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The Multifaceted Impact of Vitamin D on Cancer: A Review of Evidence and Opportunities

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A B S T R A C T :

Cancer, exemplified by breast and lung cancers, ranks among the most prevalent malignancies globally, with vitamin D emerging as a potential modulator through its active metabolite, calcitriol, extending beyond its traditional skeletal health role. Epidemiological data indicate an inverse relationship between 25-hydroxyvitamin D (25OHD) levels and cancer risk, particularly in breast and colorectal cancers, though causality remains contested. Preclinical studies showcase calcitriol's inhibition of tumor growth and enhancement of immunotherapy responses in animal models, while clinical trials like AMATERASU and SUNSHINE demonstrate improved survival outcomes in vitamin D-deficient cancer patients with supplementation. Vitamin D's bioavailability, shaped by factors such as obesity and VDR polymorphisms, underscores the need for tailored approaches. Despite these advances, challenges in dosing, measurement, and study design persist, necessitating further investigation to clarify its therapeutic potential in cancer prevention and treatment. This review aims to highlight the multifaceted interplay of vitamin D in cancer pathophysiology, integrating epidemiological, preclinical, and clinical perspectives.

Keywords: Vitamin D, Cancer, Calcitriol, Tumor Microenvironment, Apoptosis

1. Introduction

Cancer remains a leading cause of morbidity and mortality worldwide, with its etiology rooted in a complex interplay of genetic, environmental, and lifestyle factors (Gale, 2024). Among these, the role of vitamin D—a fat-soluble secosteroid traditionally recognized for its skeletal benefits—has garnered significant attention for its potential anti-cancer properties (Holick, 2004). Emerging evidence suggests that vitamin D influences cellular processes beyond calcium homeostasis, including cell proliferation, apoptosis, and immune modulation, all of which are critical in cancer development and progression (Feldman et al., 2014). This review explores the multifaceted relationship between vitamin D and cancer, drawing on epidemiological data, molecular mechanisms, preclinical studies, and therapeutic implications, with a particular focus on breast and lung cancers as highlighted in recent research. The formulation of the capsaicin emulgel involved the use of various excipients and active ingredients. The oil phase was prepared using light liquid paraffin as the oil component, with Span 20 acting as the emulsifier. The aqueous phase consisted of purified water, in which Tween 20 was dissolved to facilitate emulsification. The gel base was formulated using a suitable polymer dispersed in purified water, with triethanolamine (TEA) used to adjust the pH to a range of 6.0 to 6.5. During the final formulation step, glycerine was incorporated into the mixture in a 1:1 ratio of gel to emulsion to enhance the consistency and spreadability of the final product.

Epidemiology of Cancer and Vitamin D Status

Cancer incidence varies globally, with breast cancer being the most prevalent malignancy among women, accounting for approximately 36% of cases, and lung cancer ranking as the second most common (Smolarz et al., 2022; Siegel et al., 2023). In 2018, an estimated 2.089 million women were diagnosed with breast cancer, predominantly in developed nations, where nearly half of all cases occur (Smolarz et al., 2022). This geographic disparity suggests a link between lifestyle factors, such as vitamin D status, and cancer risk (Garland & Garland, 1980).

Vitamin D is synthesized in the skin upon exposure to ultraviolet B (UVB) radiation (290–320 nm) and obtained through dietary sources, yet deficiency remains widespread, particularly in regions with limited sunlight exposure (Binkley et al., 2007). Epidemiological studies have identified several risk factors for breast cancer that intersect with vitamin D metabolism (Smolarz et al., 2022). Sex is a primary determinant, with 99% of cases occurring in women, though men account for 1% of diagnoses (Smolarz et al., 2022). Age is another critical factor, with incidence rising across all age groups, particularly among women under 50 (Smolarz et al., 2022). Hormonal status, influenced by prolonged estrogen exposure (e.g., early menarche, late menopause), significantly increases risk, as does obesity, especially in postmenopausal women (Smolarz et al., 2022).

