Benefits of High-Dose Vitamin D in Managing Cutaneous Adverse Events Induced by Chemotherapy and Radiation Therapy

Maya L. Muldowney, BA; Bridget E. Shields, MD

PRACTICE **POINTS**

- High-dose vitamin D supplementation may be considered in the management of cutaneous injury from chemotherapy or ionizing radiation.
- Optimal dosing has not been established, so patients given high-dose vitamin D supplementation should have close clinical follow-up; however, adverse events from high-dose vitamin D supplementation have not been reported.

The use of chemotherapy and radiation for cancer treatment can result in cutaneous adverse events (AEs) such as toxic erythema of chemotherapy (TEC) and radiation-induced dermatitis. High-dose vitamin D supplementation has been suggested to potentially improve and shorten recovery for these AEs, primarily based on data from case reports and case series. In this article, we discuss the role of vitamin D in the most prevalent cancers (breast and colorectal cancer) and changes in vitamin D levels after chemotherapy or radiation treatments. We also summarize reports on high-dose vitamin D supplementation for treating chemotherapy-induced and radiation-induced skin toxicity. Larger studies and randomized controlled trials are essential to clarify the roles of vitamin D in malignancy and in cutaneous AEs associated with cancer treatment. The existing studies we reviewed lack standardized dosing regimens and exhibited heterogeneity across study populations, making it challenging to draw generalizable conclusions.

Vitamin D (VD) regulates keratinocyte proliferation and differentiation, modulates inflammatory pathways, and protects against cellular damage in the skin.[1] In the setting of tissue injury and acute skin inflammation, active vitamin D—$1,25(OH)_2D$—suppresses signaling from pro-inflammatory chemokines and cytokines such as IFN-γ and IL-17.[2,3] This suppression reduces proliferation of helper T cells (T_H1, T_H17) and B cells, decreasing tissue damage from reactive oxygen species release while enhancing secretion of the anti-inflammatory cytokine IL-10 by antigen-presenting cells.[2-4]

Suboptimal VD levels have been associated with numerous health consequences including malignancy, prompting interest in VD supplementation for improving cancer-related outcomes.[5] Beyond disease prognosis, high-dose VD supplementation has been suggested as a potential therapy for adverse events (AEs) related to cancer treatments. In one study, mice that received oral vitamin D_3 supplementation of 11,500 IU/kg daily had fewer doxorubicin-induced cardiotoxic effects on ejection fraction ($P<.0001$) and stroke volume ($P<.01$) than mice that received VD supplementation of 1500 IU/kg daily.[6]

In this review, we examine the impact of chemoradiation on 25(OH)D levels—which more accurately reflects VD stores than $1,25(OH)_2D$ levels—and the impact of suboptimal VD on cutaneous toxicities related to chemoradiation. To define the suboptimal VD threshold, we used the Endocrine Society's clinical practice

From the Department of Dermatology, University of Wisconsin, Madison.
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Correspondence: Bridget E. Shields, MD, 20 South Park St, Madison, WI 53715 (bshields@dermatology.wisc.edu).
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guidelines, which characterize suboptimal 25(OH)D levels as insufficiency (21–29 ng/mL [52.5–72.5 nmol/L]) or deficiency (<20 ng/mL [50 nmol/L])[7]; deficiency can be further categorized as severe deficiency (<12 ng/mL [30 nmol/L]).[8] This review also evaluates the evidence for vitamin D_3 supplementation to alleviate the cutaneous AEs of chemotherapy and radiation treatments.

Effects of Chemotherapy on Vitamin D Levels

A high prevalence of VD deficiency is seen in various cancers. In a retrospective review of 25(OH)D levels in 2098 adults with solid tumors of any stage (6% had metastatic disease [n=124]), suboptimal levels were found in 69% of patients with breast cancer (n=617), 75% with colorectal cancer (n=84), 72% with gynecologic cancer (n=65), 79% with kidney and bladder cancer (n=145), 83% with pancreatic and upper gastrointestinal tract cancer (n=178), 73% with lung cancer (n=73), 69% with prostate cancer (n=225), 61% with skin cancer (n=399), and 63% with thyroid cancer (n=172).[5] Suboptimal VD also has been found in hematologic malignancies. In a prospective cohort study, mean serum 25(OH)D levels in 23 patients with recently diagnosed acute myeloid leukemia demonstrated VD deficiency (mean [SD], 18.6 [6.6] nmol/L).[9] Given that many patients already exhibit a baseline VD deficiency at cancer diagnosis, it is important to understand the relationship between VD and cancer treatment modalities.[5]

