Vitamin D Insufficiency as a Risk Factor for Paclitaxel-Induced Peripheral Neuropathy in SWOG S0221

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ABSTRACT

Background: Prior work suggests that patients with vitamin D insufficiency may have a higher risk of chemotherapy-induced peripheral neuropathy (CIPN) from paclitaxel. The objective of this study was to validate vitamin D insufficiency as a CIPN risk factor. **Methods:** We used data and samples from the prospective phase III SWOG S0221 (ClinicalTrials.gov identifier: NCT00070564) trial that compared paclitaxel-containing chemotherapy regimens for early-stage breast cancer. We quantified pretreatment 25-hydroxy-vitamin D in banked serum samples using a liquid chromatography-tandem mass spectrometry targeted assay. We tested the association between vitamin D insufficiency (≤20 ng/mL) and grade ≥3 sensory CIPN via multiple logistic regression and then adjusted for self-reported race, age, body mass index, and paclitaxel schedule (randomization to weekly or every-2-week dosing). We also tested the direct effect of vitamin D deficiency on mechanical hypersensitivity in mice randomized to a regular or vitamin D–deficient diet. **Results:** Of the 1,191 female patients in the analysis, 397 (33.3%) had pretreatment vitamin D insufficiency, and 195 (16.4%) developed grade ≥3 CIPN. Patients with vitamin D insufficiency had a higher incidence of grade ≥3 CIPN than those who had sufficient vitamin D (20.7% vs 14.2%; odds ratio [OR], 1.57; 95% CI, 1.14–2.15; $P=.005$). The association retained significance after adjusting for age and paclitaxel schedule (adjusted OR, 1.65; 95% CI, 1.18–2.30; $P=.003$) but not race (adjusted OR, 1.39; 95% CI, 0.98–1.97; $P=.066$). In the mouse experiments, the vitamin D–deficient diet caused mechanical hypersensitivity and sensitized mice to paclitaxel (both $P<.05$). **Conclusions:** Pretreatment vitamin D insufficiency is the first validated potentially modifiable predictive biomarker of CIPN from paclitaxel. Prospective trials are needed to determine whether vitamin D supplementation prevents CIPN and improves treatment outcomes in patients with breast and other cancer types.

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Background

Chemotherapy-induced peripheral neuropathy (CIPN) is the major treatment-limiting toxicity of many anticancer agents, including paclitaxel. CIPN affects up to 70% of paclitaxel-treated patients, and approximately 30% experience severe symptoms.[1,2] CIPN can last for years after finishing chemotherapy,[3,4] significantly diminishing patients' long-term quality of life.[5] Although duloxetine has proven to be effective for relieving CIPN pain, there are no established strategies to prevent or treat sensory or motor CIPN symptoms.[6,7] Therefore, patients experiencing moderate or severe CIPN may require treatment alterations that reduce efficacy and survival.[8,9]

Prior research has identified nonmodifiable CIPN risk factors, such as age, race, and genetics, and potentially though not easily modifiable risk factors, such as diabetes, sedentary lifestyle, and high systemic paclitaxel exposure.[10] Several retrospective studies suggested that patients with lower pretreatment vitamin D concentrations have higher CIPN risk[11,12]; however, this has yet to be validated in a well-conducted retrospective analysis of a prospective clinical trial, referred to as a prospective-retrospective study.[13–15] Validation of vitamin D insufficiency as a CIPN risk factor is a critical first step toward developing interventional strategies to prevent CIPN,

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extend chemotherapy treatment, and improve clinical outcomes.

The objective of this study was to validate pretreatment vitamin D insufficiency as a risk factor for CIPN in patients with early-stage breast cancer receiving paclitaxel. We conducted a prospective-retrospective analysis using data and samples from the SWOG S0221 clinical trial (ClinicalTrials.gov identifier: NCT00070564). We also examined the incidence of CIPN and vitamin D insufficiency in Black patients to determine whether vitamin D insufficiency contributes to the racial disparity in CIPN risk. After validation in patients, we attempted to determine whether vitamin D deficiency causes mechanical sensitivity in mice and sensitizes mice to mechanical sensitivity caused by paclitaxel.

Methods

Study Patients and Clinical Data

This prospective-retrospective study was conducted using data and serum samples from SWOG S0221, a randomized phase III trial comparing 6 different dosing schedules of standard doxorubicin/cyclophosphamide-paclitaxel (AC-T) adjuvant chemotherapy in patients with early-stage breast cancer.[16,17] In the initial protocol, patients were randomized in a 2×2 factorial design to AC once per week for 15 doses versus every 2 weeks (Q2W) for 6 doses, followed by paclitaxel 80 mg/m^2 once per week for 12 doses versus 175 mg/m^2 Q2W for 6 doses. A revised AC regimen (Q2W for 4 doses) was added later, bringing the total study arms to 6. Information on preexisting neuropathy was not collected or used as an exclusion criterion. Adverse events were evaluated every 4 weeks while the patient was receiving protocol therapy using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.[18] The primary endpoint of this analysis was grade 3 or higher (grade ≥3) sensory CIPN that was possibly, probably, or definitely related to chemotherapy treatment.

