Check for updates

Cancer Medicine

WILEY

Cancer Medicine Open Access

RESEARCH ARTICLE OPEN ACCESS

Association of Vitamin D Status With Total and Site-Specific Cancer Mortality From Tropical to Subantarctic Latitudes: A Nationwide Population-Based Study in Chile

Gonzalo Muñoz[1] | Juan Pablo Fraga[2] | Ignacia S. Núñez-Ulloa[2] | Alvaro Passi-Solar[3] | Bruno Nervi[1,4] | Sebastián Mondaca[1] | Paula Margozzini[3,4] | Carlos A. Camargo Jr.[5] | Arturo Borzutzky[2]

[1]Department of Hematology and Oncology, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile | [2]Translational Allergy and Immunology Laboratory, Department of Pediatric Infectious Diseases and Immunology, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile | [3]School of Public Health, Pontificia Universidad Católica de Chile, Santiago, Chile | [4]Center for Cancer Prevention and Control (CECAN), Santiago, Chile | [5]Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, USA

Correspondence: Arturo Borzutzky (aborzutz@uc.cl)

Received: 10 June 2026 | **Revised:** 20 August 2026 | **Accepted:** 4 September 2026

ABSTRACT

Background: An association of low vitamin D (VD) status with increased cancer mortality has been described, and Chile provides an ideal setting to evaluate this association given its extensive latitude span (17°S–56°S).

Methods: We performed a nationwide population-based ecological study of all and specific cancer deaths from 2002 to 2020, in which mean 25(OH)D concentrations were obtained from the 2017 Chilean National Health Survey and associations with cancer deaths were assessed across 48 provinces. Multiple regression models including body mass index and tobacco use were performed to account for other carcinogenic factors.

Results: For the studied period, 446,237 cancer-associated deaths were reported. Provincial mean 25(OH)D ranged between 11.8 and 25.8 ng/mL, displaying a significant north–south decreasing gradient, and provincial mean 25(OH)D concentrations were inversely correlated with age-standardized death rates for multiple cancer types, being strongest for breast, kidney, and liver cancer. Multiple regression models revealed significant inverse associations for 21 of the 27 cancer types analyzed, being strongest for endometrial, thyroid, colorectal, liver, kidney, and larynx cancer.

Conclusions: Significant inverse associations between 25(OH)D concentrations and multiple cancer-type mortality were found across Chile, confirming the association of low VD status with colorectal and breast cancer mortality, while providing novel ecological evidence of an inverse association between 25(OH)D concentrations and several cancer types for which a relationship with VD has been less established. These findings should inform public policies regarding cancer screening and treatment across different latitudes, and prompt evaluation of VD supplementation and fortification for reduction of site-specific cancer mortality.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ASDR, Age-standardized death rate(s); BMI, Body mass index; CECAN, Center for Cancer Prevention and Control; CI, Confidence interval; CNHS, Chilean National Health Survey; CNS, Central nervous system; DEIS, Departamento de Estadísticas e Información de Salud (Department of Health Statistics and Information); ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; IU, International units; NA, Not applicable; RECORD, Reporting of studies Conducted using Observational Routinely collected health Data; UVB, Ultraviolet B radiation; VD, Vitamin D; VITAL, VITamin D and OmegA-3 TriaL.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2026 The Author(s). *Cancer Medicine* published by John Wiley & Sons Ltd.

Plain Language Summary

Vitamin D is produced by the skin exposed to sunlight, and populations living farther from the Equator tend to have lower vitamin D concentrations. Low vitamin D has been linked to a higher risk of dying from cancer. We analyzed cancer death rates across 56 provinces in Chile, a country stretching from the tropics to near the Antarctic, and found that populations living in provinces with lower vitamin D concentrations had higher cancer death rates for colorectal, thyroid, liver, kidney, and breast cancer. These findings serve as a baseline to evaluate policies to improve vitamin D status through food fortification or supplementation.

1 | Introduction

Low vitamin D (VD) concentrations affect over one billion people worldwide and therefore represent a major global public health concern with potential implications for a variety of health outcomes [1]. In humans, VD is primarily synthesized in the skin after exposure to ultraviolet B radiation. Smaller amounts can also be obtained from dietary sources and supplementation. To date, circulating 25-hydroxyvitamin D (25(OH)D) is the standard biomarker used to assess VD status [2].

In addition to its established role in bone metabolism, VD exerts pleiotropic effects, including potential antineoplastic properties. In experimental studies, the active metabolite 1,25-dihydroxyvitamin D influences key cellular processes involved in carcinogenesis, such as proliferation, differentiation, apoptosis, and angiogenesis, through VD receptor–mediated pathways [3].

Epidemiological studies indicate that low 25(OH)D concentrations, commonly defined as <20 ng/mL, are associated with increased overall cancer mortality, as well as site-specific mortality for breast and colorectal cancers [4–7]. However, findings from randomized trials and meta-analyses on VD supplementation have been inconsistent [8, 9]. On the other hand, geographic latitude has also been associated with cancer mortality, with higher rates observed at increasing distances from the Equator [10, 11]. Given the inverse relationship between latitude, solar radiation, and population 25(OH)D concentrations, VD status has been proposed as a potential mediator of this geographic variation. However, evidence from multi-country comparisons should be interpreted with caution, as cross-national differences in skin pigmentation, dietary habits, sun-exposure behavior, and clothing style can obscure or even reverse the expected latitude–25(OH)D relationship. For instance, VD status has been reported to be better in Nordic than in some Mediterranean countries despite higher latitude and less sunshine, and global multi-continent data have shown only a modest inverse correlation between latitude and serum 25(OH)D ($r=-0.36$) [12]. Within this context, Chile offers a particularly informative natural setting; in addition to its ethnic homogeneity, it spans approximately 4270 km along a north–south axis that is nearly perpendicular to the Equator, having one of the widest latitudinal ranges of any single country. From a geographic standpoint, its southernmost areas correspond to latitudes similar to those of southern Norway or southern Alaska, whereas its northern regions align with latitudes comparable to Western Sahara or Guatemala [13].

Chile's geography, together with a relatively genetically and ethnically homogeneous population composed primarily of individuals with European and Indigenous ancestry, makes it an ideal setting to investigate the effects of latitude and solar radiation on human health. Against this background, the aim of this study is to evaluate total and site-specific cancer mortality data across Chilean provinces during an 18-year period and its ecological association with population-based 25(OH)D concentrations.

2 | Material and Methods

2.1 | Total and Specific Cancer-Related Deaths

Cancer-related mortality data for the period 2002–2020 were obtained from the Open Data section of the Department of Health Statistics and Information (DEIS) of the Chilean Ministry of Health [14]. Chile is administratively divided into 16 regions, which are further subdivided into 56 provinces. Cancer types were classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Mortality data were stratified by age group (5-year intervals up to ≥ 80 years), sex, province, and calendar year.

2.2 | Population Vitamin D Status

VD status, assessed by serum 25(OH)D concentrations, was obtained from the 2017 Chilean National Health Survey (CNHS) [15]. In this survey, serum 25(OH)D concentrations were measured in a nationally representative subsample of 1567 women of childbearing age (15–49 years) residing across the country. Blood samples were centrally analyzed in a single laboratory using liquid chromatography/mass spectrometry.

The mean serum 25(OH)D concentration in this population was 20.1 ng/mL (95% CI 19.4–20.8). Provincial mean 25(OH)D concentrations were calculated by averaging values among women of childbearing age residing in each province. Of the 56 Chilean provinces, 48 were retained for the association analyses; 7 sparsely populated provinces were not sampled in the CNHS, and one further province was excluded because a single participant contributed to its provincial mean. The number of participants contributing to each provincial mean ranged from 6 to 169 (mean 34). Serum 25(OH)D concentrations were not available for similarly aged men at the provincial level but only for a sample of men ≥ 65 years; therefore, VD status in women of childbearing age was used as a population-level proxy for both sexes. The rationale for this approach is based on evidence that serum 25(OH)D concentrations among older adults (≥ 65 years) tend to be uniformly low and are more strongly influenced by factors such as supplementation and comorbidities, which may obscure geographic variation. In contrast, VD concentrations

20457634, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cam4.72273, Wiley Online Library on [21/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

in women of childbearing age more closely reflect endogenous synthesis driven by ambient ultraviolet radiation, making this group a more suitable indicator of population-level VD status for ecological analyses.