In the United States, breast and colorectal cancers were estimated to be the first and fourth most common cancers, with 313,510 and 152,810 predicted new cases in 2024, respectively.[10] This review will focus on breast and colorectal cancer when describing VD variation associated with chemotherapy exposure due to their high prevalence.

Effects of Chemotherapy on Vitamin D Levels in Breast Cancer—Breast cancer studies have shown suboptimal VD levels in 76% of females 75 years or younger with any T1, T2, or T3; N0 or N1; and M0 breast cancer, in which 38.5% (n=197) had insufficient and 37.5% (n=192) had deficient 25(OH)D levels.[11] In a study of female patients with primary breast cancer (stage I, II, or III and T1 with high Ki67 expression [≥30%], T2, or T3), VD deficiency was seen in 60% of patients not receiving VD supplementation.[12,13] A systematic review that included 7 studies of different types of breast cancer suggested that circulating 25(OH)D may be associated with improved prognosis.[14] Thus, studies have investigated risk factors associated with poor or worsening VD status in individuals with breast cancer, including exposure to chemotherapy and/or radiation treatment.[12,15-18]

A prospective cohort study assessed 25(OH)D levels in 95 patients with any breast cancer (stages I, II, IIIA, IIIB) before and after initiating chemotherapy with docetaxel, doxorubicin, epirubicin, 5-fluorouracil, or cyclophosphamide, compared with a group of 52 females without cancer.[17] In the breast cancer group, approximately 80% (76/95) had suboptimal and 50% (47/95) had deficient VD levels before chemotherapy initiation (mean [SD], 54.1 [22.8] nmol/L). In the comparison group, 60% (31/52) had suboptimal and 30% (15/52) had deficient VD at baseline (mean [SD], 66.1 [23.5] nmol/L), which was higher than the breast cancer group (P=.03). A subgroup analysis excluded participants who started, stopped, or lacked data on dietary supplements containing VD (n=39); in the remaining 56 participants, a significant decrease in 25(OH)D levels was observed shortly after finishing chemotherapy compared with the prechemotherapy baseline value (mean, −7.9 nmol/L; P=.004). Notably, 6 months after chemotherapy completion, 25(OH)D levels increased (mean, +12.8 nmol/L; P<.001). Vitamin D levels remained stable in the comparison group (P=.987).[17]

Consistent with these findings, a cross-sectional study assessing VD status in 394 female patients with primary breast cancer (stage I, II, or III and T1 with high Ki67 expression [≥30%], T2, or T3), found that a history of chemotherapy was associated with increased odds of 25(OH)D levels less than 20 ng/mL compared with breast cancer patients with no prior chemotherapy (odds ratio, 1.86; 95% CI, 1.03-3.38).[12] Although the study data included chemotherapy history, no information was provided on specific chemotherapy agents or regimens used in this cohort, limiting the ability to detect the drugs most often implicated.

Both studies indicated a complex interplay between chemotherapy and VD levels in breast cancer patients. Although Kok et al[17] suggested a transient decrease in VD levels during chemotherapy with a subsequent recovery after cessation, Fassio et al[12] highlighted the increased odds of VD deficiency associated with chemotherapy. Ultimately, larger randomized controlled trials are needed to better understand the relationship between chemotherapy and VD status in breast cancer patients.