Of the 2,849 eligible female participants receiving paclitaxel on the S0221 trial, 1,620 had at least 2 available serum samples and provided consent for further research. All these patients had received paclitaxel with the dose to body surface area within 5% of the target ratio of the assigned arm and continued paclitaxel for at least 45 days. A total of 1,191 (74%) were selected for this biomarker analysis due to budgetary limitations and power calculations, indicating that this sample size was sufficient. Patients were selected to maximize informativeness in this and future analyses. All patients who reported grade ≥3 sensory or motor CIPN (n=204) or completed the DELCaP substudy baseline questionnaires (additional n=572) were selected for vitamin D analysis. The DELCaP substudy collected additional patient-reported lifestyle information and treatment toxicity.[17,19] The remaining patients (n=415) were selected randomly from the available remaining eligible patients (n=844) to achieve the target number (supplemental eFigure 1, available with this article at JNCCN.org). Demographics were compared between patients with and without grade ≥3 sensory CIPN using *t* tests for continuous variables and chi-square tests for categorical variables.

Pretreatment Vitamin D Measurement

Blood samples were collected from study participants at enrollment, and serum was stored at −80°C. At the time of assay, samples were randomized, and 25-hydroxy vitamin D_2 and D_3 were quantified in a blinded manner using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay by Heartland Assays, which has been validated for use with archived specimens.[20–23] Vitamin D_2 or D_3 concentrations below the limit of quantification (1.5 ng/mL) were imputed with half the limit of quantification. One patient inadvertently had 2 samples analyzed, so the average of the 2 concentrations was used. The primary independent variable, vitamin D insufficiency, was defined as total vitamin D concentration ($D_2 + D_3$) ≤20 ng/mL.[24]

Regression Analysis Between CIPN and Vitamin D

The primary analysis was conducted following an a priori analysis plan agreed upon by the study team and the SWOG Statistical Data Management Center. The analysis plan specified patient inclusion and exclusion criteria, definitions of the primary independent (total vitamin D insufficiency) and dependent (grade ≥3 sensory CIPN) variables, covariates, statistical tests, and a 2-sided α level of .05. Secondary analyses that were not defined a priori were considered exploratory and hypothesis-generating. Regression analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing).

In the primary analysis, unadjusted logistic regression was used to assess the relationship between pretreatment vitamin D insufficiency and grade ≥3 sensory CIPN. The association was then adjusted for the following covariates that have been reported to be associated with CIPN risk: age (in years), self-reported race (White vs Black vs other), body mass index, and paclitaxel treatment assignment (weekly [QW] or Q2W) via multivariable logistic regression. An exploratory model including all the covariates except race was conducted to explore the possible confounding effect of race. The interaction terms were tested between any covariates and vitamin D insufficiency.

Secondary analyses were conducted similarly to the primary analysis using slight variations of the independent and dependent variables. The combination of grade ≥3 sensory and motor CIPN was used as a secondary

dependent variable. Alternative independent variables included vitamin D_3 insufficiency (≤20 ng/mL), total vitamin D deficiency (≤12 ng/mL), and total vitamin D concentration as a continuous variable. The optimal total vitamin D threshold was determined based on the area under the curve (AUC) of the receiver operating characteristic curve.

Exploratory analysis of the association was examined within the strata of each covariate using simple logistic regression. Multivariable logistic regression with covariate adjustment was also conducted in each self-reported racial group (Black, White, and other). The prevalence of pretreatment vitamin D insufficiency was compared between self-reported racial groups via simple logistic regression with a 2-sided α level of .05.

Vitamin D Deficiency Mouse Experiments

Adult (50% male and 50% female) C57BL/6J (JAX mice; The Jackson Laboratory) were acclimated and housed in a temperature-, light-, and humidity-controlled facility at Virginia Commonwealth University. Mice were randomly assigned 1:1 to a regular diet (RD) or vitamin D–deficient diet (VDD) by withdrawing vitamin D from the diet (Research Diets Inc.) for 2 months, which has been demonstrated to cause 25-hydroxy vitamin D_3 deficiency in C57BL/6J mice.[25] Mice were then randomly assigned 1:1 to intraperitoneal administration of 2 mg/kg paclitaxel or vehicle (1:1:18 mixture of 200-proof ethanol, Kolliphor, and distilled water) every other day for 4 doses. Mechanical sensitivity threshold, a commonly used mouse phenotype of sensory neurotoxicity, was tested using von Frey filaments by a study team member blinded to treatment assignments.[26,27] The mechanical threshold is expressed as the grams of force required to elicit hind paw withdrawal in 50% of the animals. Mechanical sensitivity was tested before and after 4 and 8 weeks of RD or VDD and before and at 3, 7, 14, and 21 days after paclitaxel or vehicle administration. Mechanical hypersensitivity data in mice were expressed as the mean ± SEM and analyzed using 3-way ANOVA via GraphPad Prism 9.3.0 software with an α level of .05.