Obese women exhibit higher breast cancer incidence and poorer treatment outcomes, potentially due to altered vitamin D bioavailability, as adipose tissue sequesters this lipophilic molecule (Jiralerspong & Goodwin, 2016; Bikle, 2016). Vitamin D deficiency, defined as serum 25-hydroxyvitamin D (25OHD) levels below 50 nmol/L, is implicated in heightened cancer risk (Vieth, 1999). Observational data suggest an inverse correlation between

25OHD levels and cancer mortality, particularly for breast and colorectal cancers (Engel et al., 2010; Garland et al., 1989). However, the causal nature of this relationship remains debated, necessitating further prospective studies to clarify vitamin D's protective role.

Pathophysiology of Cancer and Vitamin D's Modulatory Effects

Overview of Cancer Pathophysiology

Cancer is fundamentally a disease of dysregulated cellular homeostasis, characterized by uncontrolled proliferation, evasion of programmed cell death, and the potential for invasion and metastasis. This pathological state arises from a cascade of molecular and cellular events driven by genetic mutations, epigenetic alterations, and environmental influences (Gale, 2024). The hallmarks of cancer, as delineated by Hanahan and Weinberg, include sustained proliferative signaling, evasion of growth suppressors, resistance to apoptosis, replicative immortality, angiogenesis, and activation of invasion and metastasis (Hanahan & Weinberg, 2011). These processes are underpinned by genomic instability and an altered tumor microenvironment, which collectively enable malignant transformation and progression (Quail & Joyce, 2013).

At the cellular level, cancer begins with the accumulation of mutations in critical genes—oncogenes, tumor suppressor genes, and DNA repair genes—that regulate cell division and growth (Vogelstein et al., 2013). Oncogenes, such as MYC and RAS, when activated, promote excessive proliferation, while mutations in tumor suppressors like TP53 and PTEN disable checkpoints that halt aberrant cell cycles (Weinberg, 2014). Errors in DNA replication, often exacerbated by environmental carcinogens (e.g., tobacco smoke, ionizing radiation), or inherited genetic predispositions (e.g., BRCA1/2 mutations in breast cancer), amplify this genomic instability (Smolarz et al., 2022; Hecht, 2008). Epigenetic changes, including DNA methylation and histone modification, further silence tumor suppressor genes or activate oncogenes without altering the DNA sequence, adding another layer of complexity to cancer development (Baylin & Jones, 2011).

The tumor microenvironment (TME) plays a pivotal role in sustaining malignancy (Quail & Joyce, 2013). Comprising stromal cells, immune cells, and extracellular matrix, the TME fosters angiogenesis—the formation of new blood vessels to supply nutrients and oxygen—via vascular endothelial growth factor (VEGF) signaling (Ferrara, 2002). Cancer cells also evade immune surveillance by downregulating major histocompatibility complex (MHC) molecules or secreting immunosuppressive cytokines (e.g., TGF-β, IL-10), allowing unchecked growth (Schreiber et al., 2011). Chronic inflammation within the TME, driven by reactive oxygen and nitrogen species (RONS), further promotes DNA damage and tumor progression, as seen in colorectal cancer linked to inflammatory bowel disease or prostate cancer associated with proliferative inflammatory atrophy (PIA) (Coussens & Werb, 2002; De Marzo et al., 2007).

Specific Pathophysiology in Breast and Lung Cancer

Breast cancer, the most prevalent malignancy in women, exemplifies hormone-dependent carcinogenesis. Estrogen exposure, prolonged by early menarche or late menopause, drives epithelial cell proliferation in the mammary gland, increasing the likelihood of mutations (Smolarz et al., 2022). Obesity exacerbates this risk in postmenopausal women by elevating circulating estrogens via aromatase activity in adipose tissue, while also fostering a pro-inflammatory state (Jiralerspong & Goodwin, 2016). Genetic mutations, such as those in BRCA1/2, impair DNA repair, leading to ductal or lobular carcinomas that may metastasize to lymph nodes, bones, or lungs. Epigenetic silencing of genes like CDH1 (E-cadherin) facilitates epithelial-mesenchymal transition (EMT), a key step in metastasis (Smolarz et al., 2022; Baylin & Jones, 2011).