2.3 | Body Mass Index and Tobacco Use

Body mass index (BMI) and tobacco use data were collected from the 2017 CNHS, in which a representative sample of 6233 individuals were surveyed. Mean BMI ranged from 24.7 kg/m^2 to 31.7 kg/m^2 across provinces, whereas the percentage of active tobacco users varied between 13.5% and 44.2%.

2.4 | Age-Standardized Mortality Rates

Age-standardized death rates (ASDR) were calculated using demographic projections based on the 2017 Chilean census for each age group, sex, province, and year within the study period (2002–2020). Mortality records were combined with population data using a unique key incorporating age, sex, province, and calendar year, enabling estimation of mortality rates in relation to the population at risk. Mortality rates were adjusted for age group and sex using Segi's standard reference population, as employed in Globocan [15]. The direct method of standardization was used to allow comparison across provinces. Mean mortality rates, both crude and age-standardized, were estimated for all cancers and cancer subtypes across all provinces during the study period.

2.5 | Statistical Analysis

All estimates obtained from the 2017 CNHS, including provincial mean 25(OH)D concentrations, body-mass index, and tobacco use, were weighted and adjusted for the complex sampling design. An ecological analysis was conducted to investigate associations between mean provincial 25(OH)D concentrations and cancer mortality rates, both crude and age-standardized, overall and by cancer type. Associations were primarily assessed using linear regression models, with age-standardized cancer mortality rates as the dependent variable and provincial-level mean 25(OH)D concentrations, body-mass index, and tobacco use as independent variables. Age-standardized mortality rates were expressed as deaths per person in the regression models, and coefficients are reported multiplied by 10^7. As an initial exploratory step, univariable associations were examined for descriptive purposes, and a sensitivity analysis was performed restricting the analysis to provinces in which at least 30 subjects contributed to the provincial mean 25(OH)D concentration. All analyses were conducted using R (version 4.2.2). The Reporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines were followed in the conduct and reporting of this study [16]. The Scientific Ethics Committee of the Faculty of Medicine at Pontificia Universidad Católica de Chile approved this study.

During the preparation of this work, artificial intelligence (ChatGPT 4.0, OpenAI and Claude Opus 4.8, Anthropic) was used to assist with language editing and grammar corrections. The content was subsequently reviewed and edited as needed, and full responsibility for the content of the publication is retained by the authors.

3 | Results

3.1 | Study Population

A total of 446,237 cancer-related deaths were recorded in the period 2002–2020, across 56 provinces in Chile, with 51.9% occurring among males. Cancer mortality increased markedly with age, with approximately one quarter of deaths occurring among individuals aged ≥ 80 years (Figure 1). Over the study period, the absolute number of cancer-related deaths increased, reflecting population aging, while ASDR showed an overall declining trend, more pronounced among males than females (Figure S1 and Figure S2, respectively). The distribution of cancer-related deaths by cancer site and sex is shown in Table 1.

We then examined the regional variation in cancer mortality using ASDR, with regions ordered from north to south. Regional ASDR for the five leading cancer sites is presented in Table 2 for the total population, males, and females, respectively, with regions ordered from north to south. Across regions, ASDR varied for all cancer sites shown. In the total population, lung cancer ASDR was highest in Antofagasta, while gastric cancer ASDR tended to be higher in central–southern regions, peaking in Aysén. Gallbladder cancer ASDR showed marked geographic variation, with the highest rates observed in several southern regions, particularly Los Ríos and La Araucanía. Among males, lung cancer ASDR was highest in Antofagasta, while gastric and prostate cancer ASDR were generally higher in central–southern regions. Among females, breast cancer ASDR was highest in Magallanes, and gallbladder cancer ASDR was highest in La Araucanía and Los Ríos (Table 2). Complete regional heatmaps including all cancer sites are provided in Tables S1–S3.

Given this marked geographic variation in cancer mortality, we next examined the distribution of population-based VD status across Chilean provinces to provide a finer spatial resolution and better capture local heterogeneity. Mean population-based 25(OH)D concentrations ranged from 11.8 to 25.8 ng/mL across the 48 provinces with available data and displayed a north–south gradient, with higher values in northern provinces and lower values toward the south (Figure 2). Provincial mean 25(OH)D decreased significantly with latitude ($25(OH)D = 29.1 - 0.26 \times$ degrees of latitude; $r = -0.61$, $R^2 = 0.37$, $p < 0.0001$). In a multivariable model, latitude remained associated with 25(OH)D after adjustment for provincial mean BMI and tobacco use, whereas neither covariate was significantly associated with latitude (Table S6, Figure S3).

3.2 | Univariate Analysis of Cancer Mortality and 25(OH)D

We then examined the association between provincial variation in population-based VD status and cancer mortality. In univariate analyses, mean population-based 25(OH)D concentrations were not significantly associated with all-cancer ASDR

20457634, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cam4.72273, Wiley Online Library on [21/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

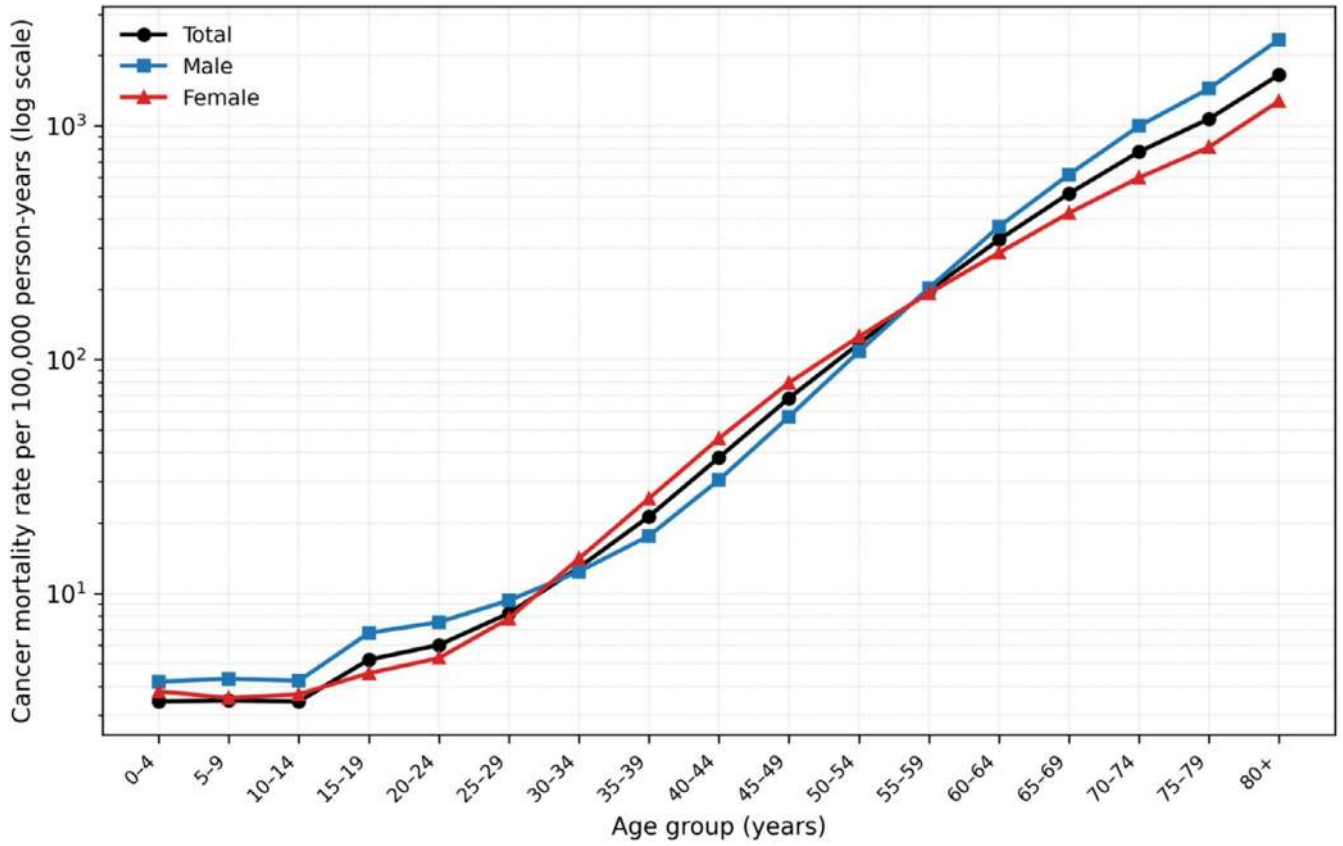


FIGURE 1 | Age-specific cancer mortality rates, overall and by sex. Rates are shown per 100,000 person-years by 5-year age group for the total population, males, and females, based on pooled cancer deaths and population denominators for Chile, 2002–2020.