Results

Study Patient Characteristics

Of the 1,191 female patients included in the analysis, the mean age of the analysis cohort was 51.1 years (SEM, 9.9 years). Patients were mostly White (83.7% vs 9.2% Black), and 52.5% received Q2W paclitaxel treatment (Table 1). The demographics were similar to the overall S0221 parent trial cohort, but the analysis cohort was purposefully enriched for patients who experienced CIPN. In all, 397 (33.3%) patients had pretreatment vitamin D insufficiency, 195 (16.4%) developed grade ≥3 sensory CIPN, and 204 (17.1%) developed grade ≥3 sensory or motor CIPN.

Vitamin D Insufficiency as a Risk Factor for CIPN

Patients who were older (odds ratio [OR], 1.02; 95% CI, 1.01–1.04; P=.005), self-reported as Black (OR, 2.48; 95% CI, 1.57–3.86; P<.001) or other race (OR, 1.84; 95% CI, 1.06–3.07; P=.025), or were randomized to Q2W paclitaxel (OR, 2.37; 95% CI, 1.73–3.29; P<.001) had a higher incidence of CIPN. In the primary univariate analysis, patients with pretreatment vitamin D insufficiency had a higher incidence of grade ≥3 sensory CIPN than those who were vitamin D sufficient (20.7% vs 14.2%; OR, 1.57; 95% CI, 1.14–2.15; P=.005) (Table 2, Figure 1). The association retained significance after adjusting for age and paclitaxel schedule (adjusted OR [aOR], 1.65; 95% CI, 1.18–2.30; P=.003) but did not retain significance after additionally adjusting for self-reported race (aOR, 1.39; 95% CI, 0.98–1.97; P=.066) (Table 2). In subgroup analyses, CIPN incidence was higher in vitamin D–insufficient patients in the middle age tertile, top body mass index tertile, and paclitaxel Q2W subgroups (Figure 2), but there was no significant interaction between any covariates and vitamin D insufficiency (data not shown).

In secondary analyses, when using the combination of grade ≥3 sensory and motor CIPN as the dependent variable, pretreatment vitamin D insufficiency was significantly associated with CIPN, including when adjusting for self-reported race (supplemental eTable 1). The results were not meaningfully different when using vitamin D_3 insufficiency, vitamin D deficiency, or vitamin D concentrations as the independent variable (supplemental eTable 2). The optimal vitamin D threshold was 17 ng/mL, but the prediction performance was not meaningfully different (17 ng/mL AUC, 55.9% vs 20 ng/mL AUC, 55.2%; supplemental eFigure 2).

Racial Disparity in Vitamin D Insufficiency and CIPN

Compared with White patients, Black patients had a higher prevalence of vitamin D insufficiency (28.2% White vs 77.1% Black vs 37.6% other; Black vs White OR, 8.56; 95% CI, 5.44–13.92; P<.001) and a higher incidence of sensory CIPN (14.3% White vs 29.4% Black vs 23.5% other; Black vs White OR, 2.48; 95% CI, 1.57–3.86; P<.001) (Table 2). The association of vitamin D insufficiency with sensory CIPN was not statistically significant in any self-reported racial subgroup but was nominally similar in the White (OR, 1.40; 95% CI, 0.95–2.27) and Black cohorts (OR, 1.42; 95% CI, 0.53–4.27) (Figure 2, supplemental eTable 3).

Vitamin D Deficiency Causes Mechanical Sensitivity in Mice

Mice receiving VDD displayed a significant and progressive decline in the mechanical sensitivity threshold

Table 1. Clinical Data for Analyzed Cohort

	All Patients n (%)	No Sensory CIPN n (%)	Sensory CIPN n (%)	*P* Value[a]
Total, n	1,191	996	195	
Age, y				**.005**
Mean	51.1	50.8	52.9	
SE	9.9	9.9	9.7	
IQR	44–59	44–58	46–60	
Race				**<.001**
White	997 (84)	854 (86)	143 (73)	
Black	109 (9)	77 (8)	32 (17)	
Other or unknown	85 (7)	65 (7)	20 (10)	
BMI, kg/m^2				.122
Mean	30.3	30.2	31.1	
SE	7.5	7.5	7.4	
IQR	25.1–34.1	24.8–33.9	25.8–35.5	
Menopausal status (n=1,182)				**<.001**
Premenopausal	549 (46)	483 (49)	66 (35)	
Postmenopausal	633 (54)	509 (51)	124 (65)	
Nodal status (n=1,188)				.295
Negative	324 (27)	268 (27)	56 (29)	
1–3 positive	438 (37)	376 (38)	62 (32)	
≥4 positive	426 (36)	350 (35)	76 (39)	
ER/PgR status (n=1,188)				.599
Negative	391 (33)	324 (33)	67 (35)	
Either positive	797 (67)	670 (67)	127 (65)	
HER2 status (n=1,184)				.996
Negative	931 (79)	780 (79)	151 (79)	
Positive	253 (21)	212 (21)	41 (21)	
Paclitaxel treatment arm				**<.001**
QW	612 (51)	546 (55)	66 (34)	
Q2W	579 (49)	450 (45)	129 (66)	
Percent of planned paclitaxel dose administered				**<.001**
Mean	87.9%	91.4%	69.7%	
SE	22.1%	20.2%	23.0%	
IQR	83.0%–100.0%	92.0%–100.0%	50.0%–83.0%	
Sensory CIPN grade 3/4	195 (16)	0 (0)	195 (100)	**<.001**
Motor CIPN grade 3/4	22 (2)	9 (1)	13 (7)	**<.001**
Sensory or motor CIPN grade 3/4	204 (17)	9 (1)	195 (100)	**<.001**
Vitamin D insufficiency (≤20 ng/mL)	397 (33)	315 (32)	82 (42)	**.006**
Vitamin D deficiency (≤12 ng/mL)	109 (9)	83 (8)	26 (13)	**.038**
Vitamin D concentration (ng/mL)				**.011**
Mean	25.4	25.8	23.6	
SE	10.6	10.6	10.6	
IQR	17.8–31.9	18.4–32.1	14.9–30.6	