Lung cancer, the second most common cancer, arises predominantly from epithelial cells in the bronchial tree, with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) as major subtypes (Siegel et al., 2023). Smoking-induced DNA adducts and oxidative stress trigger mutations in KRAS, EGFR, or TP53, initiating uncontrolled growth (Hecht, 2008). Chronic inflammation from inhaled carcinogens or infections sustains a TME rich in macrophages and neutrophils, which release RONS and cytokines (e.g., IL-6, TNF-α), promoting angiogenesis and immune evasion (Coussens & Werb, 2002). Metastasis to the brain, liver, or bones reflects the aggressive nature of lung cancer, particularly SCLC (Siegel et al., 2023).

Vitamin D's Modulatory Mechanisms

Vitamin D, through its active metabolite calcitriol (1,25-dihydroxyvitamin D), exerts profound effects on cancer pathophysiology by targeting multiple hallmarks of malignancy (Feldman et al., 2014). Synthesized from 7-dehydrocholesterol in the skin or ingested as cholecalciferol (D3) or ergocalciferol (D2), vitamin D undergoes hepatic 25-hydroxylation to 25-hydroxyvitamin D (25OHD) and renal 1α-hydroxylation to calcitriol (Holick, 2004). This secosteroid binds the vitamin D receptor (VDR), a nuclear transcription factor expressed in most tissues, including cancer cells, to regulate gene expression (Bikle, 2016). The VDR-calcitriol complex interacts with vitamin D response elements (VDREs) in DNA, modulating pathways critical to carcinogenesis (Jeon & Shin, 2018).

Inhibition of Proliferation

Calcitriol arrests the cell cycle at the G0/G1 phase, counteracting the uncontrolled proliferation characteristic of cancer (Jeon & Shin, 2018). This effect is mediated by upregulation of p53-dependent cyclin-dependent kinase (CDK) inhibitors, such as p21 (CDKN1A) and p27, which inhibit CDK2 and CDK4/6 activity (Liu et al., 1996). In breast cancer cell lines (e.g., MCF-7), calcitriol reduces retinoblastoma protein (Rb) phosphorylation, preventing G1-to-S phase transition (Jensen et al., 2001). Concurrently, it suppresses mitogenic signaling pathways, including MAPK and PI3K/AKT, and downregulates the proto-oncogene MYC, a master regulator of cell growth (Salehi-Tabar et al., 2012). In lung cancer models (e.g., A549), calcitriol

inhibits epidermal growth factor receptor (EGFR) signaling, a common driver of NSCLC proliferation (Trump et al., 2004). Additionally, calcitriol reduces telomerase reverse transcriptase (TERT) mRNA expression, limiting replicative immortality by shortening telomeres in cancer cells (Jiang et al., 2003).

Induction of Apoptosis

Apoptosis, or programmed cell death, is frequently suppressed in cancer to ensure cell survival and mutation accumulation (Hanahan & Weinberg, 2011). Calcitriol restores this process by tilting the balance toward pro-apoptotic pathways (Deeb et al., 2007). In breast cancer cells (e.g., MDA-MB-231, MCF-7), calcitriol upregulates pro-apoptotic genes like BAX, BAK1, and BAG1, which permeabilize mitochondrial membranes, releasing cytochrome c and activating caspases (Krishnan et al., 2010). Simultaneously, it downregulates anti-apoptotic genes, including BCL-2 and BCL-XL, reducing survival signals (Mathiasen et al., 1999). In prostate cancer lines (e.g., LNCaP, PC-3), calcitriol activates caspase-dependent pathways via protease cascades, while in colorectal cancer (e.g., HCT116), it enhances apoptosis through cell-specific mechanisms linked to VDR signaling (Palmer et al., 2001). Studies in VDR-knockout mice demonstrate impaired apoptosis in mammary epithelia, underscoring vitamin D's role in stromal remodeling and tumor suppression (Welsh et al., 2011).