($r=-0.051$; $p=0.73$). In contrast, inverse associations were observed for several site-specific cancers (Figure 3a). The strongest correlations were observed for breast ($r=-0.39$; $p=0.006$), kidney ($r=-0.38$; $p=0.007$), and liver cancer ($r=-0.38$; $p=0.007$). Additional inverse associations were identified for colorectal, thyroid, endometrial, cervical, central nervous system, laryngeal, melanoma, ovarian, and pancreatic cancers, as well as for non-Hodgkin lymphoma and multiple myeloma.

To explore potential sex-specific patterns, we then conducted sex-stratified univariate analyses. Among males, mean 25-hydroxyvitamin D concentrations showed inverse associations with several site-specific cancer mortality rates (Figure 3b). The strongest correlations were observed for kidney ($r=-0.41$; $p=0.003$), liver ($r=-0.37$; $p=0.008$), and esophageal cancer ($r=-0.35$; $p=0.01$). Additional significant inverse associations were identified for colorectal, laryngeal, pancreatic, and gallbladder cancers, as well as for non-Hodgkin lymphoma and multiple myeloma. Among females, inverse associations between mean 25(OH) concentrations and ASDR were also observed for multiple cancer sites (Figure 3c). The strongest correlations were seen for breast ($r=-0.41$; $p=0.004$), pancreatic ($r=-0.36$; $p=0.01$), and colorectal cancer ($r=-0.35$; $p=0.02$). Additional significant inverse associations were observed for kidney, thyroid, endometrial, cervical, central nervous system, ovarian, and gastric cancers.

Results of all univariate correlation analyses are presented in Table S4. No statistically significant positive (direct) associations were observed between mean 25(OH)D concentrations and cancer ASDR. In a sensitivity analysis restricted to the 20 provinces with at least 30 participants contributing to the provincial mean 25(OH)D concentration, inverse correlations were generally of similar or greater magnitude than in the primary analysis (Table S5). Given the reduced number of provinces and consequent loss of statistical power, statistical significance was not retained for all cancer types.

3.3 | Multivariable Analysis of Cancer Mortality

To account for factors known to be associated with cancer outcomes, we fitted multiple linear regression models including mean provincial 25(OH)D concentrations, BMI, and tobacco use. Results of these analyses are summarized in Table 3. After adjustment, significant inverse associations between mean 25(OH)D concentrations and cancer mortality were observed for 21 of the 27 cancer types analyzed. The largest inverse estimates were observed for endometrial ($\beta=-22\times10^{-7}$, $p=0.007$), thyroid ($\beta=-22\times10^{-7}$, $p=0.02$), colorectal ($\beta=-20\times10^{-7}$, $p=0.01$), liver ($\beta=-19\times10^{-7}$, $p=0.001$), kidney ($\beta=-19\times10^{-7}$, $p=0.003$), and larynx cancer ($\beta=-19\times10^{-7}$, $p=0.02$).

In sex-stratified analyses, the largest inverse estimates among males were observed for liver ($\beta=-51\times10^{-7}$, $p=0.002$), gallbladder ($\beta=-46\times10^{-7}$, $p=0.005$), and multiple myeloma ($\beta=-39\times10^{-7}$, $p=0.008$). Among females, the largest inverse estimates were observed for endometrial ($\beta=-48\times10^{-7}$,

20457634, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cam4.72273, Wiley Online Library on [21/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | Absolute number (and percentage) of cancer-related deaths by cancer type and sex.

Cancer type	Total deaths, *n* (%)	Male deaths, *n* (%)	Female deaths, *n* (%)
Gastric cancer	60,775 (13.6%)	40,480 (17.5%)	20,295 (9.5%)
Lung cancer	52,512 (11.8%)	32,064 (13.8%)	20,448 (9.5%)
Colorectal cancer	39,203 (8.8%)	18,976 (8.2%)	20,227 (9.4%)
Prostate cancer	35,342 (7.9%)	35,342 (15.2%)	NA
Gallbladder cancer	33,143 (7.4%)	9702 (4.2%)	23,441 (10.9%)
Breast cancer	25,615 (5.7%)	183 (0.1%)	25,432 (11.9%)
Pancreatic cancer	22,385 (5.0%)	10,138 (4.4%)	12,247 (5.7%)
Liver cancer	20,418 (4.6%)	10,985 (4.7%)	9433 (4.4%)
Acute leukemia	13,010 (2.9%)	6869 (3.0%)	6141 (2.9%)
Esophageal cancer	12,791 (2.9%)	7935 (3.4%)	4856 (2.3%)
Kidney cancer	12,784 (2.9%)	8268 (3.6%)	4516 (2.1%)
Cervix cancer	11,865 (2.7%)	NA	11,865 (5.5%)
Non-Hodgkin lymphoma	11,422 (2.6%)	6122 (2.6%)	5300 (2.5%)
Bladder cancer	8538 (1.9%)	5580 (2.4%)	2958 (1.4%)
Multiple myeloma	8311 (1.9%)	4288 (1.8%)	4023 (1.9%)
CNS cancer	7761 (1.7%)	4159 (1.8%)	3602 (1.7%)
Ovarian cancer	7752 (1.7%)	NA	7752 (3.6%)
Oral cavity & pharynx cancer	4394 (1.0%)	2976 (1.3%)	1418 (0.7%)
Non-melanoma skin cancer	3806 (0.9%)	2106 (0.9%)	1700 (0.8%)
Melanoma	3432 (0.8%)	1815 (0.8%)	1617 (0.8%)
Endometrial cancer	3271 (0.7%)	NA	3271 (1.5%)
Thyroid/other glands cancer	3002 (0.7%)	1087 (0.5%)	1915 (0.9%)
Larynx cancer	2564 (0.6%)	2206 (1.0%)	358 (0.2%)
Bone & cartilage cancer	2532 (0.6%)	1387 (0.6%)	1145 (0.5%)
Testicular cancer	1932 (0.4%)	1932 (0.8%)	NA
Hodgkin lymphoma	1089 (0.2%)	577 (0.2%)	512 (0.2%)
Other malignant tumors/non-specified	36,588 (8.2%)	16,615 (7.2%)	19,973 (9.2%)

Abbreviations: CNS, central nervous system; NA, not applicable.

$p = 0.008$), thyroid ($\beta = -47 \times 10^{-7}$, $p = 0.02$), kidney ($\beta = -41 \times 10^{-7}$, $p = 0.006$), and colorectal cancer ($\beta = -37 \times 10^{-7}$, $p = 0.006$).

Consistent with the univariate analyses, no statistically significant associations were observed when considering all cancers combined. In addition, no statistically significant positive associations were identified.

4 | Discussion

In this nationwide ecological study spanning an extensive latitudinal gradient, higher population-based 25(OH)D concentrations were inversely associated with mortality from multiple cancer types across Chile. Associations remained significant for several malignancies after adjusting for body mass index and tobacco use, suggesting that VD status may be independently related to cancer mortality in this population. In line with previous studies, breast and colorectal cancer displayed the most consistent associations, followed by kidney, liver, thyroid, and endometrial cancers [17–21]. In contrast, VD status and all-cancer age-standardized mortality did not show a statistically significant association, likely reflecting the heterogeneity of cancer as a composite outcome encompassing distinct etiologies and, in some cases, opposing risk factors.

The inverse associations observed for several specific cancer types in our study are consistent with a substantial body of epidemiological evidence linking VD status to cancer mortality [22]. Prospective studies conducted over several decades have evaluated the association between circulating 25(OH)D concentrations

20457634, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cam4.72273, Wiley Online Library on [21/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 | Age-standardized death rates per 100,000 by region for the five leading cancer sites in the total population (Chile, 2002–2020).