Bold indicates statistically significant *P* value.
Abbreviations: BMI, body mass index; CIPN, chemotherapy-induced peripheral neuropathy; ER, estrogen receptor; PgR, progesterone receptor; Q2W, every 2 weeks; QW, weekly.
[a]*P* values are from comparing patients with and without grade ≥3 sensory CIPN using a *t* test for continuous variables and a chi-square test for categorical variables. Clinical variables were missing in a small number of patients.

Table 2. ORs of Unadjusted and Multivariable Models of Sensory Peripheral Neuropathy Predicted by Vitamin D Insufficiency

	Unadjusted		Adjusted for All Covariates[a]		Adjusted for All Covariates Except Race[b]	
	OR (95% CI)	*P* Value	aOR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
Vitamin D insufficiency	1.57 (1.14–2.15)	**.005**	1.39 (0.98–1.97)	.066	1.65 (1.18–2.30)	**.003**
Paclitaxel (Q2W vs QW)	2.37 (1.73–3.29)	**<.001**	2.41 (1.74–3.35)	**<.001**	2.37 (1.72–3.30)	**<.001**
Age (y)	1.02 (1.01–1.04)	**.005**	1.03 (1.01–1.04)	**.002**	1.03 (1.01–1.04)	**.003**
Race						
Black vs White	2.48 (1.57–3.86)	**<.001**	2.30 (1.39–3.74)	**.001**	NA	NA
Other vs White	1.84 (1.06–3.07)	**.025**	1.93 (1.09–3.28)	**.019**	NA	NA
BMI (kg/m^2)	1.02 (1.00–1.03)	.127	1.01 (0.98–1.03)	.572	1.01 (0.99–1.03)	.505

Bold indicates statistically significant *P* value.
Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; NA, not applicable; OR, odds ratio; Q2W, every 2 weeks; QW, weekly.
[a]Adjusted for paclitaxel schedule, age, self-reported race, and BMI.
[b]Adjusted for paclitaxel schedule, age, and BMI.

and had greater mechanical sensitivity than mice receiving RD at weeks 4 (P=.037) and 8 (P=.016) (Figure 3A). Following the 8-week VDD, mice receiving 4 doses of paclitaxel (VDD-PAC) displayed a significant and progressive decline in mechanical sensitivity compared with vehicle-treated mice receiving RD (RD-VEH) (Figure 3B). VDD-PAC mice had significantly greater mechanical sensitivity compared with paclitaxel-treated mice receiving RD (RD-PAC) on day 14 (P=.044) (Figure 3B).

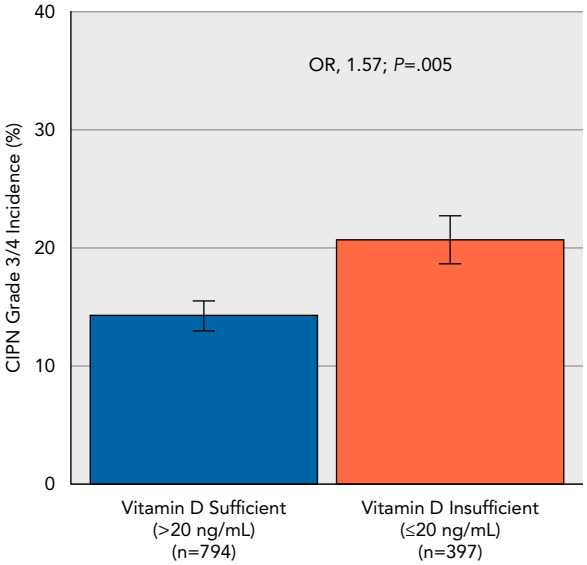

Figure 1. Incidence of sensory peripheral neuropathy by vitamin D sufficiency. Incidence of grade 3/4 sensory CIPN in patients who were vitamin D sufficient or insufficient prior to treatment. Patients with vitamin D insufficiency had a higher incidence of CIPN (20.7% vs 14.2%; OR, 1.57; 95% CI, 1.14–2.15; P=.005). Error bars represent sampling error.
Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; OR, odds ratio.

Discussion

Our prospective-retrospective analysis of the SWOG S0221 clinical trial confirms that patients with pretreatment vitamin D insufficiency have a higher incidence of CIPN and suggests that this may partially explain the higher incidence of CIPN in Black patients. The mouse experiment indicates that vitamin D deficiency directly causes neurotoxicity and sensitization to paclitaxel.