Effects of Chemotherapy on Vitamin D Levels in Colorectal Cancer—Similar to patterns seen in breast cancer, a systematic review with 6 studies of different types of colorectal cancer suggested that circulating 25(OH)D levels may be associated with prognosis.[14] Studies also have investigated the relationship between colorectal chemotherapy regimens and VD status.[15,16,18,19]

A retrospective study assessed 25(OH)D levels in 315 patients with any colorectal cancer (stage I–IV).[15] Patients were included in the analysis if they received less than 400 IU daily of VD supplementation at baseline. For the whole study sample, the mean (SD) VD level was 23.7 (13.71) ng/mL. Patients who had not received chemotherapy within 3 months of the VD level assessment were categorized as the no chemotherapy group, and the others were designated as the chemotherapy group; the latter group was exposed to various chemotherapy regimens, including combinations of irinotecan, oxaliplatin, 5-fluorouracil, leucovorin, bevacizumab, or cetuximab. Multivariate analysis showed that the chemotherapy group was 3.7 times more likely to have very low VD

levels (≤15 ng/mL) compared with those in the no chemotherapy group ($P<.0001$).[15]

A separate cross-sectional study examined serum 25(OH)D concentrations in 1201 patients with any newly diagnosed colorectal carcinoma (stage I–III); 91% of cases were adenocarcinoma.[18] In a multivariate analysis, chemotherapy plus surgery was associated with lower VD levels than surgery alone 6 months after diagnosis (mean, −8.74 nmol/L; 95% CI, −11.30 to −6.18 nmol/L), specifically decreasing by a mean of 6.7 nmol/L (95% CI, −9.8 to −3.8 nmol/L) after adjusting for demographic and lifestyle factors.[18] However, a prospective cohort study demonstrated different findings.[19] Comparing 58 patients with newly diagnosed colorectal adenocarcinoma (stages I–IV) who underwent chemotherapy and 36 patients who did not receive chemotherapy, there was no significant change in 25(OH)D levels from the time of diagnosis to 6 months later. Median VD levels decreased by 0.7 ng/mL in those who received chemotherapy, while a minimal (and not significant) increase of 1.6 ng/mL was observed in those without chemotherapy intervention ($P=.26$). Notably, supplementation was not restricted in this cohort, which may have resulted in higher VD levels in those taking supplements.[19]

Since time of year and geographic location can influence VD levels, one prospective cohort study controlled for differential sun exposure due to these factors in their analysis.[16] Assessment of 25(OH)D levels was completed in 81 chemotherapy-naïve cancer patients immediately before beginning chemotherapy as well as 6 and 12 weeks into treatment. More than 8 primary cancer types were represented in this study, with breast (34% [29/81]) and colorectal (14% [12/81]) cancer being the most common, but the cancer stages of the participants were not detailed. Vitamin D levels decreased after commencing chemotherapy, with the largest drop occurring 6 weeks into treatment. From the 6- to 12-week end points, VD increased but remained below the original baseline level (baseline: mean [SD], 49.2 [22.3] nmol/L; 6 weeks: mean [SD], 40.9 [19.0] nmol/L; 12 weeks: mean [SD], 45.9 [19.7] nmol/L; $P=.05$).[16]

Although focused on breast and colorectal cancers, these studies suggest that various chemotherapy regimens may confer a higher risk for VD deficiency compared with VD status at diagnosis and/or prior to chemotherapy treatment. However, most of these studies only discussed stage-based differences, excluding analysis of the variety of cancer subtypes that comprise breast and colorectal malignancies, which may limit our ability to extrapolate from these data. Ultimately, larger randomized controlled trials are needed to better understand the relationship between chemotherapy and VD status across various primary cancer types.

Effects of Radiation Therapy on Vitamin D Levels

Unlike chemotherapy, studies on the association between radiation therapy and VD levels are minimal, with most reports in the literature discussing the use of VD to potentiate the effects of radiation therapy. In one cross-sectional analysis of 1201 patients with newly diagnosed stage I, II, or III colorectal cancer of any type (94% were adenocarcinoma), radiation plus surgery was associated with slightly lower 25(OH)D levels than surgery alone for tumor treatment 6 months after diagnosis (mean, −3.17; 95% CI, −6.07 to −0.28 nmol/L). However, after adjustment for demographic and lifestyle factors, this decrease in VD levels attributable to radiotherapy was not statistically significant compared with the surgery-only cohort (mean, −1.78; 95% CI, −5.07 to 1.52 nmol/L).[18]

Similarly, a cross-sectional study assessing VD status in 394 female patients with primary breast cancer (stage I, II, or III and T1 with high Ki67 expression [≥30%], T2, or T3), found that a history of radiotherapy was not associated with a difference in serum 25(OH)D levels compared with those with breast cancer without prior radiotherapy (odds ratio, 0.90; 95% CI, 0.52-1.54).[12] From the limited existing literature specifically addressing variations of VD levels with radiation, radiation therapy does not appear to significantly impact VD levels.