Region (mean °S latitude)	Cancer types (total population)					Cancer types (males)					Cancer types (females)				
	Gastric	Lung	Colorectal	Prostate	Gall bladder	Gastric	Lung	Colorectal	Prostate	Gall bladder	Gastric	Lung	Colorectal	Breast	Gall bladder
Arica y Parinacota (18°28'S)	10	16	8	6	9	15	23	9	15	6	5	10	7	11	9
Tarapacá (20°12'S)	12	15	7	7	7	18	23	9	16	6	7	9	6	10	7
Antofagasta (23°38'S)	11	30	9	7	5	17	48	10	16	6	6	16	8	10	8
Atacama (27°21'S)	11	14	6	6	9	17	20	8	14	5	6	8	5	10	9
Coquimbo (29°54'S)	12	10	8	6	9	18	15	9	15	5	8	6	7	9	10
Valparaíso (33°02'S)	13	14	9	6	10	20	21	11	16	6	8	9	8	12	10
Metropolitana de Santiago (33°26'S)	11	13	8	6	8	18	19	9	16	6	6	9	7	11	8
Libertador B. O'Higgins (34°09'S)	12	9	8	8	11	19	12	9	18	4	7	7	8	10	10
Maule (35°25'S)	17	9	7	8	11	27	12	8	17	5	9	5	7	9	12
Ñuble (36°36'S)	17	6	8	7	14	25	8	9	17	4	9	5	8	11	16
Bíobío (36°49'S)	18	8	8	7	12	28	11	9	18	5	10	6	7	11	12
La Araucanía (38°44'S)	17	7	8	6	16	26	9	9	14	5	10	5	8	10	17
Los Ríos (39°48'S)	17	8	8	6	17	26	11	9	15	5	9	5	7	9	17

(Continues)

20457634, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cam4.72273, Wiley Online Library on [21/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 | (Continued)

Region (mean °S latitude)	Cancer types (total population)					Cancer types (males)					Cancer types (females)				
	Gastric	Lung	Colorectal	Prostate	Gall bladder	Gastric	Lung	Colorectal	Prostate	Gall bladder	Gastric	Lung	Colorectal	Breast	Gall bladder
Los Lagos (41°28′S)	16	10	8	6	12	24	13	9	15	6	10	7	7	8	12
Aisén del Gral. C. Ibáñez del Campo (45°34′S)	18	11	10	6	8	26	14	11	14	7	10	9	9	10	8
Magallanes y de La Antártica Chilena (53°09′S)	13	13	11	6	9	20	18	13	14	7	6	8	9	14	8

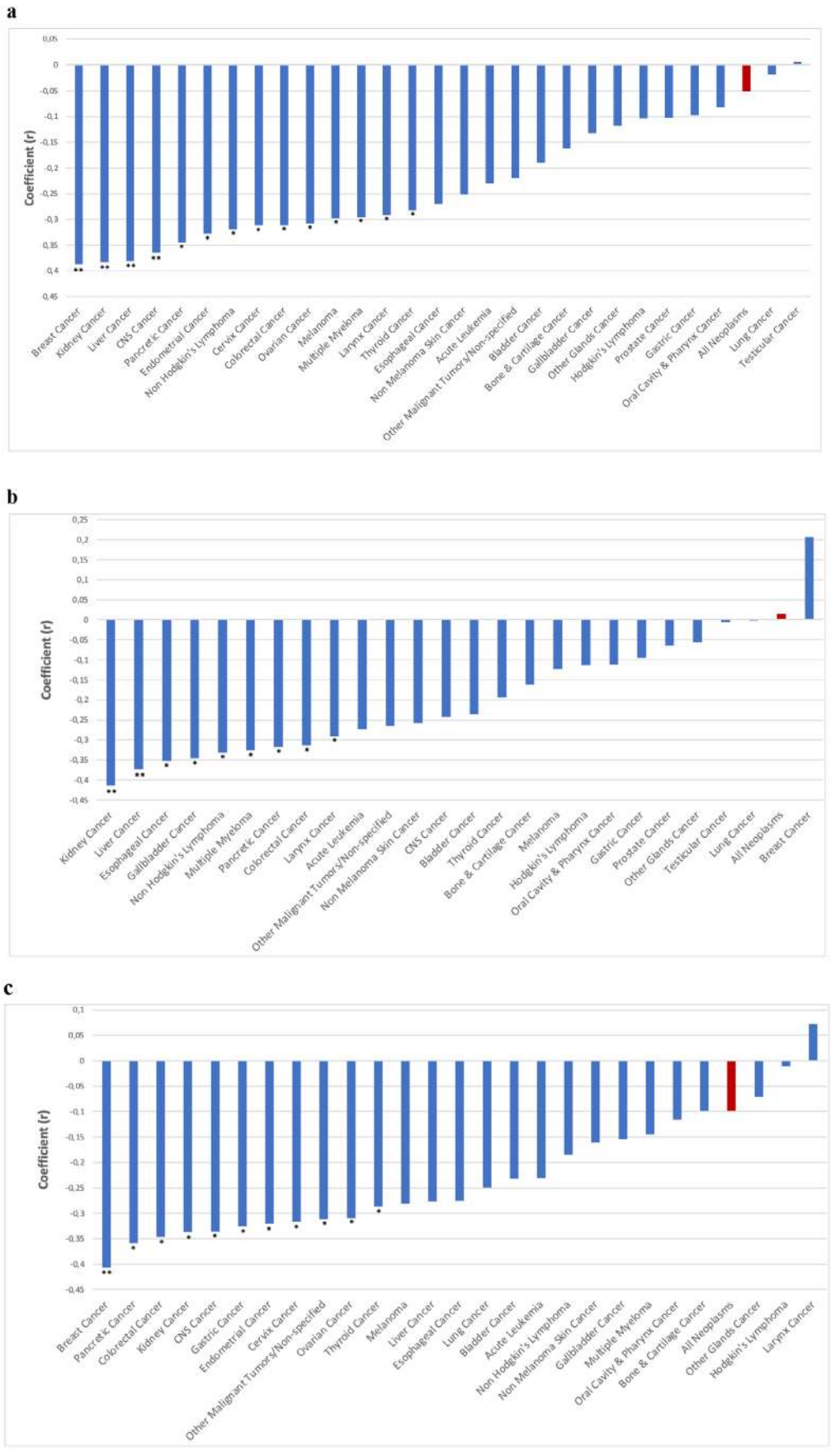
Note: ASDR are presented per 100,000 population. Regions are ordered from north to south. Full heatmaps including all cancer sites are provided in Tables S1–S3.
Abbreviation: ASDR, age-standardized death rates.

and cancer outcomes, reporting inverse relationships with cancer-specific and all-cancer mortality. A meta-analysis by Han et al. pooled data from 16 prospective studies and more than 100,000 participants and found an association between higher 25(OH)D concentrations and a lower risk of cancer mortality, supporting the robustness of this association [23]. Although inverse associations with overall cancer mortality were reported in that meta-analysis, this relationship was not observed in our study. Differences in study design may partly explain this discrepancy, as the studies included in the meta-analysis were based on individual-level measurements of circulating 25(OH)D, whereas our analysis relied on population-based estimates of VD status. In addition, all-cancer mortality represents a heterogeneous outcome combining malignancies with distinct biological mechanisms and risk profiles, which may attenuate associations when cancers are analyzed collectively. Evidence supporting temporality has also been reported, as inverse associations have been observed between diagnostic serum 25(OH)D concentrations and subsequent cancer-specific mortality [24].

Beyond the overall risk reduction reported in meta-analyses, individual-level cohort data further indicate that this association is not linear across the full range of 25(OH)D concentrations. Schöttker et al. [25] reported that the inverse association between 25(OH)D concentrations and mortality was most pronounced among individuals with VD deficiency (< 30 nmol/L, approximately 12 ng/mL) or insufficiency (30–50 nmol/L, approximately 12–20 ng/mL), with cancer mortality risk significantly increased in the deficient group compared with those with sufficient concentrations, whereas the association became markedly weaker above this range. In our study, approximately half of Chilean provinces had mean population-based 25(OH)D concentrations below this threshold (Figure 2), placing

FIGURE 2 | Association between latitude and provincial mean 25(OH)D concentration. Each point represents one of the 48 provinces included in the association analyses. The solid line shows the fitted linear regression and dashed lines the 95% confidence interval. The fitted regression line is 25(OH)D (ng/mL) = 29.1 − 0.26 × latitude (°S); $r = -0.61$, $R^2 = 0.37$, $p < 0.0001$.

20457634, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cam4.72273, Wiley Online Library on [21/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License



* *P* value <0.05. ** *P* value <0.01. CNS: Central Nervous System.

FIGURE 3 | Legend on next page.

20457634, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cam4.72273, Wiley Online Library on [21/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

FIGURE 3 | Association between provincial mean 25(OH)D concentrations and cancer age-standardized death rates (ASDR) by cancer type. (a) Total population; (b) Male population; (c) Female population. Bars show Pearson's correlation coefficients describing univariable associations between provincial mean 25(OH)D concentrations and ASDR by cancer type.