Promotion of Differentiation

Cancer cells often exhibit dedifferentiated, aggressive phenotypes conducive to metastasis (Hanahan & Weinberg, 2011). Calcitriol promotes differentiation, restoring mature cellular characteristics and reducing invasiveness (Jeon & Shin, 2018). This effect is mediated by regulation of transcription factors such as β-catenin, c-Jun N-terminal kinase (JNK), PI3K, and nuclear factor kappa B (NF-κB) (Díaz et al., 2015). In breast cancer, calcitriol modulates Wnt/β-catenin signaling, inhibiting EMT and stabilizing E-cadherin expression (Sferrazza et al., 2020). In colorectal cancer, it enhances enterocyte-like phenotypes, reducing metastatic potential (Palmer et al., 2001). While only a subset of cancer cells responds robustly, this pro-differentiation effect complements vitamin D's anti-proliferative and pro-apoptotic actions, offering a multi-pronged approach to tumor control (Feldman et al., 2014).

Anti-Inflammatory Effects

Chronic inflammation fuels carcinogenesis by generating RONS, which damage DNA, and by recruiting immune cells that secrete tumor-promoting cytokines (Coussens & Werb, 2002). Calcitriol mitigates this process through its anti-inflammatory properties (Bikle, 2016). It suppresses cyclooxygenase-2 (COX-2), a key enzyme in prostaglandin synthesis, reducing inflammation-driven proliferation in colorectal and prostate cancers (Krishnan et al., 2010). In prostate models, calcitriol inhibits PIA, a precursor to prostatic intraepithelial neoplasia (PIN), by attenuating RONS and cytokine production (De Marzo et al., 2007). In lung cancer, it dampens NF-κB signaling, decreasing IL-6 and TNF-α levels in the TME (Chen et al., 2022). These actions disrupt the inflammation-cancer nexus, positioning calcitriol as a potential preventive agent in inflammation-associated malignancies (Deeb et al., 2007).

Modulation of the Tumor Microenvironment

Vitamin D influences the TME by inhibiting angiogenesis and enhancing immune surveillance (Quail & Joyce, 2013). Calcitriol downregulates VEGF expression, limiting blood vessel formation in tumors, as observed in breast cancer xenografts (Mantell et al., 2000). It also enhances innate immunity by upregulating antimicrobial peptides (e.g., cathelicidin) and modulates adaptive immunity via VDR expression in T cells and macrophages (Adams & Hewison, 2008). In preclinical models, calcitriol reduces immunosuppressive stromal components, potentially sensitizing tumors to immunotherapy (Krishnan et al., 2010). This TME modulation is particularly relevant in lung cancer, where immune evasion is a major barrier to treatment (Schreiber et al., 2011).

Vitamin D Metabolism and Bioavailability

Vitamin D exists in multiple forms, with vitamin D2 (ergocalciferol) derived from plant sources and vitamin D3 (cholecalciferol) synthesized in the skin or obtained from animal-based foods (Holick, 2004). Both undergo hepatic 25-hydroxylation to form 25OHD (calcidiol), the primary circulating biomarker of vitamin D status, followed by renal 1α-hydroxylation to yield calcitriol (Bikle, 2016). This two-step activation is tightly regulated by parathyroid hormone, calcium, and phosphate levels, with feedback inhibition by calcitriol itself (Christakos et al., 2016).