Vitamin D Levels and the Severity of Chemotherapy- or Radiation Therapy–Induced AEs

A prospective cohort of 241 patients did not find an increase in the incidence or severity of chemotherapy-induced cutaneous toxicities in those with suboptimal $1,25(OH)_2D_3$ levels (≤75 nmol/L).[20] Eight different primary cancer types were represented, including breast and colorectal cancer; the tumor stages of the participants were not detailed. Forty-one patients had normal $1,25(OH)_2D_3$ levels, while the remaining 200 had suboptimal levels. There was no significant association between serum VD levels and the following dermatologic toxicities: desquamation ($P=.26$), xerosis ($P=.15$), mucositis ($P=.30$), or painful rash ($P=.87$). Surprisingly, nail changes and hand-foot reactions occurred with greater frequency in patients with normal VD levels ($P=.01$ and $P=.03$, respectively).[20] Hand-foot reaction is part of the toxic erythema of chemotherapy (TEC) spectrum, which is comprised of a range of cytotoxic skin injuries that typically manifest within 2 to 3 weeks of exposure to the offending chemotherapeutic agents, often characterized by erythema, pain, swelling, and blistering, particularly in intertriginous and acral areas.[21-23] Recovery from TEC generally takes at least 2 to 4 weeks and may necessitate cessation of the offending chemotherapeutic agent.[21,24] Notably, this study measured $1,25(OH)_2D_3$ levels instead of 25(OH)D levels, which may not reliably indicate body stores of VD.[7,20] These results underscore the complex nature between chemotherapy and VD; however, VD levels alone do not appear to be a sufficient biomarker for predicting chemotherapy-associated cutaneous AEs.

Interestingly, radiation therapy–induced AEs may be associated with VD levels. A prospective cohort study of 98 patients with prostate, bladder, or gynecologic cancers

(tumor stages were not detailed) undergoing pelvic radiotherapy found that females and males with 25(OH)D levels below a threshold of 35 and 40 nmol/L, respectively, were more likely to experience higher Radiation Therapy Oncology Group (RTOG) grade acute proctitis compared with those with VD above these thresholds.[25] Specifically, VD below these thresholds was associated with increased odds of RTOG grade 2 or higher radiation-induced proctitis (OR, 3.07; 95% CI, 1.27-7.50 [P=.013]). Additionally, a weak correlation was noted between VD below these thresholds and the RTOG grade, with a Spearman correlation value of −0.189 (P=.031).[25]

One prospective cohort study included 28 patients with any cancer of the oral cavity, oropharynx, hypopharynx, or larynx stages II, III, or IVA; 93% (26/28) were stage III or IVA.[26] The 20 (71%) patients with suboptimal 25(OH)D levels (≤75 nmol/L) experienced a higher prevalence of grade II radiation dermatitis compared with the 8 (29%) patients with optimal VD levels (χ^2_2 =5.973; P=.0505). This pattern persisted with the severity of mucositis; patients from the suboptimal VD group presented with higher rates of grades II and III mucositis compared with the VD optimal group (χ^2_2 =13.627; P=.0011).[26] Recognizing the small cohort evaluated in the study, we highlight the importance of further studies to clarify these associations.

Chemotherapy-Induced Cutaneous Events Treated with High-Dose Vitamin D

Chemotherapeutic agents are known to induce cellular damage, resulting in a range of cutaneous AEs that can invoke discontinuation of otherwise effective chemotherapeutic interventions.[27,28] Recent research has explored the potential of high-dose vitamin D_3 as a therapeutic agent to mitigate cutaneous reactions.[29,30]