TABLE 3 | Association between provincial mean 25(OH)D and cancer ASDR in multivariable linear regression models adjusted for BMI and smoking, by cancer type.

	Total population		Male population		Female population	
Cancer type	**Estimate $\times 10^{-7}$ (95% CI)**	***p***	**Estimate $\times 10^{-7}$ (95% CI)**	***p***	**Estimate $\times 10^{-7}$ (95% CI)**	***p***
All cancer types	−19 (−126 to 89)	0.74	−2 (−150 to 145)	0.97	−25 (−115 to 65)	0.58
Gastric cancer	−5 (−33 to 24)	0.76	−7 (−51 to 38)	0.76	−36* (−63 to −9)	**0.01**
Lung cancer	−10 (−54 to 34)	0.67	−15 (−88 to 58)	0.69	−35* (−69 to −1)	**0.047**
Colorectal cancer	−20* (−35 to −5)	**0.01**	−37** (−64 to −11)	**0.008**	−37** (−62 to −12)	**0.006**
Prostate cancer	−7 (−20 to 7)	0.32	−13 (−40 to 15)	0.37	NA	NA
Gallbladder cancer	−8 (−29 to 12)	0.43	−46** (−77 to −16)	**0.005**	−16 (−47 to 14)	0.30
Breast cancer	−17** (−28 to −7)	**0.003**	4 (−1 to 8)	0.13	−33** (−54 to −13)	**0.002**
Pancreatic cancer	−16** (−28 to −4)	**0.009**	−30* (−53 to −7)	**0.01**	−33** (−54 to −11)	**0.005**
Liver cancer	−19** (−31 to −8)	**0.001**	−51** (−81 to −21)	**0.002**	−29* (−55 to −4)	**0.03**
Acute leukemia	−14 (−29 to 1)	0.07	−39* (−73 to −4)	**0.04**	−31 (−65 to 3)	0.08
Esophageal cancer	−12 (−26 to 1)	0.08	−36* (−63 to −9)	**0.01**	−19* (−38 to −1)	**0.048**
Kidney cancer	−19** (−32 to −7)	**0.003**	−37** (−58 to −17)	**0.001**	−41** (−69 to −13)	**0.006**
Cervix cancer	−11* (−21 to −2)	**0.02**	NA	NA	−26* (−48 to −5)	**0.02**
Non-Hodgkin lymphoma	−15* (−26 to −4)	**0.01**	−33** (−55 to −10)	**0.007**	−9 (−25 to 8)	0.30
Bladder cancer	−17 (−36 to 2)	0.08	−32* (−62 to −2)	**0.04**	−20 (−41 to 1)	0.06
Multiple myeloma	−19* (−33 to −5)	**0.01**	−39** (−66 to −11)	**0.008**	−5 (−18 to 8)	0.45
CNS cancer	−14** (−23 to −4)	**0.008**	−14 (−33 to 4)	0.14	−32* (−57 to −6)	**0.02**
Ovarian cancer	−15* (−27 to −3)	**0.02**	NA	NA	−30* (−53 to −6)	**0.02**
Oral cavity & pharynx cancer	−2 (−10 to 7)	0.72	−5 (−20 to 11)	0.57	−6 (−21 to 9)	0.43
Non-melanoma skin cancer	−13* (−25 to −1)	**0.04**	−34* (−64 to −4)	**0.03**	−4 (−14 to 5)	0.38
Melanoma	−14* (−26 to −3)	**0.02**	−3 (−17 to 10)	0.60	−32* (−58 to −7)	**0.02**
Endometrial cancer	−22** (−38 to −7)	**0.007**	NA	NA	−47** (−81 to −14)	**0.008**
Thyroid cancer	−22* (−40 to −4)	**0.02**	−9 (−24 to 7)	0.28	−47* (−85 to −9)	**0.02**
Larynx cancer	−19* (−34 to −4)	**0.02**	−36* (−65 to −7)	**0.02**	1 (−6 to 8)	0.82
Bone & cartilage cancer	−4 (−13 to 6)	0.43	−7 (−24 to 10)	0.42	−6 (−27 to 15)	0.60
Testicular cancer	0 (−6 to 7)	0.94	0 (−14 to 14)	1.00	NA	NA
Hodgkin lymphoma	−3 (−14 to 9)	0.65	−5 (−26 to 17)	0.67	−2 (−14 to 9)	0.70
Other malignant tumors/ non-specified	−14 (−27 to 0)	0.07	−30* (−53 to −5)	**0.02**	−36* (−63 to −10)	**0.01**

Note: An estimate of -20×10^{-7} corresponds to a decrease of 0.20 deaths per 100,000 population per 1 ng/mL increase in 25(OH)D. Bold indicates significant *p*-values.
Abbreviations: CNS, central nervous system; NA, not applicable.
*p-value < 0.05.
**p-value < 0.01.

20457634, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cam4.72273, Wiley Online Library on [21/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

a substantial proportion of the population within the range in which VD status is most likely to influence cancer mortality. This dose–response pattern provides additional biological plausibility for the associations observed in the present ecological analysis and suggests that correcting VD deficiency, rather than maximizing 25(OH)D concentrations beyond sufficiency, may be the primary target for reducing cancer mortality risk at the population level.

While our analysis does not allow causal inference at the individual level, the observed associations are consistent with several criteria commonly considered in causal frameworks, including consistency across populations, biological plausibility, coherence with established mechanistic evidence, and temporality as supported by prior prospective studies linking pre-diagnostic VD status to cancer survival.

Through its effects on both innate and adaptive immune responses, VD may modulate anti-tumor immunity, a mechanism of particular relevance given the recognized role of immune evasion in cancer progression [26]. Experimental studies indicate that VD signaling can influence immune cell function, including T-cell activation and antigen presentation, and may also affect the gut microbiome in ways that enhance immune-mediated tumor control [27, 28]. Although these findings provide biologically plausible pathways, their clinical relevance in humans remains an area of ongoing investigation. In addition to its immunomodulatory effects, VD has demonstrated antiproliferative activity through effects on cell-cycle regulation, differentiation, apoptosis, and angiogenesis, providing further biological support for its role in cancer progression and survival, consistent with the mortality-focused associations observed in the present study [29, 30].

While associations between VD status and breast and colorectal cancer have been more extensively reported, inverse associations were also observed for kidney, thyroid, and endometrial cancers, malignancies that have been less frequently examined in VD-related epidemiological studies. In kidney cancer, VD–induced growth inhibition has been reported in experimental models for several decades, although the underlying mechanisms remain incompletely understood [31]. Inhibition of angiogenesis has been suggested as a potential pathway, particularly given the central role of angiogenic signaling in renal cancer biology, but supporting evidence remains limited [32]. For endometrial cancer, a definitive molecular link with VD signaling has not yet been convincingly established; however, experimental studies have demonstrated increased apoptotic cell death in endometrial cancer cell cultures following VD exposure [33]. In thyroid cancer, VD has been shown to inhibit tumor cell growth through induction of cell-cycle arrest in experimental models [34].

By contrast, the observed association with liver cancer should be interpreted with caution. Owing to limitations in disease classification, hepatocellular carcinoma and intrahepatic cholangiocarcinoma are grouped together under the category of "liver cancer" despite representing biologically distinct entities. This heterogeneity limits biological interpretation, and a clear mechanistic explanation for the observed association cannot currently be proposed.

An additional noteworthy finding of our study was the inverse association between 25(OH)D and both melanoma and non-melanoma skin cancer (NMSC) mortality, although with a sex-specific pattern: NMSC among males and melanoma among females. This finding may appear counterintuitive, as ultraviolet radiation exposure, the main driver of cutaneous VD synthesis, is also the principal risk factor for skin cancer. However, the skin itself is capable of locally metabolizing VD into its active form, 1,25-dihydroxyvitamin D, which can in turn regulate keratinocyte proliferation, differentiation, and apoptosis [35]. This local metabolic capacity suggests that the observed protective association may not solely reflect circulating 25(OH)D concentrations, but also the skin's own capacity to synthesize and utilize active VD, potentially counterbalancing the carcinogenic effects of UV exposure.