Sources of vitamin D include sunlight, fatty fish (e.g., salmon, mackerel), fortified foods (e.g., milk, cereals), and supplements (Holick, 2007). UVB-induced synthesis in the skin, converting 7-dehydrocholesterol to previtamin D3, is the most efficient route, yet its efficacy varies with factors such as skin pigmentation, latitude, and sunscreen use (Holick, 2004). For example, 15 minutes of midday sun exposure can generate 10,000 IU of cholecalciferol, while limited exposure (e.g., hands and face) yields 200–600 IU (Holick, 1995). Dietary intake, typically 15 mcg (600 IU) daily for adults per U.S. FDA guidelines, often falls short in populations with low sun exposure or high obesity rates, where vitamin D is sequestered in fat tissue (Food and Drug Administration, 2016).

Pharmacokinetically, oral vitamin D is absorbed in the small intestine, peaking in serum within 24 hours, with 25OHD levels stabilizing over 7–14 days (Jones, 2008). Bioavailability varies widely due to individual factors (e.g., body mass index, liver function) and the form administered (D3 is more effective than D2 at raising 25OHD) (Ramasamy, 2020). Notably, total 25OHD measurements include protein-bound (90%, via vitamin D-binding protein, DBP) and free fractions, yet free 25OHD may better reflect anti-cancer activity, as it diffuses into cells lacking megalin-cubilin receptors

(Bikle et al., 1986). This distinction has implications for assessing vitamin D status in cancer patients, where bioavailable levels correlate more strongly with survival outcomes (e.g., hepatocellular carcinoma) (Finkelmeier et al., 2015).

Anti-Cancer Properties of Vitamin D

The anti-cancer effects of vitamin D are mediated through genomic and non-genomic pathways (Deeb et al., 2007). Genomically, calcitriol-VDR complexes bind DNA, regulating genes involved in proliferation, apoptosis, and differentiation (Trochoutsou et al., 2015). Preclinical studies demonstrate that calcitriol inhibits tumor growth in breast cancer xenografts (MCF-7) and prostate cancer models (TRAMP) by modulating aromatase expression and suppressing mitogenic signaling (Swami et al., 2012). Its anti-proliferative action is further enhanced by reducing CDK2 activity and telomerase expression, key drivers of cancer cell replication (Jiang et al., 2003).

Apoptosis induction is another hallmark of vitamin D's anti-cancer profile (Feldman et al., 2014). In breast cancer models, calcitriol upregulates pro-apoptotic pathways while counteracting stromal remodeling that supports tumor survival (Krishnan et al., 2010). Similar effects are observed in colorectal and prostate cancers, where VDR-mediated gene regulation restores apoptotic balance disrupted in malignancy (Palmer et al., 2001). Differentiation, though less pronounced, reduces metastatic potential by promoting mature phenotypes, as seen in a subset of cancer cells exposed to calcitriol (Jeon & Shin, 2018).

Vitamin D's anti-inflammatory properties, mediated by calcitriol, also contribute to cancer prevention (Krishnan & Feldman, 2011). Chronic inflammation, a known risk factor for cancers like colorectal and prostate, is mitigated by calcitriol's suppression of cyclooxygenase-2 (COX-2) and reactive oxygen species (ROS) (Krishnan & Feldman, 2011). In prostate carcinogenesis, calcitriol reduces proliferative inflammatory atrophy (PIA), a precursor to intraepithelial neoplasia (PIN), highlighting its role in interrupting inflammation-driven oncogenesis (De Marzo et al., 2007).

Preclinical Evidence from Animal Models

Animal models provide critical insights into vitamin D's anti-cancer efficacy (Feldman et al., 2014). In breast cancer xenografts (MCF-7), calcitriol and its analogs (e.g., EB1089) inhibit tumor growth and induce apoptosis, with synergistic effects when combined with radiation or retinoids (Swami et al., 2012). Prostate cancer models, such as the transgenic adenocarcinoma of the mouse prostate (TRAMP), show that calcitriol prevents PIN formation and slows progression, partly via CYP27B1-mediated local activation (Mordan-McCombs et al., 2010). Mouse models of colorectal cancer further demonstrate reduced tumor burden with vitamin D supplementation, linked to VDR signaling (Palmer et al., 2001).