Prior studies have reported that patients with vitamin D insufficiency have a higher risk of CIPN from paclitaxel.[11,12] In our prior pilot study, patients with vitamin D insufficiency reported more severe sensory CIPN on the CIPN20 questionnaire (36 vs 16 [0 to 100 scale]).[12] Another group also found lower pretreatment vitamin D concentrations (10.3 vs 15.4 ng/mL) in paclitaxel-treated patients who developed CIPN.[11] Our analysis of data from S0221 confirms the association between vitamin D insufficiency and higher CIPN incidence and satisfies the 3 requirements of a confirmatory prospective-retrospective study: (1) enough patients from a prospective trial to have adequate statistical power and be representative of the parent trial, (2) an analytically validated test, and (3) a prespecified statistical analysis plan.[15]

Vitamin D insufficiency has also been suggested to be a risk factor for CIPN caused by other neurotoxic anticancer agents, including oxaliplatin,[28] bortezomib, and thalidomide,[29–32] and in other disease states, including diabetic neuropathy[33] and autoimmune-mediated CIPN.[34,35] Although this correlative association could be due to confounding from an unrelated variable such as diet or lifestyle, our animal study suggests that vitamin D deficiency directly causes mechanical hypersensitivity and sensitizes mice to paclitaxel. A recent mouse study reported that vitamin D deficiency induces mechanical

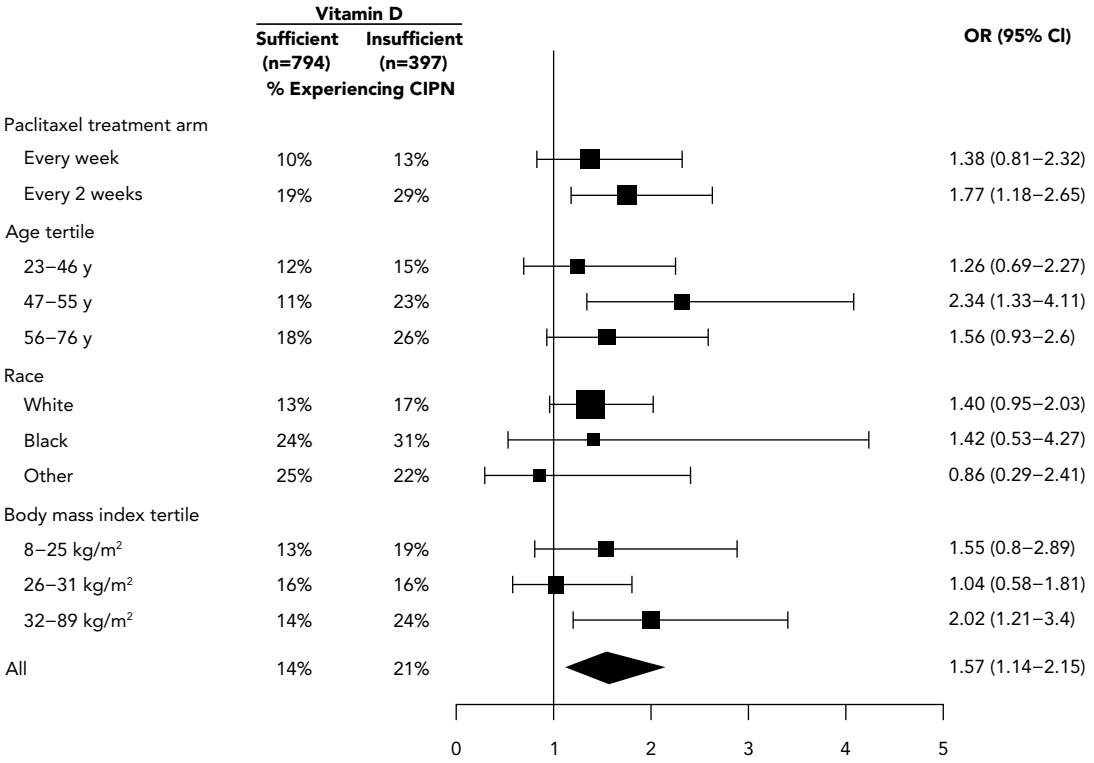

Figure 2. Association between vitamin D insufficiency and grade 3/4 sensory CIPN incidence in covariate subgroups. ORs and 95% confidence intervals were from simple logistic regression. The size of the box represents the exponent of the subgroup size.
Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; OR, odds ratio.

hypersensitivity through microglial activation in the brain and spinal cord,[36] similar to the effects of paclitaxel,[37–43] which provides a plausible mechanistic explanation for our finding. Vitamin D supplementation may ameliorate these effects by increasing axon regeneration and myelination, possibly via stimulation of nerve growth factor[44] or inhibition of proinflammatory cytokines,[45,46] which we are testing in ongoing murine studies.[25,47,48]

It is unclear why Black patients have a higher incidence of CIPN[49,50] and neuropathy from other etiologies.[51,52] Our analysis suggests this may be due to the higher incidence of vitamin D insufficiency,[53] which has been previously suggested.[52] An alternative possibility is that the apparent association with vitamin D and CIPN is due to racial confounding; however, our mouse study demonstrates a direct causal effect of vitamin D insufficiency on neurotoxicity, strengthening the hypotheses that vitamin D insufficiency increases CIPN risk and may be partially responsible for the higher CIPN incidence in Black patients.