Beyond the aforementioned mechanistic considerations, the association between latitude and cancer mortality has been investigated for more than a century. In 1915, Hoffman reported higher cancer mortality among populations living at higher latitudes [36]. Subsequent ecological studies, including analyses by Grant across European countries and country-specific evaluations in France, reported higher mortality at higher latitudes for several cancer sites, including breast, colorectal, kidney, ovarian, pancreatic, esophageal, and prostate cancers, as well as non-Hodgkin lymphoma and multiple myeloma [37]. Similar findings have been reported in Asia: in China, ecological studies using multivariable models adjusting for dietary, occupational, and lifestyle factors have linked solar ultraviolet-B irradiance with lower cancer mortality and incidence, as well as improved cancer survival [38–40]; and in Japan, multilevel and ecological analyses have similarly reported inverse associations between solar radiation and cancer mortality, including for pancreatic cancer [41–44]. Comparable associations have also been described in Australia, where pancreatic cancer mortality was higher in southern, lower-UV states [45]. Collectively, these studies suggest that a subset of cancers may exhibit latitude-related variation, with latitude often serving as a proxy for population vitamin D status [46].

Our findings highlight substantial geographic heterogeneity in cancer mortality across Chile, even when using ASDR. Regional differences were not uniform across cancer sites and differed by sex, with particularly high lung cancer mortality in Antofagasta, higher gastric cancer mortality across several central–southern regions, and pronounced clustering of gallbladder cancer mortality in the south, especially in La Araucanía and Los Ríos. These patterns likely reflect a combination of factors, including variation in environmental exposures, socioeconomic conditions, healthcare access, multiple and timeliness of diagnosis and treatment, as well as differences in the prevalence of site-specific risk factors across regions. Although our study design does not allow causal inference at the individual level, the consistent geographic clustering of specific cancer sites supports the need for strengthened population-based cancer surveillance and regionally tailored prevention strategies.

As pointed out earlier, Chile offers an ideal setting to examine latitude-related variations in VD status, given its long north–south span and marked differences in solar radiation exposure (a key determinant of endogenous VD synthesis). This geographic setting also has important implications for how evidence from VD interventions should be interpreted at the population level. VD supplementation has yielded heterogeneous results with

20457634, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cam4.72273, Wiley Online Library on [21/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

respect to cancer outcomes. The VITAL trial, which randomized more than 25,000 participants to receive VD at a dose of 2000 IU per day or placebo, did not demonstrate a reduction in invasive cancer incidence after a median follow-up of 5.3 years. Notably, mean 25(OH)D concentration among participants in the VD treatment arm was 31 ng/mL, indicating that many participants may not have had a clinically significant deficiency at baseline. Despite this, a significant protective effect on all-cancer incidence was observed among participants with BMI $<25\,kg/m^2$, suggesting that body composition may modulate the biological response to VD supplementation [8, 9]. In a secondary analysis of VITAL, however, VD supplementation significantly reduced advanced (metastatic or fatal) cancer overall (HR 0.83, 95% CI 0.69–0.99), with the reduction concentrated among participants of normal weight (BMI $<25\,kg/m^2$: HR 0.62, 95% CI 0.45–0.86); the reduction in cancer mortality was of similar magnitude but did not reach statistical significance [46]. This gradient, from no effect on overall incidence to a significant effect on metastatic or fatal disease, is relevant to the present study, whose outcome is mortality rather than incidence. Another large study, the D-Health trial, which randomized more than 21,000 older Australian adults to monthly high-dose VD supplementation or placebo, found no significant reduction in cancer mortality [47]. These findings should not be interpreted as inconsistent with the associations reported in the present study. Both trials enrolled participants with a mean baseline 25(OH)D concentration of approximately 30–31 ng/mL, corresponding to the upper, comparatively flat portion of the dose–response curve linking VD status to cancer mortality, where further increases in 25(OH)D concentration are not expected to yield additional benefit. A lack of benefit in these VD-replete populations is therefore consistent with, rather than contradictory to, a dose–response relationship in which the largest reductions in risk are concentrated among individuals with VD deficiency or insufficiency. This distinction suggests that population-level supplementation strategies are likely to yield the greatest benefit when targeted at populations, or subgroups, with a high prevalence of VD deficiency, such as those identified in the present study.

Importantly, the potential impact of supplementation at the population level is also influenced by implementation. Although VD supplementation is widely recommended and practiced for the prevention of rickets in newborns and infants, recommendations for supplementation among older adults vary across countries, and regular supplement use remains limited in children and adults [48]. In this context, food fortification represents an alternative population-level strategy to improve VD status. Modeling studies suggest that food fortification achieves increases in serum 25(OH)D concentrations comparable to supplementation while being more cost-effective [49]. In countries with wide latitudinal gradients, such as Chile, population-wide approaches may therefore be particularly relevant for addressing VD deficiency and its potential implications for cancer mortality. Consistent with this approach, a bill was passed in Chile in 2022 to implement a nationwide VD food fortification policy starting in June 2026 [50, 51].

This study has several strengths. It is based on nationwide mortality data collected over an 18-year period, which reduces the influence of short-term fluctuations and year-specific events on the observed associations. Chile's administrative division into provinces with reliable death registries enables analyses at a detailed subnational level and high geographic resolution. In addition, the country's exceptional latitudinal span within a long and narrow territory, together with a relatively genetically and ethnically homogeneous population, provides a suitable setting to examine latitude-related variation in VD status and cancer mortality. Serum 25(OH)D concentrations were measured centrally using a standardized analytical method, limiting measurement variability across provinces. Finally, this study includes nearly half a million cancer-related deaths from a Latin American population that has been less frequently examined in previous VD and cancer studies.

Despite these strengths, several limitations should be considered. A key limitation is the use of a single population-based 25(OH)D measurement to assess cancer mortality over an 18-year period. However, available evidence suggests that serum 25(OH)D concentrations tend to remain relatively stable over time in the absence of supplementation or food fortification, which were not implemented among women of childbearing age in Chile during the study period. Provincial mean 25(OH)D concentrations were derived from a national survey that was not designed to be representative at the provincial level, and the number of contributing participants varied substantially across provinces. Provinces with few participants therefore have imprecise exposure estimates. However, inverse associations were generally of similar or greater magnitude when the analysis was restricted to provinces with at least 30 contributing participants (Table S5), suggesting that the true associations may be at least as strong as those observed. An additional limitation is the exclusion of educational attainment and socioeconomic status from the regression models. These factors may act as proxies for healthcare access, an important determinant of cancer case fatality. As the study outcome was mortality, which reflects both cancer incidence and case fatality, it is therefore not possible to disentangle whether the observed associations with 25(OH)D concentrations relate primarily to cancer development or to survival after diagnosis.

In conclusion, this nationwide ecological analysis demonstrates inverse associations between population-based VD status and mortality from multiple cancer types across a broad latitudinal gradient in Chile. To our knowledge, this is the first study to examine these associations across such an extensive latitudinal range within a single Latin American country. Our findings confirm previously reported associations between low VD status and colorectal and breast cancer mortality, while providing novel ecological evidence linking 25(OH)D concentrations to thyroid, liver, and kidney cancer mortality—cancer types for which a relationship with VD has been less established. These findings raise the possibility that VD status may represent a modifiable population-level factor influencing mortality across a broader spectrum of malignancies than previously recognized, and provide a valuable baseline for evaluating the impact of emerging VD fortification and supplementation policies in Chile and other high-latitude countries. Prospective and interventional studies are warranted to clarify causal pathways and assess the effects of VD interventions on site-specific cancer outcomes.

20457634, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cam4.72273, Wiley Online Library on [21/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Author Contributions

Juan Pablo Fraga: investigation, data curation, formal analysis, writing – original draft. **Carlos A. Camargo Jr.:** conceptualization, writing – review and editing. **Arturo Borzutzky:** conceptualization, data curation, methodology, investigation, formal analysis, supervision, validation, writing – review and editing. **Alvaro Passi-Solar:** formal analysis, investigation, methodology, visualization, writing – review and editing. **Ignacia S. Núñez-Ulloa:** data curation, formal analysis, investigation, writing – original draft. **Paula Margozzini:** writing – review and editing, data curation, investigation, formal analysis. **Gonzalo Muñoz:** data curation, formal analysis, writing – original draft, investigation, methodology, visualization. **Bruno Nervi:** methodology, resources, writing – review and editing, supervision. **Sebastián Mondaca:** methodology, conceptualization, supervision, writing – review and editing.

Acknowledgments

Medical writing support was provided by María Soledad Lange, PhD, STORM Ltd. (Chile).

Funding

This work was funded by the ANID FONDAP 152220002 (CECAN).

Ethics Statement

The Scientific Ethics Committee of the Faculty of Medicine at Pontificia Universidad Católica de Chile approved this study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. J. C. Gallagher and C. J. Rosen, "Vitamin D: 100 Years of Discoveries, Yet Controversy Continues," *Lancet Diabetes and Endocrinology* 11, no. 5 (2023): 362–374, https://doi.org/10.1016/S2213-8587(23)00060-8.

