical inactivity (less outdoor activity, less sun exposure), poor diet, and chronic illness — all of which independently affect cancer risk, potentially creating spurious associations. Reverse causation is also a concern: subclinical or undiagnosed cancer, and the inflammation and reduced outdoor activity it causes, may lower vitamin D levels, making low vitamin D a consequence rather than a cause of (incipient) cancer. These limitations mean that the observational associations, while hypothesis-generating, required testing by randomized trials to establish causation. [9]

## V. THE RANDOMIZED TRIALS: A CRITICAL APPRAISAL

### ➢ *The VITAL Trial*

The VITAL (Vitamin D and Omega-3 Trial) was a large, rigorous, randomized, double-blind, placebo-controlled trial that randomized over 25,000 US adults to vitamin D3 (2000 IU/day) and/or omega-3 fatty acids versus placebo, with cancer (and cardiovascular disease) as primary endpoints, followed for a median of approximately 5.3 years. For the primary cancer endpoint, VITAL found that vitamin D supplementation did NOT significantly reduce the incidence of total invasive cancer compared with placebo. This was a pivotal result, as the largest and most rigorous trial designed to test the hypothesis, and its failure to show reduced cancer incidence substantially tempered the enthusiasm for vitamin D as a cancer-prevention agent. [10]

However, VITAL's findings were nuanced and require careful interpretation. While total cancer incidence was not reduced, secondary and exploratory analyses suggested possible benefits: a reduction in cancer mortality emerged in some analyses (particularly when excluding the early years of follow-up, accounting for the latency of any mortality benefit); and a possible reduction in cancer incidence and mortality among normal-weight individuals (but not among overweight/obese individuals, suggesting a body-weight interaction whereby higher body weight may blunt the response). These secondary findings, while hypothesis-generating rather than definitive, contributed to the nuanced contemporary view that vitamin D may not prevent cancer occurrence broadly but might reduce cancer mortality and benefit specific subgroups. [11]

### ➢ *D-Health, ViDA, and Other Trials*

Other large RCTs have generally reinforced the picture. The D-Health trial (Australia) randomized over 21,000 older adults to monthly high-dose vitamin D3 (60,000 IU) or placebo; it found no significant reduction in cancer incidence or, in the primary analysis, cancer mortality, though some analyses suggested possible mortality benefit. The ViDA trial (New Zealand) used monthly bolus dosing and found no cancer benefit. The Women's Health Initiative (WHI) calcium plus vitamin D trial (lower dose, 400 IU/day) found no reduction in colorectal or total cancer. Notably, the trials using infrequent large bolus dosing (D-Health monthly, ViDA monthly) may be

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jul700

less effective than daily dosing (the more physiological approach used in VITAL), a factor in interpreting the mortality signal. [12, 13]

- *The Incidence-Versus-Mortality Distinction and Meta-Analyses*

Synthesizing the RCT evidence, a crucial distinction has emerged between cancer incidence and cancer mortality. Meta-analyses of vitamin D RCTs have consistently found NO significant effect on cancer incidence, supporting the conclusion that vitamin D supplementation does not prevent cancer from developing in general populations. However, meta-analyses have more consistently suggested a reduction in cancer MORTALITY — by approximately 12-13% — with vitamin D supplementation, with this benefit being more apparent with daily (rather than bolus) dosing. This distinction suggests that vitamin D may not prevent cancer occurrence but might favorably influence the progression or lethality of cancer once it occurs, consistent with the preclinical effects on differentiation and progression. This remains debated and not definitively established, but represents the most promising and consistent signal. [14, 15]

The critical appraisal of the vitamin D-cancer evidence yields several important conclusions. First, the discrepancy between the strong observational associations and the largely null RCT results for cancer incidence is a paradigmatic example of how confounding and reverse causation can produce misleading observational associations, underscoring the necessity of randomized trials for causal inference — an important lesson in evidence-based medicine. Second, vitamin D supplementation does not appear to prevent cancer incidence in general (largely vitamin D-replete) populations. Third, a more promising but still-debated signal exists for reduced cancer mortality, particularly with daily dosing. Fourth, specific subgroups (normal-weight individuals, those with baseline deficiency) may derive benefit, motivating a more targeted rather than population-wide approach. This balanced interpretation avoids both the over-enthusiasm of the observational era and the dismissiveness that the negative incidence results might prompt.