A randomized, double-blind, placebo-controlled trial investigated the use of a single high dose of oral 25(OH)D to treat topical nitrogen mustard (NM)–induced rash.[29] To characterize baseline inflammatory responses from NM injury without intervention, clinical measures, serum studies, and tissue analyses from skin biopsies were performed on 28 healthy adults after exposure to topical NM—a chemotherapeutic agent classified as a DNA alkylator. Two weeks later, participants were exposed to topical NM a second time and were split into 2 groups: 14 patients received a single 200,000-IU dose of oral 25(OH)D while the other 14 participants were given a placebo. Using the inflammatory markers induced from baseline exposure to NM alone, posttreatment analysis revealed that the punch biopsies from the 25(OH)D group expressed fewer NM-induced inflammatory markers compared with the placebo group at both 72 hours and 6 weeks following NM injury (72 hours: 12 vs 17 inflammatory markers; 6 weeks: 4 vs 11 inflammatory markers). Notably, NM inflammatory markers were enriched for IL-17 signaling pathways in the placebo biopsies but not in the 25(OH)D intervention group. This study also identified mild and severe patterns of inflammatory responses to NM that were independent of the 25(OH)D intervention. Biomarkers specific to skin biopsies from participants with the severe response included CCL20, CCL2, and CXCL8 (adjusted P<.05). At 6 weeks posttreatment, the 25(OH)D group showed a 67% reduction in NM injury markers compared with a 35% reduction in the placebo group. Despite a reduction in tissue inflammatory markers, there were no clinically significant changes observed in skin redness, swelling, or histologic structure when comparing the 25(OH)D-supplemented group to the placebo group at any time during the study, necessitating further research into the mechanistic roles of high doses VD supplementation.[29]

Although Ernst et al[29] did not observe any clinically significant improvements with VD treatment, a case series of 6 patients with either glioblastoma multiforme, acute myeloid leukemia, or aplastic anemia did demonstrate clinical improvement of TEC after receiving high-dose vitamin D_3.[30] The mean time to onset of TEC was noted at 8.5 days following administration of the inciting chemotherapeutic agent, which included combinations of anthracycline, antimetabolite, kinase inhibitor, B-cell lymphoma 2 inhibitor, purine analogue, and alkylating agents. A combination of clinical and histologic findings was used to diagnose TEC. Baseline 25(OH)D levels were not established prior to treatment. The treatment regimen for 1 patient included 2 doses of 50,000 IU of VD spaced 1 week apart, totaling 100,000 IU, while the remaining 5 patients received a total of 200,000 IU, also split into 2 doses given 1 week apart. All patients received their first dose of VD within a week of the cutaneous eruption. Following the initial VD dose, there was a notable improvement in pain, pruritus, or swelling by the next day. Reduction in erythema also was observed within 1 to 4 days.[30]

No AEs associated with VD supplementation were reported, suggesting a potential beneficial role of high-dose VD in accelerating recovery from chemotherapy-induced rashes without evident safety concerns.

Radiation Therapy–Induced Cutaneous Events Treated with High-Dose Vitamin D

Radiation dermatitis is a common and often severe complication of radiation therapy that affects more than 90% of patients undergoing treatment, with half of these individuals experiencing grade 2 toxicity, according to the National Cancer Institute's Common Terminology Criteria for Adverse Events.[31,32] Radiation damage to basal keratinocytes and hair follicle stem cells disrupts the renewal of the skin's outer layer, while a surge of free radicals causes irreversible DNA damage.[33] Symptoms of radiation dermatitis can vary from mild pink erythema to tissue ulceration and necrosis, typically within 1 to 4 weeks of radiation exposure.[34] The resulting dermatitis can take 2 to 4 weeks to heal, notably impacting patient quality of life and often necessitating modifications or interruptions in cancer therapy.[33]

Prior studies have demonstrated the use of high-dose VD to improve the healing of UV-irradiated skin. A randomized controlled trial investigated high-dose vitamin D_3 to treat experimentally induced sunburn in 20 healthy adults. Compared with those who received a placebo, participants receiving the oral dose of 200,000 IU of vitamin D_3 demonstrated suppression of the pro-inflammatory mediators tumor necrosis factor α ($P=.04$) and inducible nitric oxide synthase ($P=.02$), while expression of tissue repair enhancer arginase 1 was increased ($P<.005$).[35] The mechanism of this enhanced tissue repair was investigated using a mouse model, in which intraperitoneal 25(OH)D was administered following severe UV-induced skin injury. On immunofluorescence microscopy, mice treated with VD showed enhanced autophagy within the macrophages infiltrating UV-irradiated skin.[36] The use of high-dose VD to treat UV-irradiated skin in these studies established a precedent for using VD to heal cutaneous injury caused by ionizing radiation therapy.