Genetically engineered mouse models (GEMMs) offer a sophisticated platform to study cancer immunology (Gould et al., 2015). Unlike syngeneic models, GEMMs recapitulate de novo tumor microenvironments, including immunosuppressive stroma, which influences immunotherapy responses (Quail & Joyce, 2013). For instance, PTEN loss in melanoma GEMMs creates an immunosuppressive milieu reversible by vitamin D, suggesting a role in enhancing immunotherapeutic efficacy (Peng et al., 2016). These findings underscore the need for models integrating human MHC and antigen-specific responses to bridge preclinical and clinical outcomes (Palmer et al., 2001).

Therapeutic Implications and Clinical Evidence

Therapeutically, vitamin D holds promise as an adjuvant in cancer management (Deeb et al., 2007). Randomized controlled trials (RCTs) provide mixed but encouraging results. The AMATERASU trial (n=417) found that vitamin D supplementation (2000 IU/day) improved relapse-free survival (HR 0.66) in digestive tract cancer patients with low bioavailable 25OHD, though benefits were absent in those with high baseline levels (Urashima et al., 2019). Similarly, the SUNSHINE trial (n=139) reported enhanced progression-free survival (HR 0.64) in colorectal cancer patients receiving high-dose vitamin D3 (4000 IU/day) versus standard doses (400 IU/day) (Ng et al., 2019). These outcomes suggest a threshold effect, where benefits are most pronounced in deficient individuals (Manson et al., 2019; Urashima et al., 2019; Ng et al., 2019).

Vitamin D's anti-inflammatory and anti-tumor effects also support its use in palliation, improving quality of life (QoL) in advanced cancer (Krishnan & Feldman, 2011). Observational studies link higher 25OHD levels to better QoL, though RCTs are needed to confirm causality (Goodwin et al., 2008). Challenges in clinical translation include variability in 25OHD measurement, optimal dosing, and long-term safety, particularly regarding hypercalcemia risk with high-dose regimens (Vieth, 1999).

Future Research Directions

Future investigations should address several gaps. First, trials must prioritize patients with vitamin D deficiency (<50 nmol/L) to test threshold effects, though ethical concerns arise with placebo controls in deficient cohorts. Second, measuring free or bioavailable 25OHD, rather than total levels, could refine assessments of vitamin D status, given its stronger association with survival in cancers like hepatocellular carcinoma. Third, RCTs exploring vitamin D as a therapeutic agent, rather than a preventive measure, are scarce and warrant expansion, incorporating longer follow-ups and diverse populations.

Additional endpoints, such as QoL, progression-free survival, and tumor response, should complement traditional outcomes (e.g., overall survival) to accelerate insights. Genetic factors, such as VDR polymorphisms (e.g., BsmI, rs7968585), may modulate vitamin D's efficacy, as seen in colorectal adenoma prevention, necessitating personalized approaches. The ongoing VITAL trial's analysis of gene variants exemplifies this direction, promising to tailor supplementation strategies.

2. Conclusion

Vitamin D emerges as a multifaceted player in cancer biology, influencing proliferation, apoptosis, differentiation, and inflammation through VDR-mediated pathways. Epidemiological and preclinical data support its protective role, particularly in breast and colorectal cancers, while clinical trials highlight therapeutic potential in deficient patients. However, inconsistencies in dosing, measurement, and study design underscore the need for rigorous, well-powered RCTs. By focusing on bioavailable 25OHD, integrating biological and genetic markers, and expanding clinical endpoints, future research can unlock vitamin D's full potential in cancer prevention and treatment, offering hope for improved patient outcomes.

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