## VI. VITAMIN D IN CANCER PATIENTS AND SURVIVAL

Beyond prevention, vitamin D status and supplementation in patients with established cancer have been studied in relation to survival and outcomes. Vitamin D deficiency is highly prevalent among cancer patients (related to reduced outdoor activity, poor nutrition, the illness itself, and treatment effects), and observational studies have associated lower vitamin D status with worse survival in several cancers, particularly colorectal cancer. This has raised the question of whether vitamin D supplementation in cancer patients improves outcomes. Some randomized trials in cancer patients (such as the SUNSHINE trial in metastatic colorectal cancer, which combined vitamin D with chemotherapy) have suggested possible benefits in progression-free survival, though the evidence is limited and not definitive. [16]

The role of vitamin D in cancer patients includes: the high prevalence of deficiency warranting attention; the correction of deficiency for general health and bone health (particularly important in patients on treatments affecting bone, such as aromatase inhibitors or androgen deprivation therapy); and the possible, though unproven, benefit on cancer outcomes. Current evidence supports correcting vitamin D deficiency in cancer patients for established reasons (bone health, general health) and does not support high-dose vitamin D as an anticancer treatment outside of trials, but the survival signal warrants continued investigation. The distinction between correcting deficiency (reasonable) and using vitamin D as an anticancer therapy (unproven) is important. The mortality/survival signal, if confirmed, would suggest that vitamin D's value lies more in influencing cancer outcomes than in preventing cancer occurrence.

## VII. INDIAN CONTEXT

India presents a striking and paradoxical vitamin D situation: despite abundant sunshine across most of the country, vitamin D deficiency is highly prevalent — affecting an estimated 50-90% of the population across various studies, including in sunny regions. This 'sunshine paradox' reflects multiple factors: darker skin pigmentation (higher melanin reduces cutaneous vitamin D synthesis, requiring more sun exposure); cultural and lifestyle factors (extensive skin covering with clothing, indoor lifestyles, urbanization, avoidance of midday sun); air pollution (reducing UVB reaching the skin in cities); limited dietary vitamin D (low consumption of vitamin D-rich foods and limited food fortification); and possibly genetic factors. This widespread deficiency makes vitamin D a significant public health issue in India, independent of any cancer consideration. [17]

The high prevalence of vitamin D deficiency in India is relevant to the cancer question in a specific way: while the RCTs (conducted largely in vitamin D-replete Western populations) found no cancer-incidence benefit, it is hypothesized — though not proven — that supplementation might be more beneficial in genuinely deficient populations (correcting a true deficiency rather than supplementing replete individuals). India's high deficiency prevalence means that, if a benefit of correcting deficiency exists, a larger proportion of the Indian population might be in the relevant deficient range. However, this remains hypothetical, and the RCT evidence does not support vitamin D supplementation specifically for cancer prevention even in this context. India's cancer burden is large and growing, making cancer prevention and management important, but the evidence does not support vitamin D as a cancer-prevention strategy. [18]

Indian considerations regarding vitamin D and cancer include: the very high prevalence of vitamin D deficiency

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jul700

warranting attention for its established consequences (bone health, and the general health for which deficiency is a marker); the importance of correcting deficiency for bone and general health (and in cancer patients for the established reasons); the lack of evidence supporting vitamin D supplementation specifically for cancer prevention (even given high deficiency); the need for India-specific research on vitamin D status, the determinants of the sunshine paradox, and any role in the Indian cancer context; the role of food fortification and public health measures to address the widespread deficiency; and the avoidance of over-supplementation and the misperception of vitamin D as a cancer-prevention agent. The high deficiency prevalence makes addressing vitamin D status a genuine Indian public health priority for its established benefits, distinct from the unproven cancer-prevention claims. [19]

Indian research and education priorities related to vitamin D and cancer include: characterization of vitamin D status across Indian populations and the determinants of the sunshine paradox; research on the consequences of the widespread deficiency and the benefits of correction for established outcomes; the role (if any) of vitamin D in the Indian cancer context, with appropriate skepticism given the RCT evidence; public health strategies (food fortification, awareness, sensible sun exposure) to address deficiency; and pharmacology education addressing vitamin D metabolism and the VDR, the preclinical antineoplastic mechanisms and their translational limitations, the critical distinction between observational associations and RCT evidence (an exemplary lesson in evidence appraisal and the role of confounding/reverse causation), the incidence-versus-mortality distinction, and the distinctive Indian context of paradoxical widespread deficiency. The vitamin D-cancer story is a valuable teaching example of evidence-based medicine, distinguishing genuine public health priorities (addressing deficiency) from over-interpreted claims (cancer prevention).