Validation of vitamin D insufficiency as a CIPN risk factor justifies testing vitamin D supplementation to prevent CIPN in vitamin D–insufficient patients receiving paclitaxel. A previous analysis in S0221 found that use of vitamin D–containing multivitamins was preventive of CIPN,[17] and there is a case report of vitamin D supplementation improving CIPN in a patient receiving bortezomib.[31] However, the effect of vitamin D supplementation on CIPN is not evaluable in existing prospective clinical trials that did not report CIPN,[54] did not have a no-supplement comparator arm,[55] or used different taxane doses between the supplement and no-supplement arms.[56] Prospective clinical trials of vitamin D supplementation to prevent paclitaxel-induced peripheral neuropathy are needed[57,58]; such a phase II trial is ongoing (ClinicalTrials.gov identifier: NCT05259527). Outside of CIPN, vitamin D supplements have been suggested to improve diabetic neuropathy in vitamin D–insufficient patients.[59] Considering the minimal cost and toxicity of vitamin D supplementation and the use of vitamin D to prevent bone loss in patients with breast cancer who are receiving aromatase inhibitors,[60] vitamin D supplementation may be a reasonable intervention to prevent CIPN during paclitaxel treatment in some high-risk patients, even in the absence of confirmatory clinical trial evidence.

This prospective-retrospective analysis was conducted in a large prospective clinical trial cohort using a validated assay and prespecified analysis plan.[15] Despite these strengths, this study has several limitations that should be acknowledged. First, S0221 did not collect grade 2 CIPN or document detailed paclitaxel dosing information. It is possible that some patients who would have experienced grade ≥3 CIPN were misclassified as no-CIPN controls because of paclitaxel treatment alteration.[61] Second, the

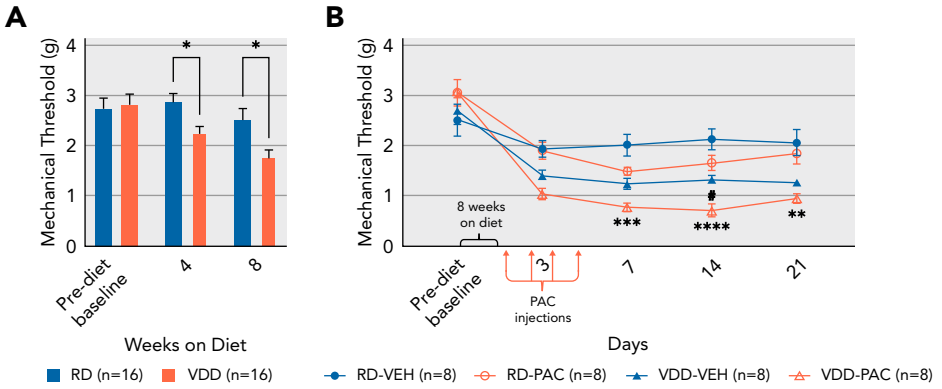

Figure 3. Vitamin D deficiency induces mechanical hypersensitivity and worsens paclitaxel-induced mechanical hypersensitivity in mice. **(A)** Time course showing the development of mechanical hypersensitivity in mice consuming a VDD compared with mice consuming a RD before being treated with paclitaxel. Significance from RD group indicated as $^{*}P<.05$. **(B)** Time course showing the impact of PAC or VEH on mechanical hypersensitivity in mice following 8 weeks of RD or VDD. Significance of VDD-PAC compared with RD-VEH indicated as $^{**}P<.01$, $^{***}P<.001$, $^{****}P<.0001$, and compared with RD-PAC indicated as $\#P<.05$.
Abbreviations: PAC, paclitaxel; RD, regular diet; VDD, vitamin D–deficient diet; VEH, vehicle.

CTCAE is considered less sensitive than patient-reported outcome (PRO) questionnaires for detecting subjective toxicities, including CIPN.[1] We chose to use CTCAE data as the primary CIPN endpoint because they were available in all trial participants, whereas PRO data[62] were available only in the subset of patients that participated in the DELCaP substudy[17] and because of our concerns regarding the use of PRO data in CIPN biomarker analyses.[63] Third, S0221 did not collect data on other CIPN risk factors, including preexisting peripheral neuropathy and diabetes status.[52] Fourth, there was a limited number of non-White participants in this analysis, and larger numbers are needed to further elucidate the interplay between race, vitamin D, and CIPN, which perhaps can be achieved in the EAZ171 (NCT04001829) study. Finally, we plan to investigate whether this association also applies to paclitaxel and docetaxel used in other tumor types by using data and samples collected within the prospective observational SWOG S1714 study (NCT03939481). Confirmation of the association in a second prospective-retrospective analysis would satisfy the fourth and final criteria for prospective-retrospective biomarker validation.[15]

Conclusions

Pretreatment vitamin D insufficiency is associated with a higher risk of CIPN from paclitaxel. Prospective trials are needed to investigate the potential effectiveness of vitamin D supplementation for CIPN prevention. Vitamin D insufficiency may be a clinically useful biomarker to inform personalized supplementation to reduce CIPN occurrence, improve long-term quality of life, and perhaps enable patients to remain on effective paclitaxel treatment and improve survival.