2. M. F. Holick, "Vitamin D Deficiency," *New England Journal of Medicine* 357, no. 3 (2007): 266–281, https://doi.org/10.1056/NEJMRA070553.

3. D. Feldman, A. V. Krishnan, S. Swami, E. Giovannucci, and B. J. Feldman, "The Role of Vitamin D in Reducing Cancer Risk and Progression," *Nature Reviews Cancer* 14, no. 5 (2014): 342–357, https://doi.org/10.1038/nrc3691.

4. C. R. Johnson, D. V. Dudenkov, K. C. Mara, P. R. Fischer, J. A. Maxson, and T. D. Thacher, "Serum 25-Hydroxyvitamin D and Subsequent Cancer Incidence and Mortality: A Population-Based Retrospective Cohort Study," *Mayo Clinic Proceedings* 96, no. 8 (2021): 2157–2167, https://doi.org/10.1016/j.mayocp.2020.12.037.

5. L. Dai, M. Liu, and L. Chen, "Association of Serum 25-Hydroxyvitamin D Concentrations With All-Cause and Cause-Specific Mortality Among Adult Patients With Existing Cardiovascular Disease," *Frontiers in Nutrition* 8 (2021): 740855, https://doi.org/10.3389/FNUT.2021.740855/BIBTEX.

6. Y. Kim and Y. Je, "Vitamin D Intake, Blood 25(OH)D Levels, and Breast Cancer Risk or Mortality: A Meta-Analysis," *British Journal of Cancer* 110, no. 11 (2014): 2772–2784, https://doi.org/10.1038/BJC.2014.175;SUBJMETA.

7. D. Huang, S. Lei, Y. Wu, et al., "Additively Protective Effects of Vitamin D and Calcium Against Colorectal Adenoma Incidence, Malignant Transformation and Progression: A Systematic Review and Meta-Analysis," *Clinical Nutrition* 39, no. 8 (2020): 2525–2538, https://doi.org/10.1016/J.CLNU.2019.11.012.

8. J. E. Manson, N. R. Cook, I. M. Lee, et al., "Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease," *New England Journal of Medicine* 380, no. 1 (2019): 33–44, https://doi.org/10.1056/NEJMOA1809944;ISSUE:ISSUE:DOI.

9. S. Kuznia, A. Zhu, T. Akutsu, et al., "Efficacy of Vitamin D3 Supplementation on Cancer Mortality: Systematic Review and Individual Patient Data Meta-Analysis of Randomised Controlled Trials," *Ageing Research Reviews* 87 (2023): 101923, https://doi.org/10.1016/J.ARR.2023.101923.

10. W. B. Grant, "An Ecological Study of Cancer Incidence and Mortality Rates in France With Respect to Latitude, an Index for Vitamin D Production," *Dermato-Endocrinology* 2, no. 2 (2010): 62–67, https://doi.org/10.4161/DERM.2.2.13624;WGROUP:STRING:PUBLICATION.

11. W. B. Grant, "An Ecologic Study of Cancer Mortality Rates in Spain With Respect to Indices of Solar UVB Irradiance and Smoking," *International Journal of Cancer* 120, no. 5 (2007): 1123–1128, https://doi.org/10.1002/IJC.22386;CTYPE:STRING:JOURNAL.

12. N. van Schoor and P. Lips, "Global Overview of Vitamin D Status," *Endocrinology and Metabolism Clinics of North America* 46, no. 4 (2017): 845–870, https://doi.org/10.1016/j.ecl.2017.07.002.

13. S. Cabrera, D. Benavente, M. Alvo, P. De Pablo, and C. J. Ferro, "Vitamin B12 Deficiency Is Associated With Geographical Latitude and Solar Radiation in the Older Population," *Journal of Photochemistry and Photobiology. B* 140 (2014): 8–13, https://doi.org/10.1016/J.JPHOTOBIOL.2014.07.001.

14. Departamento de Estadisticas e Información de Salud, "Website," (2025), https://deis.minsal.cl/#datosabiertos.

15. WHO, Cancer Over Time (2025), https://gco.iarc.fr/overtime/en.

16. E. I. Benchimol, L. Smeeth, A. Guttmann, et al., "The REporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) Statement," *PLoS Medicine* 12, no. 10 (2015): e1001885, https://doi.org/10.1371/JOURNAL.PMED.1001885.

17. G. Wu, M. Xue, Y. Zhao, et al., "Low Circulating 25-Hydroxyvitamin D Level Is Associated With Increased Colorectal Cancer Mortality: A Systematic Review and Dose-Response Meta-Analysis," *Bioscience Reports* 40, no. 7 (2020): BSR20201008, https://doi.org/10.1042/BSR20201008/225834.

18. S. B. Mohr, E. D. Gorham, J. Kim, H. Hofflich, and C. F. Garland, "Meta-Analysis of Vitamin D Sufficiency for Improving Survival of Patients With Breast Cancer," *Anticancer Research* 34, no. 3 (2014): 1163–1166.

19. M. Li, P. Chen, J. Li, R. Chu, D. Xie, and H. Wang, "Review: The Impacts of Circulating 25-Hydroxyvitamin D Levels on Cancer Patient Outcomes: A Systematic Review and Meta-Analysis," *Journal of Clinical Endocrinology and Metabolism* 99, no. 7 (2014): 2327–2336, https://doi.org/10.1210/JC.2013-4320.

20. H. Maalmi, J. M. Ordóñez-Mena, B. Schöttker, and H. Brenner, "Serum 25-Hydroxyvitamin D Levels and Survival in Colorectal and Breast Cancer Patients: Systematic Review and Meta-Analysis of Prospective Cohort Studies," *European Journal of Cancer* 50, no. 8 (2014): 1510–1521, https://doi.org/10.1016/j.ejca.2014.02.006.

21. A. A. N. Rose, C. Elser, M. Ennis, and P. J. Goodwin, "Blood Levels of Vitamin D and Early Stage Breast Cancer Prognosis: A Systematic Review and Meta-Analysis," *Breast Cancer Research and Treatment* 141, no. 3 (2013): 331–339, https://doi.org/10.1007/S10549-013-2713-9.

22. S. J. Wimalawansa, "Vitamin D's Impact on Cancer Incidence and Mortality: A Systematic Review," *Nutrients* 17, no. 14 (2025): 2333, https://doi.org/10.3390/NU17142333/S1.

20457634, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cam4.72273, Wiley Online Library on [21/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

23. J. Han, X. Guo, X. Yu, et al., "25-Hydroxyvitamin D and Total Cancer Incidence and Mortality: A Meta-Analysis of Prospective Cohort Studies," *Nutrients* 11, no. 10 (2019): 2295, https://doi.org/10.3390/NU11102295.

24. NIPH, "Cancer Survival and Serum Levels of Vitamin D," (2025), https://www.fhi.no/en/nva-projects/ongoing/cancer-survival-and-serum-levels-of-vitamin-D/.

25. B. Schöttker, U. Haug, L. Schomburg, et al., "Strong Associations of 25-Hydroxyvitamin D Concentrations With All-Cause, Cardiovascular, Cancer, and Respiratory Disease Mortality in a Large Cohort Study," *American Journal of Clinical Nutrition* 97, no. 4 (2013): 782–793, https://doi.org/10.3945/ajcn.112.047712.

26. C. Aranow, "Vitamin D and the Immune System," *Journal of Investigative Medicine* 59, no. 6 (2011): 881–886, https://doi.org/10.2310/JIM.0B013E31821B8755.

27. M. T. Cantorna, L. Snyder, Y. D. Lin, and L. Yang, "Vitamin D and 1,25(OH)2D Regulation of T Cells," *Nutrients* 7, no. 4 (2015): 3011–3021, https://doi.org/10.3390/NU7043011.

28. N. Charoenngam, A. Shirvani, T. A. Kalajian, A. Song, and M. F. Holick, "The Effect of Various Doses of Oral Vitamin D3 Supplementation on Gut Microbiota in Healthy Adults: A Randomized, Double-Blinded, Dose-Response Study," *Anticancer Research* 40, no. 1 (2020): 551–556, https://doi.org/10.21873/ANTICANRES.13984.

29. F. P. Boscoe and M. J. Schymura, "Solar Ultraviolet-B Exposure and Cancer Incidence and Mortality in the United States, 1993-2002," *BMC Cancer* 6 (2006): 6, https://doi.org/10.1186/1471-2407-6-264.