## VIII. SUMMARY TABLES

Table 1. Overview of Vitamin D Metabolism and Activation Pathway

| Step | Site | Enzyme | Product / Outcome |
|---|---|---|---|
| **Synthesis** | Skin (upon exposure to UVB radiation) | — | Vitamin $D_3$ (Cholecalciferol) synthesized from 7-dehydrocholesterol |
| **First Hydroxylation** | Liver | 25-Hydroxylase (CYP2R1) | 25-Hydroxyvitamin D [25(OH)D, Calcidiol] – the major circulating form and clinical marker of vitamin D status |
| **Second Hydroxylation** | Kidney (primarily) and extra-renal tissues | 1α-Hydroxylase (CYP27B1) | 1,25-Dihydroxyvitamin D [$1,25(OH)_2D$, Calcitriol] – the biologically active form |
| **Action** | Target tissues (intestine, bone, kidney, immune cells, prostate, breast, colon, etc.) | Vitamin D Receptor (VDR)-Retinoid X Receptor (RXR) complex binds to Vitamin D Response Elements (VDREs) | Regulation of gene transcription controlling calcium homeostasis, cell proliferation, differentiation, apoptosis, and immune responses |
| **Extra-renal Activation** | Cancer cells, immune cells (macrophages, dendritic cells), placenta, skin, and other tissues | CYP27B1 | Local production of calcitriol for autocrine and paracrine regulation of cellular functions, independent of systemic calcium metabolism |

Table 2. Anticancer Mechanisms of Vitamin D: Evidence from Preclinical Studies

| Mechanism | Effect |
|---|---|
| **Antiproliferative** | Slows cancer cell growth by causing G1/S cell cycle arrest (↑ p21, p27). |
| **Pro-differentiation** | Promotes the development of mature, less aggressive cancer cells. |
| **Pro-apoptotic** | Induces programmed cell death (apoptosis) in cancer cells. |
| **Anti-angiogenic** | Prevents the formation of new blood vessels that supply tumors. |
| **Anti-invasive / Anti-metastatic** | Reduces cancer cell invasion and spread to other organs. |
| **Immunomodulatory** | Enhances and regulates the body's anti-tumor immune response. |
| **Limitation** | Most beneficial effects are observed at vitamin D concentrations higher than those safely achievable in humans. |

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jul700

Table 3. Major Randomized Controlled Trials Evaluating Vitamin D Supplementation and Cancer Outcomes

| Clinical Trial | Vitamin D Dose | Cancer Incidence | Cancer Mortality |
|---|---|---|---|
| **VITAL** | 2,000 IU/day | No significant reduction | Possible reduction in secondary analyses |
| **D-Health** | 60,000 IU/month | No significant reduction | No significant reduction (some positive trend) |
| **ViDA** | 100,000 IU/month | No significant reduction | No significant reduction |
| **WHI (Calcium + Vitamin D)** | 400 IU/day | No significant reduction | No significant reduction |
| **Meta-analyses** | Various doses | No significant effect | Approximately 12–13% reduction, particularly with daily supplementation |

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| **WHI (Calcium + Vitamin D)** | 400 IU/day | No significant reduction | No significant reduction |
| **Meta-analyses** | Various doses | No significant effect | Approximately **12–13% reduction**, particularly with daily supplementation |

Table 4. Evidence Comparing the Effects of Vitamin D Supplementation on Cancer Incidence and Cancer Mortality

| Question | Evidence | Conclusion |
|---|---|---|
| **Does vitamin D prevent cancer?** | Most clinical trials found no reduction in cancer cases. | No clear evidence that vitamin D prevents cancer. |
| **Does vitamin D reduce cancer deaths?** | Some studies show about a 12–13% reduction in cancer deaths, especially with daily supplementation. | May help reduce cancer mortality. |
| **What do observational studies show?** | Low vitamin D levels are linked to a higher cancer risk. | The association may be due to other factors. |
| **Who may benefit the most?** | People with vitamin D deficiency or normal body weight may benefit more. | More research is needed to confirm this. |
| **Does the dose schedule matter?** | Daily supplementation appears more effective than large monthly doses. | Daily dosing may provide better outcomes. |

Table 5. Vitamin D Deficiency and Public Health Considerations in India

| Aspect | Current Status in India | Key Points |
|---|---|---|
| **Vitamin D deficiency** | Very common (≈50–90%) | High prevalence despite abundant sunlight. |
| **Reasons for deficiency** | Multiple contributing factors | Darker skin pigmentation, limited sun exposure, clothing, air pollution, and poor dietary intake. |
| **Skin pigmentation** | Higher melanin content | Reduces vitamin D synthesis in the skin. |
| **Dietary intake** | Generally low | Limited consumption of vitamin D-rich or fortified foods. |
| **Air pollution** | High in many urban areas | Decreases UVB exposure required for vitamin D production. |
| **Cancer prevention** | Evidence is insufficient | Current evidence does not support vitamin D supplementation solely for cancer prevention. |
| **Correction of deficiency** | Recommended | Important for maintaining bone health and overall health. |
| **Public health strategies** | Fortification and awareness | Promote food fortification, supplementation in high-risk groups, and public education. |
| **Clinical relevance** | High | Highlights the importance of evidence-based practice and addressing widespread deficiency. |

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jul700

## IX. FUTURE DIRECTIONS

Several directions will shape the future of vitamin D-cancer research and practice. First, the most promising signal — the possible reduction in cancer mortality with vitamin D supplementation, particularly daily dosing — warrants confirmation through dedicated trials with cancer mortality as a primary endpoint, adequate duration to capture mortality effects, and daily dosing. Second, the hypothesis that supplementation benefits specifically those with baseline deficiency (rather than replete populations) should be tested through trials enrolling deficient individuals, which would be particularly relevant to high-deficiency populations like India; the prevailing 'one-size-fits-all' supplementation of replete populations is not supported.