Some studies have focused on the role of VD for treating acute radiation dermatitis. A study of 23 patients with ductal carcinoma in situ or localized invasive ductal carcinoma breast cancer compared the effectiveness of topical calcipotriol to that of a standard hydrating ointment.[37] Participants were randomized to 1 of 2 treatments before starting adjuvant radiotherapy to evaluate their potential in preventing radiation dermatitis. In 87% (20/23) of these patients, no difference in skin reaction was observed between the 2 treatments, suggesting that topical VD application may not offer any advantage over the standard hydrating ointment for the prevention of radiation dermatitis.[37]

Benefits of high-dose oral VD for treating radiation dermatitis also have been reported. Nguyen et al[38] documented 3 cases in which patients with neuroendocrine carcinoma of the pancreas, tonsillar carcinoma, and breast cancer received 200,000 IU of oral ergocalciferol distributed over 2 doses given 7 days apart for radiation dermatitis. These patients experienced substantial improvements in pain, swelling, and redness within a week of the initial dose. Additionally, a case of radiation recall dermatitis, which occurred a week after vinorelbine chemotherapy, was treated with 2 doses totaling 100,000 IU of oral ergocalciferol. This patient also had improvement in pain and swelling but continued to have tumor-related induration and ulceration.[39]

Although topical VD did not show significant benefits over standard treatments for radiation dermatitis, high-dose oral VD appears promising in improving patient outcomes of pain and swelling more rapidly than current practices. Further research is needed to confirm these findings and establish standardized treatment protocols.

Final Thoughts

Suboptimal VD levels are prevalent in numerous cancer types. Chemotherapy often is associated with acute, potentially transient worsening of VD status in patients with breast and colorectal cancer. Although 25(OH)D levels have not corresponded with increased frequency of chemotherapy-related dermatologic AEs, suboptimal 25(OH)D levels appear to be associated with increased severity of radiation-induced mucositis and dermatitis.[20,25,26] The use of high-dose VD as a therapeutic agent shows promise in mitigating chemotherapy-induced and radiation therapy–induced rashes in multiple cancer types with reduction of inflammatory markers and a durable anti-inflammatory impact. Although the mechanisms of cellular injury vary among chemotherapeutic agents, the anti-inflammatory and tissue repair properties of VD may make it an effective treatment for chemotherapy-induced cutaneous damage regardless of injury mechanism.[2-4,35] However, reports of clinical improvement vary, and further objective studies to classify optimal dosing, administration, and outcome measures are needed. The absence of reported AEs associated with high-dose VD supplementation is encouraging, but selection of a safe and optimal dosing regimen can only occur with dedicated clinical trials.