30. A. Muñoz and W. B. Grant, "Vitamin D and Cancer: An Historical Overview of the Epidemiology and Mechanisms," *Nutrients* 14, no. 7 (2022): 1448, https://doi.org/10.3390/NU14071448.

31. K. Nagakura, E. Abe, T. Suda, M. Hayakawa, H. Nakamura, and H. Tazaki, "Inhibitory Effect of Lct,25-Dihydroxyvitamin D3 on the Growth of the Renal Carcinoma Cell Line," *Kidney International* 29 (1986): 834–840, https://doi.org/10.1038/ki.1986.74.

32. T. Fujioka, M. Hasegawa, K. Ishikura, Y. Matsushita, M. Sato, and S. Tanji, "Inhibition of Tumor Growth and Angiogenesis by Vitamin D3 Agents in Murine Renal Cell Carcinoma," *Journal of Urology* 160, no. 1 (1998): 247–251, https://doi.org/10.1016/S0022-5347(01)63098-2.

33. Y. Kim, Y. S. Kim, M. Kim, J. M. Kim, H. H. Lee, and T. H. Kim, "Thioredoxin-Interacting Protein (TXNIP) Mediates Thioredoxin-Dependent Antioxidant Mechanism in Endometrial Cancer Cells Treated With 1α,25-Dihydroxyvitamin D3," *Anticancer Research* 39, no. 9 (2019): 4795–4803, https://doi.org/10.21873/ANTICANRES.13664.

34. W. Liu, S. L. Asa, I. G. Fantus, P. G. Walfish, and S. Ezzat, "Vitamin D Arrests Thyroid Carcinoma Cell Growth and Induces p27 Dephosphorylation and Accumulation Through PTEN/Akt-Dependent and -Independent Pathways," *American Journal of Pathology* 160, no. 2 (2002): 511–519, https://doi.org/10.1016/S0002-9440(10)64870-5.

35. D. D. Bikle, Y. Oda, and Z. Xie, "Vitamin D and Skin Cancer: A Problem in Gene Regulation," *Journal of Steroid Biochemistry and Molecular Biology* 97, no. 1–2 (2005): 83–91, https://doi.org/10.1016/j.jsbmb.2005.06.001.

36. F. L. Hoffman, "The Mortality From Cancer Throughout the World. Newark, NJ: Prudential Press. Internet Archive," (1915), https://archive.org/details/mortalityfromcan00hoffrich/page/viii/mode/2up.

37. W. B. Grant, "An Ecologic Study of the Role of Solar UV-B Radiation in Reducing the Risk of Cancer Using Cancer Mortality Data, Dietary Supply Data, and Latitude for European Countries," Biologic Effects of Light 2001, 267–276, (2002), https://doi.org/10.1007/978-1-4615-0937-0_26.

38. W. B. Grant, "Does Solar Ultraviolet Irradiation Affect Cancer Mortality Rates in China?," *Asian Pacific Journal of Cancer Prevention* 8, no. 2 (2007): 236–242.

39. W. Chen, B. K. Armstrong, B. Rahman, R. Zheng, S. Zhang, and M. Clements, "Relationship Between Cancer Survival and Ambient Ultraviolet B Irradiance in China," *Cancer Causes & Control* 24, no. 7 (2013): 1323–1330, https://doi.org/10.1007/s10552-013-0210-4.

40. W. Chen, M. Clements, B. Rahman, S. Zhang, Y. Qiao, and B. K. Armstrong, "Relationship Between Cancer Mortality/Incidence and Ambient Ultraviolet B Irradiance in China," *Cancer Causes & Control* 21, no. 10 (2010): 1701–1709, https://doi.org/10.1007/S10552-010-9599-1.

41. Y. Fukuda, T. Nakaya, H. Nakao, Y. Yahata, and H. Imai, "Multilevel Analysis of Solar Radiation and Cancer Mortality Using Ecological Data in Japan," *Bioscience Trends* 2, no. 6 (2008): 235–240.

42. T. Mizoue, "Ecological Study of Solar Radiation and Cancer Mortality in Japan," *Health Physics* 87, no. 5 (2004): 532–538, https://doi.org/10.1097/01.HP.0000137179.03423.0B.

43. S. Kinoshita, Y. Wagatsuma, and M. Okada, "Geographical Distribution for Malignant Neoplasm of the Pancreas in Relation to Selected Climatic Factors in Japan," *International Journal of Health Geographics* 6 (2007): 34, https://doi.org/10.1186/1476-072X-6-34.

44. I. Kato, K. Tajima, T. Kuroishi, and S. Tominaga, "Latitude and Pancreatic Cancer," *Japanese Journal of Clinical Oncology* 15, no. 2 (1985): 403–413.

45. R. E. Neale, D. R. Youlden, L. Krnjacki, M. G. Kimlin, and J. C. Van Der Pols, "Latitude Variation in Pancreatic Cancer Mortality in Australia," *Pancreas* 38, no. 4 (2009): 387–390, https://doi.org/10.1097/MPA.0B013E31819975F4.

46. P. D. Chandler, W. Y. Chen, O. N. Ajala, et al., "Effect of Vitamin D3 Supplements on Development of Advanced Cancer: A Secondary Analysis of the VITAL Randomized Clinical Trial," *JAMA Network Open* 3, no. 11 (2020): e2025850, https://doi.org/10.1001/jamanetworkopen.2020.25850.

47. R. E. Neale, C. Baxter, B. D. Romero, et al., "The D-Health Trial: A Randomised Controlled Trial of the Effect of Vitamin D on Mortality," *Lancet Diabetes and Endocrinology* 10, no. 2 (2022): 120–128, https://doi.org/10.1016/S2213-8587(21)00345-4.

48. T. Niedermaier, T. Gredner, S. Kuznia, et al., "Vitamin D Food Fortification in European Countries: The Underused Potential to Prevent Cancer Deaths," *European Journal of Epidemiology* 37, no. 4 (2022): 309–320, https://doi.org/10.1007/S10654-022-00867-4.

49. T. Niedermaier, T. Gredner, S. Kuznia, B. Schöttker, U. Mons, and H. Brenner, "Potential of Vitamin d Food Fortification in Prevention of Cancer Deaths—A Modeling Study," *Nutrients* 13, no. 11 (2021): 3986, https://doi.org/10.3390/NU13113986/S1.

50. C. Leiva, A. Borzutzky, C. Le Roy, L. Rojas, and Centro de Políticas Públicas UC, "Vitamin D Deficiency: A Proposed Chilean Model for a National Food Fortification Policy," *Temas de la Agenda Pública* 15, no. 124 (2020): 1–18.

51. Biblioteca del Congreso Nacional, "Ley Chile—Decreto 29. Modifica Decreto Supremo N° 977, De 1996, Del Ministerio De Salud, Reglamento Sanitario De Los Alimentos," Ministerio De Salud, SubsecretarÍa De Salud PÚblica, (2024), https://www.bcn.cl/leychile/navegar?idNorma=1204340.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Age-standardized death rate heat table by cancer type and region (sorted by latitude) for total population. **Table S2:** Age-standardized death rate heat table by cancer type and region (sorted by latitude) for male population. **Table S3:** Age-standardized death rate heat table by cancer type and region (sorted by latitude) for female population. **Table S4:** Pearson correlation coefficients for provincial mean 25(OH)D concentrations and age-standardized death rate per cancer type for total, male and female population. **Table S5:** Sensitivity analysis of Pearson correlation

20457634, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cam4.72273, Wiley Online Library on [21/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

coefficients between provincial mean 25(OH)D concentrations and age-standardized death rates (ASDR) by cancer type, for the total, male, and female populations, restricted to provinces in which at least 30 subjects contributed to the provincial mean 25(OH)D concentration. **Table S6:** Multiple linear regression of provincial mean 25(OH)D concentration on latitude, body mass index and tobacco use (48 provinces). **Figure S1:** Absolute number of cancer related deaths and cancer mortality rate by year. **Figure S2:** Crude and age-standardized cancer mortality rate by year. **Figure S3:** Provincial mean body mass index and tobacco use in relation to latitude. Each point represents one of the 48 provinces included in the association analyses. (a) Mean body mass index and (b) tobacco use, plotted against latitude. Solid lines show the fitted linear regression and shaded areas the 95% confidence interval of the fit. The corresponding relationship for mean 25(OH)D concentration is shown in Figure 2.

20457634, 2026, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cam4.72273, Wiley Online Library on [21/09/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License