Third, the body-weight interaction observed in VITAL (benefit in normal-weight but not overweight/obese individuals) warrants investigation, including whether weight-adjusted dosing might extend benefit. Fourth, the role of vitamin D in cancer patients (survival, outcomes, and the correction of the prevalent deficiency) requires continued study, distinguishing the established value of correcting deficiency from the unproven anticancer role. Fifth, Mendelian randomization studies (using genetic variants affecting vitamin D as instruments to assess causation, less subject to confounding) have generally not supported a causal protective effect on cancer incidence, consistent with the RCTs, and continued genetic epidemiology will refine causal understanding.

Sixth, for the Indian context, the priorities include addressing the genuine public health problem of widespread vitamin D deficiency (for its established consequences) through fortification and awareness, India-specific research on vitamin D status and the sunshine paradox, appropriate skepticism regarding cancer-prevention claims, and the avoidance of both deficiency and over-supplementation. The vitamin D-cancer story, properly understood, teaches the importance of rigorous evidence (RCTs over observational associations), the distinction between markers and causes, and the difference between addressing genuine deficiency (worthwhile) and pursuing unproven prevention claims (not supported) — lessons of broad value in evidence-based medicine and public health.

## X. CONCLUSION

Vitamin D, with its well-characterized antiproliferative, pro-differentiating, pro-apoptotic, anti-angiogenic, and immunomodulatory effects in preclinical cancer models and its widespread receptor expression including in cancers, has been one of the most extensively investigated and contentious topics in preventive oncology. The large body of observational evidence consistently associating higher vitamin D status with lower cancer incidence and mortality generated enormous enthusiasm for vitamin D supplementation as a cancer-prevention strategy. However, rigorous appraisal reveals a more sobering and nuanced picture that is essential for evidence-based practice.

The major randomized controlled trials — VITAL, D-Health, ViDA, and others — have largely failed to demonstrate a reduction in cancer incidence with vitamin D supplementation, contradicting the observational associations and indicating that low vitamin D is more likely a marker of poor health (through confounding and reverse causation) than a cause of cancer. This discrepancy is a paradigmatic lesson in the limitations of observational nutritional epidemiology and the necessity of randomized trials for causal inference. Vitamin D supplementation does not appear to prevent cancer occurrence in general, largely replete populations.

However, the picture is not simply negative: a more consistent, though still-debated, signal has emerged for a reduction in cancer mortality (approximately 12-13% in meta-analyses, particularly with daily dosing), and possible benefit in specific subgroups (normal-weight individuals, those with baseline deficiency). This suggests vitamin D may influence cancer progression and lethality more than occurrence — the most promising avenue for future confirmation. The distinction between cancer incidence and cancer mortality, and between supplementing replete populations and correcting genuine deficiency, is central to a balanced understanding.

For the Indian context, vitamin D deficiency is paradoxically highly prevalent despite abundant sunshine, owing to pigmentation, cultural, pollution, and dietary factors, making it a genuine public health priority for its established consequences. However, this widespread deficiency does not translate into evidence-supported cancer prevention through supplementation. Pharmacology educators should emphasize the vitamin D-cancer story as an exemplary teaching case in evidence-based medicine — illustrating vitamin D metabolism and the VDR, the preclinical mechanisms and their translational limitations, the critical distinction between observational associations and randomized evidence (and the roles of confounding and reverse causation), the incidence-versus-mortality distinction, and the distinctive Indian context — and should help distinguish the genuine priorities (addressing deficiency for established benefits) from the over-interpreted and unsupported claims (cancer prevention). The vitamin D-cancer narrative remains a valuable, instructive, and ongoing story at the intersection of pharmacology, nutrition, oncology, and the principles of rigorous evidence appraisal.

## ACKNOWLEDGMENTS

The authors thank the Department of Pharmacology and the Management of Malla Reddy College of Pharmacy,

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26jul700

Secunderabad, for institutional support, and the library and information resource centre for facilitating literature access.

➢ *Conflict of Interest*

The authors declare no conflict of interest, financial or otherwise.

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