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Vitamin D Insufficiency as a Risk Factor for Paclitaxel-Induced Peripheral Neuropathy in SWOG S0221

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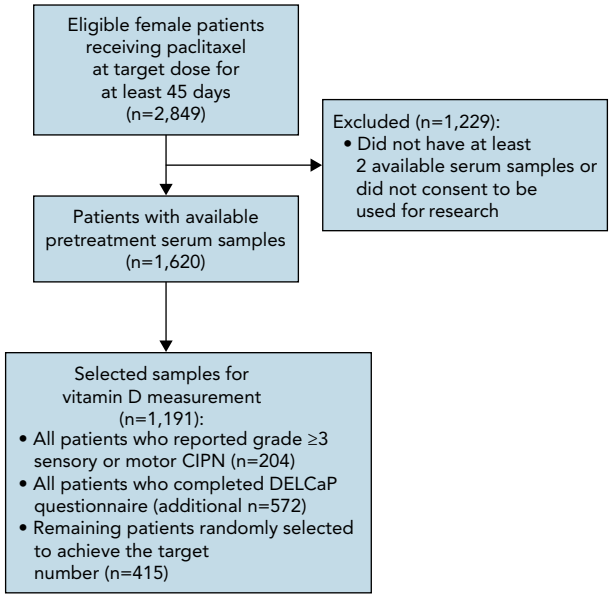
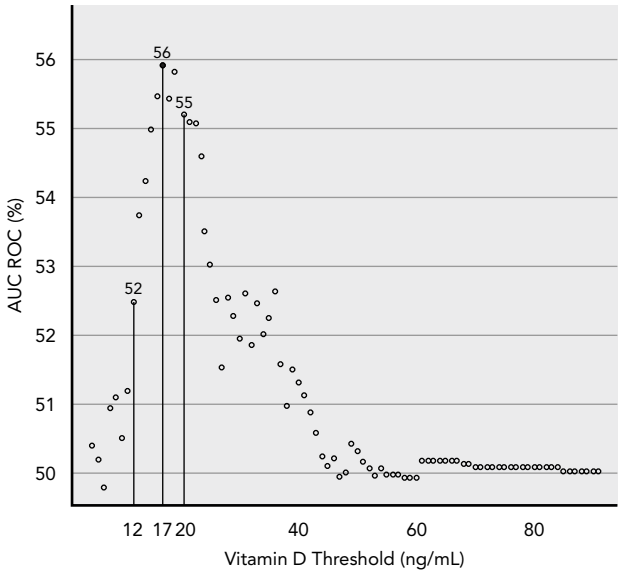


eFigure 1. CONSORT diagram of study patients included in vitamin D analyses.
Abbreviation: CIPN, chemotherapy-induced peripheral neuropathy.



eFigure 2. AUC ROC curve of different vitamin D thresholds. The optimal vitamin D threshold was 17 ng/mL (AUC ROC, 55.9%).
Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

eTable 1. ORs of Unadjusted and Adjusted Models of Sensory or Motor Peripheral Neuropathy Predicted by Vitamin D Insufficiency

	Unadjusted		Adjusted for All Covariates[a]		Adjusted for All Covariates Except Race[b]	
	OR (95% CI)	*P* Value	aOR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
Vitamin D insufficiency	1.75 (1.28–2.38)	**<.001**	1.59 (1.12–2.23)	**.008**	1.81 (1.31–2.51)	**<.001**
Paclitaxel – Q2W vs QW	2.21 (1.62–3.04)	**<.001**	2.25 (1.64–3.11)	**<.001**	2.24 (1.63–3.08)	**<.001**
Age (y)	1.02 (1.01–1.04)	**.003**	1.03 (1.01–1.04)	**.001**	1.03 (1.01–1.04)	**.002**
Race – Black vs White	2.31 (1.46–3.58)	**<.001**	1.95 (1.19–3.16)	**.007**	NA	NA
Race – other vs White	1.71 (0.98–2.86)	**.047**	1.80 (1.02–3.06)	**.034**	NA	NA
BMI (kg/m^2)	1.02 (1.00–1.04)	**.017**	1.01 (0.99–1.03)	.186	1.01 (0.99–1.03)	.170

Bold indicates statistically significant *P* value.
Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; NA, not applicable; OR, odds ratio; Q2W, every 2 weeks; QW, every week.
[a]Adjusted for paclitaxel schedule, age, self-reported race, and BMI.
[b]Adjusted for paclitaxel schedule, age, and BMI.

eTable 2. ORs of Unadjusted and Adjusted Models of Sensory Peripheral Neuropathy Using Alternative Vitamin D Predictors