REFERENCES

1. Bikle DD. Vitamin D and the skin: physiology and pathophysiology. *Rev Endocr Metab Disord*. 2012;13:3-19. doi:10.1007/s11154-011-9194-0
2. Penna G, Adorini L. 1α,25-Dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. *J Immunol*. 2000;164:2405-2411. doi:10.4049/jimmunol.164.5.2405
3. Penna G, Amuchastegui S, Cossetti C, et al. Treatment of experimental autoimmune prostatitis in nonobese diabetic mice by the vitamin D receptor agonist elocalcitol. *J Immunol*. 2006;177:8504-8511. doi:10.4049/jimmunol.177.12.8504
4. Heine G, Niesner U, Chang HD, et al. 1,25-dihydroxyvitamin D3 promotes IL-10 production in human B cells. *Eur J Immunol*. 2008;38:2210-2218. doi:10.1002/eji.200838216
5. Hauser K, Walsh D, Shrotriya S, et al. Low 25-hydroxyvitamin D levels in people with a solid tumor cancer diagnosis: the tip of the iceberg? *Support Care Cancer*. 2014;22:1931-1939. doi:10.1007/s00520-014-2154-y
6. Lee KJ, Wright G, Bryant H, et al. Cytoprotective effect of vitamin D on doxorubicin-induced cardiac toxicity in triple negative breast cancer. *Int J Mol Sci*. 2021;22:7439. doi:10.3390/ijms22147439
7. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:1911-1930. doi:10.1210/jc.2011-0385
8. Amrein K, Scherkl M, Hoffmann M, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. *Eur J Clin Nutr*. 2020;74:1498-1513. doi:10.1038/s41430-020-0558-y
9. Thomas X, Chelghoum Y, Fanari N, et al. Serum 25-hydroxyvitamin D levels are associated with prognosis in hematological malignancies. *Hematology*. 2011;16:278-283. doi:10.1179/102453311X13085644679908
10. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74:12-49. doi:10.3322/caac.21820
11. Goodwin PJ, Ennis M, Pritchard KI, et al. Prognostic effects of 25-hydroxyvitamin D levels in early breast cancer. *J Clin Oncol*. 2009;27:3757-3763. doi:10.1200/JCO.2008.20.0725
12. Fassio A, Porciello G, Carioli G, et al. Post-diagnosis serum 25-hydroxyvitamin D concentrations in women treated for breast cancer participating in a lifestyle trial in Italy. *Reumatismo*. 2024;76:21-34.
13. Augustin LSA, Libra M, Crispo A, et al. Low glycemic index diet, exercise and vitamin D to reduce breast cancer recurrence (DEDiCa): design of a clinical trial. *BMC Cancer*. 2017;17:69. doi:10.1186/s12885-017-3064-4

14. Toriola AT, Nguyen N, Scheitler-Ring K, et al. Circulating 25-hydroxyvitamin D levels and prognosis among cancer patients: a systematic review. *Cancer Epidemiol Biomarkers Prev*. 2014;23:917-933. doi:10.1158/1055-9965.EPI-14-0053
15. Fakih MG, Trump DL, Johnson CS, et al. Chemotherapy is linked to severe vitamin D deficiency in patients with colorectal cancer. *Int J Colorectal Dis*. 2009;24:219-224. doi:10.1007/s00384-008-0593-y
16. Isenring EA, Teleni L, Woodman RJ, et al. Serum vitamin D decreases during chemotherapy: an Australian prospective cohort study. *Asia Pac J Clin Nutr*. 2018;27:962-967. doi:10.6133/apjcn.042018.01
17. Kok DE, van den Berg MMGA, Posthuma L, et al. Changes in circulating levels of 25-hydroxyvitamin D3 in breast cancer patients receiving chemotherapy. *Nutr Cancer*. 2019;71:756-766. doi:10.1080/01635581.2018.1559938
18. Wesselink E, Bours MJL, de Wilt JHW, et al. Chemotherapy and vitamin D supplement use are determinants of serum 25-hydroxyvitamin D levels during the first six months after colorectal cancer diagnosis. *J Steroid Biochem Mol Biol*. 2020;199:105577. doi:10.1016/j.jsbmb.2020.105577
19. Savoie MB, Paciorek A, Zhang L, et al. Vitamin D levels in patients with colorectal cancer before and after treatment initiation. *J Gastrointest Cancer*. 2019;50:769-779. doi:10.1007/s12029-018-0147-7
20. Kitchen D, Hughes B, Gill I, et al. The relationship between vitamin D and chemotherapy-induced toxicity—a pilot study. *Br J Cancer*. 2012;107:158-160. doi:10.1038/bjc.2012.194
21. Demircay Z, Gürbüz O, Alpdogan TB, et al. Chemotherapy-induced acral erythema in leukemic patients: a report of 15 cases. *Int J Dermatol*. 1997;36:593-598. doi:10.1046/j.1365-4362.1997.00040.x
22. Valks R, Fraga J, Porras-Luque J, et al. Chemotherapy-induced eccrine squamous syringometaplasia. a distinctive eruption in patients receiving hematopoietic progenitor cells. *Arch Dermatol*. 1997;133;873-878. doi:10.1001/archderm.133.7.873
23. Webber KA, Kos L, Holland KE, et al. Intertriginous eruption associated with chemotherapy in pediatric patients. *Arch Dermatol*. 2007;143:67-71. doi:10.1001/archderm.143.1.67
24. Hunjan MK, Nowsheen S, Ramos-Rodriguez AJ, et al. Clinical and histopathological spectrum of toxic erythema of chemotherapy in patients who have undergone allogeneic hematopoietic cell transplantation. *Hematol Oncol Stem Cell Ther*. 2019;12:19-25. doi:10.1016/j.hemonc.2018.09.001
25. Ghorbanzadeh-Moghaddam A, Gholamrezaei A, Hemati S. Vitamin D deficiency is associated with the severity of radiation-induced proctitis in cancer patients. *Int J Radiat Oncol Biol Phys*. 2015;92:613-618. doi:10.1016/j.ijrobp.2015.02.011
26. Bhanu A, Waghmare CM, Jain VS, et al. Serum 25-hydroxy vitamin-D levels in head and neck cancer chemoradiation therapy: potential in cancer therapeutics. *Indian J Cancer*. Published online February 27, 2003. doi:10.4103/ijc.ijc_358_20
27. Yang B, Xie X, Wu Z, et al. DNA damage-mediated cellular senescence promotes hand-foot syndrome that can be relieved by thymidine prodrug. *Genes Dis*. 2022;10:2557-2571. doi:10.1016/j.gendis.2022.10.004
28. Lassere Y, Hoff P. Management of hand-foot syndrome in patients treated with capecitabine (Xeloda®). *Eur J Oncol Nurs*. 2004;8 (suppl 1):S31-S40. doi:10.1016/j.ejon.2004.06.007
29. Ernst MK, Evans ST, Techner JM, et al. Vitamin D_3 and deconvoluting a rash. *JCI Insight*. 2023;8:E163789.
30. Nguyen CV, Zheng L, Zhou XA, et al. High-dose vitamin d for the management of toxic erythema of chemotherapy in hospitalized patients. *JAMA Dermatol*. 2023;159:219-221. doi:10.1001/jamadermatol.2022.5397
31. Fisher J, Scott C, Stevens R, et al. Randomized phase III study comparing best supportive care to biafine as a prophylactic agent for radiation-induced skin toxicity for women undergoing breast irradiation: Radiation Therapy Oncology Group (RTOG) 97-13. *Int J Radiat Oncol Biol Phys*. 2000;48:1307-1310. doi:10.1016/s0360-3016(00)00782-3
32. Pignol JP, Olivotto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *J Clin Oncol*. 2008;26:2085-2092. doi:10.1200/JCO.2007.15.2488
33. Hymes SR, Strom EA, Fife C. Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. *J Am Acad Dermatol*. 2006;54:28-46. doi:10.1016/j.jaad.2005.08.054
34. Ryan JL. Ionizing radiation: the good, the bad, and the ugly. *J Invest Dermatol*. 2012;132(3 pt 2):985-993. doi:10.1038/jid.2011.411
35. Scott JF, Das LM, Ahsanuddin S, et al. Oral vitamin D rapidly attenuates inflammation from sunburn: an interventional study. *J Invest Dermatol*. 2017;137:2078-2086. doi:10.1016/j.jid.2017.04.040
36. Das LM, Binko AM, Traylor ZP, et al. Vitamin D improves sunburns by increasing autophagy in M2 macrophages. *Autophagy*. 2019;15:813-826. doi:10.1080/15548627.2019.1569298
37. Nasser NJ, Fenig S, Ravid A, et al. Vitamin D ointment for prevention of radiation dermatitis in breast cancer patients. *NPJ Breast Cancer*. 2017;3:10. doi:10.1038/s41523-017-0006-x
38. Nguyen CV, Zheng L, Lu KQ. High-dose vitamin D for the management acute radiation dermatitis. *JAAD Case Rep*. 2023;39:47-50. doi:10.1016/j.jdcr.2023.07.001
39. Nguyen CV, Lu KQ. Vitamin D_3 and its potential to ameliorate chemical and radiation-induced skin injury during cancer therapy. *Disaster Med Public Health Prep*. 2024;18:E4. doi:10.1017/dmp.2023.211