	Unadjusted		Adjusted for All Covariates[a]		Adjusted for All Covariates Except Race[b]	
	OR (95% CI)	*P* Value	aOR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
Vitamin D_3 insufficiency (<20 ng/mL)						
Vitamin D_3 insufficiency	1.39 (1.02–1.90)	**.035**	1.23 (0.87–1.73)	.236	1.65 (1.18–2.30)	**.003**
Paclitaxel – Q2W vs QW	2.37 (1.73–3.29)	**<.001**	2.41 (1.74–3.36)	**<.001**	2.37 (1.72–3.30)	**<.001**
Age (y)	1.02 (1.01–1.04)	**.005**	1.03 (1.01–1.04)	**.002**	1.03 (1.01–1.04)	**.003**
Race – Black vs White	2.48 (1.57–3.86)	**<.001**	2.41 (1.46–3.93)	**<.001**	NA	NA
Race – other vs White	1.84 (1.06–3.07)	**.025**	1.95 (1.11–3.32)	**.016**	NA	NA
BMI (kg/m^2)	1.02 (1.00–1.03)	.127	1.01 (0.99–1.03)	.475	1.01 (0.99–1.03)	.505
Total vitamin D deficiency (<12 ng/mL)						
Vitamin D deficiency	1.69 (1.04–2.67)	**.028**	1.20 (0.69–2.03)	.499	1.63 (0.98–2.64)	.054
Paclitaxel – Q2W vs QW	2.37 (1.73–3.29)	**<.001**	2.40 (1.73–3.34)	**<.001**	2.35 (1.70–3.27)	**<.001**
Age (y)	1.02 (1.01–1.04)	**.005**	1.03 (1.01–1.04)	**.003**	1.02 (1.01–1.04)	**.007**
Race – Black vs White	2.48 (1.57–3.86)	**<.001**	2.51 (1.51–4.11)	**<.001**	NA	NA
Race – other vs White	1.84 (1.06–3.07)	**.025**	1.99 (1.13–3.37)	**.014**	NA	NA
BMI (kg/m^2)	1.02 (1.00–1.03)	.127	1.01 (0.99–1.03)	.422	1.01 (0.99–1.03)	.322
Vitamin D concentration (ng/mL)						
Vitamin D concentration	0.98 (0.97–1.00)	**.011**	0.99 (0.97–1.00)	.105	0.98 (0.96–0.99)	**.007**
Paclitaxel – Q2W vs QW	2.37 (1.73–3.29)	**<.001**	2.40 (1.74–3.35)	**<.001**	2.36 (1.71–3.28)	**<.001**
Age (y)	1.02 (1.01–1.04)	**.005**	1.03 (1.01–1.04)	**.002**	1.03 (1.01–1.04)	**.003**
Race – Black vs White	2.48 (1.57–3.86)	**<.001**	2.33 (1.41–3.80)	**.001**	NA	NA
Race – other vs White	1.84 (1.06–3.07)	**.025**	1.95 (1.10–3.31)	**.017**	NA	NA
BMI (kg/m^2)	1.02 (1.00–1.03)	.127	1.01 (0.98–1.03)	.591	1.01 (0.98–1.03)	.540

Bold indicates statistically significant *P* value.
Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; NA, not applicable; OR, odds ratio; Q2W, every 2 weeks; QW, every week.
[a]Adjusted for paclitaxel schedule, age, self-reported race, and BMI.
[b]Adjusted for paclitaxel schedule, age, and BMI.

eTable 3. Odds Ratios of Unadjusted and Adjusted Models of Sensory Peripheral Neuropathy Stratified by Self-Reported Race

	Unadjusted		Adjusted for All Covariates Except Race[a]	
	OR (95% CI)	*P* Value	aOR (95% CI)	*P* Value
White (n=997)				
Vitamin D insufficiency	1.40 (0.95–2.03)	.082	1.47 (0.98–2.18)	.057
Paclitaxel – Q2W vs QW	2.63 (1.81–3.86)	**<.001**	2.61 (1.79–3.86)	**<.001**
Age (y)	1.03 (1.01–1.05)	**.004**	1.03 (1.01–1.05)	**.004**
BMI (kg/m^2)	1.01 (0.99–1.03)	.286	1.01 (0.98–1.03)	.566
Black (n=109)				
Vitamin D insufficiency	1.42 (0.53–4.27)	.504	1.53 (0.54–4.89)	.441
Paclitaxel – Q2W vs QW	1.43 (0.63–3.31)	.394	1.27 (0.53–3.07)	.597
Age (y)	1.02 (0.98–1.06)	.349	1.02 (0.98–1.06)	.363
BMI (kg/m^2)	1.03 (0.98–1.09)	.258	1.02 (0.97–1.08)	.413
Other (n=85)				
Vitamin D insufficiency	0.86 (0.29–2.41)	.780	1.03 (0.33–3.08)	.955
Paclitaxel – Q2W vs QW	2.90 (1.03–9.06)	.052	3.10 (1.07–9.98)	**.044**
Age (y)	1.01 (0.96–1.08)	.662	1.03 (0.96–1.10)	.409
BMI (kg/m^2)	0.97 (0.87–1.06)	.486	0.96 (0.86–1.06)	.440

Bold indicates statistically significant *P* value.
Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; OR, odds ratio; Q2W, every 2 weeks; QW, every week.
[a]Adjusted for paclitaxel schedule, age, and BMI.